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PhD Thesis in Science

PhD Thesis Under Supervision of:

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Título da Tese de Doutoramento:

Análise objectiva das propriedades e deterioração dos materiais, em polímeros de lentes de contacto, utilizando diferentes técnicas

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"When you can measure what you are speaking about, and express it in numbers,
you know something about it; but when you cannot measure it,
when you cannot express it in numbers,
your knowledge is of a meagre and unsatisfactory kind"

Ratner B et al, 1994. In Contact Lens Practice; Chapter 47, pp1088,
citing Lord Kelvin (1891)

Objective analysis of properties and material deterioration in contact lens polymers using different techniques

Abstract

Biocompatibility of contact lens polymers is the ability of the material to be worn in direct contact with the ocular surface without an adverse response of the host. In the contact lens field, it depends strongly on the ability of the material to respect the physiological needs of the ocular surface, and avoid or minimize other different forms of interaction. With modern lenses, many aspects that caused problems in the past (i.e. oxygen transmissibility), have been solved, however, the impact of contact lenses on the ocular surface due to both topographic and mechanical characteristics and the dehydration process followed after insertion are still a matter of concern. In order to analyze some of these aspects, the present Thesis work was developed, covering the following main issues:

1) The evaluation of the pattern of contact lens fitting in Portugal and the symptoms more commonly associated with contact lens wear which are covered in chapters 1 and 2;

2) Literature review of the main properties that characterize the contact lens materials and how they can interact with the ocular tissue as a consequence of wear and/or material deterioration being covered by chapters 3 and 4;

3) Evaluation of different contact lens materials using different techniques to analyze some properties at the contact lens surface and the bulk of the material which are covered in chapters 5 to 10;

4) Analyze how some of those properties can change as a consequence of contact lens wear which is covered in chapters 11 to 13.

Chapter 14 addresses the overall discussion of the results, some conclusions and proposals for future work to be developed in this filed with the body of knowledge acquired during the realization of this work.

In the two introductory chapters we have observed that soft contact lenses are the most widely fitted in Portugal, with silicone hydrogel materials experiencing a significant increase and already account for more than 20% of the new fits and refits despite the limited proportion of brands within this field so far. Contact lens wearers usually report symptoms related with contact lens discomfort most frequently than non-contact lens wearers, and most of them could be related to dryness as the end of day discomfort, scratchiness and eye redness.

The first experimental part of the Thesis has evidenced a specific and different behavior of silicone hydrogel materials regarding the relationship of equilibrium water content (EWC) and refractive index of the material if we compare them with the classical relationships

followed by conventional hydrogels. These findings are of particular relevance when we need to characterize the dehydration of materials as a result of wear. Regarding microscopy, the microscopic technique that allows us to evaluate contact lenses in a less invasive way and in the natural hydrated state was atomic force microscopy (AFM). Again silicone hydrogel materials show a remarkable different pattern of surface topography, particularly those of the first generation including surface treatment to improve wettability. This technique also allows us to obtain information about the mechanical behavior of the material, with a nanometric precision. Complimentary, the oxygen permeability (Dk) and transmissibility (Dk/t) of some silicone hydrogel contact lens materials have been evaluated. These studies concluded that silicone hydrogel materials within a range of high oxygen permeability, are not expected to induce significant differences in their oxygen performance in physiological terms (i.e. evaluating the actual amount of oxygen reaching the contact lens-cornea interface) even with significant changes in their Dk/t values. The in vitro dehydration process of silicone hydrogel and conventional hydrogel materials is characteristic of each material, depending essentially on their EWC. Several quantitative parameters have been obtained using this new approach.

The second experimental part has been focused on the evaluation of the effects of wear on some characteristics of contact lens materials, particularly the topographic and mechanical parameters at the lens surface, their EWC and in vitro dehydration process. In the corresponding chapters, it has been observed that materials become less elastic and harder with wear, which is reflected as an increase in the elastic modulus of worn lenses when compared against unworn samples of the same materials under the same experimental conditions. Topographic information shows an overall increase of surface roughness of polymer surface, except in some samples where the high irregular surface of the unworn samples results in a partial uniformization of the surface elevation pattern because of the deposits that form films over the contact lens surface. The *in vitro* dehydration process shows a remarkable change in qualitative and quantitative terms with significantly higher initial dehydration rates. Samples worn for periods of one month demonstrated changes in their EWC with a trend towards decreasing EWC even after several days left to re-equilibrate in saline.

Overall, the present work demonstrates objectively that some contact lens materials become more irregular and more rigid in their surfaces, decrease the EWC and increase their initial dehydration rates under *in vitro* conditions. These changes could cause a significant increase in the negative interactions between contact lenses and the most superficial tissues in the ocular surface.

Análise objectiva das propriedades e deterioração dos materiais, em polímeros de lentes de contacto, utilizando diferentes técnicas

Resumo

A biocompatibilidade dos materiais para lentes de contacto representa a capacidade dos mesmos para serem utilizados em contacto directo com a superfície ocular sem causar respostas adversas no olho. No âmbito das lentes de contacto, esta biocompatibilidade depende da capacidade do material para respeitar as necessidades fisiológicas da superfície ocular e evitar ou minimizar outros tipos de interacção. Nas lentes actuais, muitos dos aspectos que afectam a tolerância foram já melhorados como é o caso da transmissibilidade ao oxigénio nas lentes de silicone hidrogel. No entanto, o impacto destas lentes na superfície ocular pelas suas características superficiais, pelas propriedades mecânicas, pela adesão de depósitos ou pela resistência dos materiais à desidratação, são ainda aspectos a resolver. Com o objectivo de estudar alguns destes aspectos mais aprofundadamente, foi desenvolvida esta Tese, que inclui os seguintes aspectos:

1) A avaliação dos padrões actuais de prescrição e adaptação de lentes de contacto em Portugal e quais os sintomas que referem os usuários com maior frequência. Desenvolvido nos capítulos 1 e 2;

2) Revisão da literatura sobre as principais propriedades que caracterizam os materiais para lentes de contacto, como se relacionam com a superfície ocular e como podem mudar estas relações pelo processo natural de deterioração dos materiais com o seu uso. Desenvolvido nos capítulos 3 e 4;

3) Avaliação de distintos materiais de lentes de contacto utilizando diferentes técnicas para analisar algumas das propriedades da superfície e do interior das lentes de contacto. Desenvolvido nos capítulos 5 a 10;

4) Avaliar em que medida sofrem alterações algumas das propriedades dos materiais como consequência do uso. Desenvolvido nos capítulos 11 a 13.

O capítulo 14 proporciona uma discussão geral dos resultados da Tese e as suas conclusões mais importantes, apontando ainda linhas de trabalho futuro utilizando o conhecimento adquirido durante a preparação deste trabalho de Tese.

Nos dois capítulos introdutórios, observou-se que as lentes de contacto mais utilizadas em Portugal são as lentes hidrofílicas, e dentro destas destacam-se as lentes de silicone hidrogel, que já representam mais de 20% das novas adaptações e readaptações, apesar de ainda existir um número limitado de marcas disponíveis neste segmento. Os usuários de lentes de contacto, geralmente apresentam mais queixas de desconforto que os não usuários e muitas destas queixas podem ser associadas à secura ocular.

A primeira parte experimental da Tese evidenciou que os materiais de silicone hidrogel apresentam uma relação entre o seu teor de água e o índice de refracção do material

hidratado que é diferente do que até agora se admitia para os materiais de hidrogel convencional. Isto é importante para se poder avaliar o grau de desidratação das lentes de contacto de silicone hidrogel mediante técnicas de refractometria. No que diz respeito à microscopia, a técnica que permite uma melhor visualização das lentes de contacto hidrofílicas no seu estado hidratado é a microscopia de força atómica (AFM). Neste aspecto as lentes de silicone hidrogel apresentam também um padrão topográfico característico, principalmente as lentes da primeira geração que utilizam tratamentos de superfície para melhorar a humectabilidade. Esta técnica também permite obter informação relativamente ao comportamento mecânico dos materiais com elevada resolução. De um modo complementar também se estudou a permeabilidade ao oxigénio (Dk) e a transmissibilidade (Dk/t) de distintos materiais de silicone hidrogel. Estes estudos concluíram que as lentes de silicone hidrogel de alta permeabilidade não devem induzir alterações significativas na superfície ocular, quanto à quantidade de oxigénio que atinge a superfície corneal mesmo que se produzissem mudanças significativas no valor da transmissibilidade. Foi ainda avaliado o processo de desidratação *in vitro* para distintas lentes de hidrogel e de silicone hidrogel, demonstrando que este processo é característico de cada material e depende essencialmente do seu teor de água. Foram obtidos diferentes parâmetros quantitativos que caracterizam este processo utilizando este novo método de análise.

A segunda parte experimental está focada na avaliação dos efeitos do uso em algumas propriedades dos materiais das lentes de contacto, em particular nos parâmetros topográficos e mecânicos da superfície das lentes, no teor de água e no processo de desidratação. Nos capítulos correspondentes, observou-se que, com o uso, os materiais se tornam menos elásticos e mais duros. A informação da topografia da superfície mostra que no geral, aumenta a rugosidade da superfície das lentes após o uso. Foi ainda verificado que nalguns materiais inicialmente mais rugosos, os depósitos tornavam a superfície mais regular. O processo de desidratação *in vitro* mostra também alterações importantes em termos qualitativos e quantitativos, com um aumento nos parâmetros de desidratação inicial. As amostras usadas também demonstraram uma menor capacidade do polímero para recuperar a sua hidratação original mesmo após vários dias em solução salina.

Este trabalho permitiu observar que os materiais de lentes de contacto que foram analisados se tornaram mais irregulares e rígidos nas suas superfícies, diminuindo também a sua capacidade de hidratação e principalmente, a sua capacidade de retenção da hidratação em condições de medida da desidratação *in vitro*. Estas alterações poderão ter consequências negativas para o relacionamento entre a superfície dos materiais de lentes de contacto e a superfície ocular.

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General Overview of Results, Conclusions and Future Work

Glossary of Terms and Abbreviations

Å: angstrom.

AC: air conditioning.

AFM: atomic force microscopy.

AIK: asymptomatic infiltrative keratitis.

AT: air temperature.

Barrer: 10^{-11} (cm^2/sec)[ml O_2/(ml x mm Hg)]).

Barrer/cm: 10^{-09} (cm ml O_2)/(ml sec mmHg).

BCR: base curve radius.

BOAT: biological oxygen apparent transmissibility.

BR: burning.

CD: absolute cumulative dehydration as a the percentage of water lost compared to the initial lens weight (%).

CD_{PH-I}: absolute cumulative dehydration at the end of phase I.

CL: contact lens.

CLGPC: contact lens giant papillary conjunctivitis.

CLARE: contact lens acute red eye.

CLE: surface cleaner.

CLPU: contact lens peripheral ulcer.

CLs : contact lenses.

CO: continuous.

COL: color lens.

CRT: cathode ray tube.

CryoSEM: cryo-scanning electron microscopy.

CT: central thickness.

Dk/L: oxygen transmissibility considering L as the harmonic thickness of powered lenses.

Dk/t: oxygen transmissibility considering "t" as the local thickness of the lens.

Dk/t_{app}: apparent oxygen transmissibility.

Dk: oxygen permeability.

DMA: *N,N*-dimethyl acrylamide.

DR: dehydration rate (% per min).

DW: daily wear.

ED: end of day.

EL: early in the day.

ENZ: enzymatic cleaner.

EOP: equivalent oxygen percentage.

EW: extended wear.

EWC: equilibrium water content.

FDA: food & drug administration.

FSA: fluor silicone acrylate.

GMA: glycerol methacrylate.

HEMA: 2-hydroxyethyl methacrylate.

HIB: hybrid contact lens.

HU: heating units.

HYD: conventional hydrogel.

IK: infiltrative keratitis.

IT: itchiness.

j_c: oxygen flux to the cornea.

KCS: keratoconjunctivitis sicca.

L: harmonic thickness of powered lenses, also known as t_{av}.

LE: linear expansion.

MA: methacrylic acid.

MK: microbial keratitis.

MMA: methyl methacrylate.

MPa: megapascal.

MPS: multipurpose solution.

MTF: multifocal.

NCVE: (*N*-carboxyvinyl ester).

PC: phosphorylcholine.

n_d: refractive index.

nm: nanometer.

NVP: *N*-vinyl pyrrolidone.

OF: often.

PBS: piggyback system.

PBVC: (poly[dimethysiloxy] di [silylbutanol] bis[vinyl carbamate]).

PC: phophorylcholine.

PER: hydrogen peroxide.

Phase I: part of the dehydration curve (in DR units) characterized by a high and relatively stable average dehydration rate.

Phase II: part of the dehydration curve (in DR units) characterized by a rapid and progressive decrease in the dehydration rate.

Phase III: part of the dehydration rate curve characterized by dehydration rate approaching to zero.

p_{tc}: partial pressure of oxygen at the lens-cornea interface.

PVP: polyvinyl pyrrolidone.

Ra: average surface roughness measured with AFM; it represents the average distance of the roughness profile to the center plane of the topographic profile.

RE: red eye.

RGP: rigid gas permeable.

RH: relative humidity.

RI: refractive index.

Rmax: maximum high peak of roughness analysis.

Rms: root mean square of roughness measured with AFM; represents the standard deviation from the mean surface plane.

SA: silicone acrylate.

SC: scratchiness.

SCL: soft contact lens.

SCLs: soft contact lenses.

SEM: scanning electron microscopy.

Si-Hi: silicone hydrogel.

SO: sometimes.

SPH: spherical.

SS: Sjögren syndrome.

ST: surface treatment.

T: temperature.

$T_{-0.05\%/'}$: time to reach a dehydration rate of -0.05%/minute.

$T_{-0.1\%/'}$: time to reach a dehydration rate of -0.1%/minute.

$T_{-0.5\%/'}$: time to reach a dehydration rate of -0.5%/minute.

$T_{-1\%/'}$: time to reach a dehydration rate of -1%/minute.

TD: total diameter.

TFT: thin film transistor.

TOR: toric.

T_{PH-I}: duration of phase I.

TPVC: (tris-(trimethylsiloxysilyl) propylvinyl carbamate).

TRIS: 3-methacryloxy-2-hydroxypropyloxy propylbis(trimethylsiloxy)methylsilane.

USAN: United States Adopted Names Council.

VD: valid dehydration or relative dehydration of the polymer as a percentage of the total equilibrium water content (%).

$VD_{20'}$: valid dehydration at 20 minutes.

$VD_{40'}$: valid dehydration at 40 minutes.

$VD_{60'}$: valid dehydration at 60 minutes.

$VD_{80'}$: valid dehydration at 80 minutes.

VDT: video display terminal.

VP: vinyl pyrrolidone.

$W_{T(0)}$: initial sample weight.

$W_{T(f)}$: final sample weight.

$W_{T(n)}$: sample weight at time n with intervals of 1 minute.

$W_{T(n-1)}$: sample weight at time n-1 with intervals of 1 minute.

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$$Dk = 1.67 \cdot e^{0.038 \cdot EWC}$$ (Equation 3.1)

$$\%LE = -0.9 + 0.5 \cdot EWC$$ (Equation 3.2)

$$j = \left(\frac{Dk}{L}\right)_{app} \cdot (P_2 - P_1)$$ (Equation 3.3)

$$EOP = 14.139 \cdot \log_{10}(Dk/t) - 8.960$$ (Equation 3.4)

$$EOP = 13.062 \cdot \log_{10}(Dk/t) - 9.0056$$ (Equation 3.5)

$$Dk/t_{BOAT} = 7.70 + 0.158 \cdot Dk/t$$ (Equation 3.6)

$$Dk/t_{BOAT} = 11.14 + 0.0305 \cdot Dk/t$$ (Equation 3.7)

$$E_r = \frac{\sqrt{\pi}}{2} \cdot \frac{slope}{\sqrt{A}}$$ (Equation 6.1)

$$A = \pi \cdot r^2$$ (Equation 6.2)

$$r = \sqrt{R \cdot h_{\max}}$$ (Equation 6.3)

$$F = \frac{2 \cdot E \cdot r \cdot h}{\left(1 - \nu^{2)}\right)}$$ (Equation 6.4)

$$F_{sphere} = \frac{4}{3} \cdot \frac{E}{(1-\nu)} \cdot \sqrt{r \cdot h^{3/2}}$$ (Equation 6.5)

$$F_{cone} = \frac{\pi}{2} \cdot \frac{E}{(1-\nu)} \cdot \tan(\alpha) \cdot h^2$$ (Equation 6.6)

$$F_{cone} = \frac{2}{\pi} \cdot \frac{E}{\left(1-\nu^2\right)} \cdot \tan(\alpha) \cdot h^2$$ (Equation 6.7)

$$\frac{1}{E_r} = \frac{1-\nu_s^{\,2}}{E_s} + \frac{1-\nu_i^{\,2}}{E_i}$$ (Equation 6.8)

$$E = \frac{\sqrt{\pi} \cdot \left(\frac{dF}{dh}\right)}{2 \cdot \sqrt{A}}$$ (Equation 6.9)

$$E = \frac{\sqrt{\pi} \cdot \left(\frac{dF}{dh}\right)}{2 \cdot \sqrt{A} \cdot \beta}$$ (Equation 6.10)

$$H = \frac{F_{\max}}{A_{\max}}$$ (Equation 6.11)

$$\frac{H}{E_r^{\,2}} = \frac{4}{\pi} \cdot \frac{F_{\max}}{slope^2}$$ (Equation 6.12)

$$\frac{F_{\max}}{S^2} = \frac{H}{E_r^{\,2}} \cdot \frac{\pi}{4}$$ (Equation 6.13)

$$A_1 = \frac{1}{2} \cdot b \cdot h$$ (Equation 6.14)

$$A = 4 \cdot \tan\alpha \cdot h^2$$ (Equation 6.15)

$$EWC = 100 - \%Brix$$ (Equation 7.1)

$$Nominal\ EWC_{SI\text{-}HI} = (Atago\ \text{N-2E}_{SI\text{-}HI}EWC\ /\ 0.4575) - 35.886$$ (Equation 7.2)

$$Nominal\ RI_{SI\text{-}HI} = (CLR\ 12\text{-}70_{SI\text{-}HI}\ /\ 0.7155) - 0.4037$$ (Equation 7.3)

$$EWC = 100 - \%Brix$$ (Equation 8.1)

$$EWC = 952.85 \cdot RI^2 - 3193.9 \cdot RI + 2664$$ (Equation 8.2)

$$EWC = 834.62 \cdot RI^2 - 2852.3 \cdot RI + 2417.4$$ (Equation 8.3)

$$RI = 8 \cdot 10^{-06} \cdot EWC^2 - 0{,}0029 \cdot EWC + 1.5447$$ (Equation 8.4)

$$RI = 8 \cdot 10^{-06} \cdot EWC^2 - 0{,}0029 \cdot EWC + 1.5454$$ (Equation 8.5)

$$O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$$ (Equation 9.1)

$$4Ag \rightarrow 4Ag^+ + 4e^-$$ (Equation 9.2)

$$\left(\frac{Dk}{t_{av}}\right)_{app} = \frac{I}{n \cdot F \cdot A \cdot \Delta p} = B \cdot I$$ (Equation 9.3)

$$slope = \frac{d(dDk/t)}{d(t)} = \frac{t}{Dk} \div \frac{t}{1} = \frac{1}{Dk}$$ (Equation 9.4)

$$Dk = \frac{1}{\frac{d(dDk/t)}{d(t)}}$$ (Equation 9.5)

$$BOAT = \frac{Dk}{t_{app}} \cdot \left(\frac{p - p_{tc}}{p}\right)$$ (Equation 9.6)

$$EOP = \frac{p_{tc} \cdot p'}{p}$$ (Equation 9.7)

$$EOP = 0.135 \cdot p_{tc}$$ (Equation 9.8)

$$j_c = \frac{BOAT \cdot p}{100}$$ (Equation 9.9)

$$CD = \left[\frac{\left(W_{T(n)} - W_{T(0)}\right)}{W_{T(0)}}\right] \cdot 100$$ (Equation 10.1)

$$DR = \left[\frac{\left(W_{T(n)} - W_{T(n-1)}\right)}{W_{T(n)}}\right] \cdot 100$$ (Equation 10.2)

$$VD = \left(\frac{W_{T(0)} - W_{T(n)}}{W_{T(0)} - W_{T(f)}}\right) \cdot 100$$ (Equation 10.3)

$$WRI_1 = \left(\frac{dVD}{dT}\right) \cdot 100$$ (Equation 10.4)

$$WRI2 = \left(\frac{1}{MeanCD}\right) \cdot 100$$ (Equation 10.5)

$$EWC_N = 2.153 \cdot EWC_R - 76.64$$ (Equation 13.1)

Publications Related With This Thesis (2003-07)

Publications in the following list have been elaborated by the candidate or in collaboration with other authors and co-authors directly related with the contents of this Thesis. Some of them are fully presented as chapters of the Thesis manuscript and are highlighted in bold within the list.

For other publications made by the candidate and colleagues during this period, but not directly related to the subjects of this Thesis, please see following section and Curriculum Vitae.

(1) Gonzalez-Meijome JM, Lopez-Alemany A, Almeida JB, Parafita MA, Refojo MF. Qualitative and quantitative characterization of the In vitro dehydration process of hydrogel contact lenses. *J Biomed Mater Res B Appl Biomater.* 2007;81B:*(in press)*.

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Introduction and Research Rationale

Currently there are more than 100 million contact lens (CL) wearers world-wide. Of them, over 80% wear soft contact lenses. Despite the continuous increasing in CL fittings, different problems of intolerance are responsible for almost 2 million people ceasing contact lens wear each year. These problems are probably an expression of lack of biocompatibility of contact lenses and contact lens solutions with the ocular surface in the medium and long-term. In order to contribute to the understanding of the current problems with CL materials and their tolerance we have conducted several studies to understand the current pattern of CL fitting, the most frequent symptoms reported by wearers as well as different experimental research works to evaluate the physic-chemical properties of contact lens materials and the impact of wear on some of these properties.

The present Thesis integrates a research series nurtured by the candidate during the last 3 years in the context of this Thesis project entitled "*Objective analysis of properties and material degradation in contact lens polymers using different techniques"*. The main goal of this work was to investigate how to obtain objective measurements of contact lens polymers in order to apply them to the analysis of worn contact lenses and, if possible, to find out objective indicators of contact lens deterioration.

In order to make the work easy to follow for the reader, the presentation of the Thesis begins with a brief summary of the rational of the present organization of chapters, and the reasons why they have been organized in this manner. This will be essential for the reader to understand how research in each chapter interacts with the remaining contents to form a unit of diverse subjects with a common line of reasoning linking the whole work.

Chapter 1
Contact Lens Fitting Profile in Portugal: Strategies for First-fits and Re-fits

This chapter presents a study on the current trends in contact lens fitting in Portugal, which are the main motivations, how they are worn by the patients, which are the care products used for CL care and the symptoms most commonly associated to CL wear. This chapter helps us to understand in which types of lenses the remaining work should be focused to cover the most fitted contact lenses and those with the highest potential for the immediate future.

Chapter 2

Symptoms in a Population of Contact Lens and Non-Contact Lens Wearers under Different Environmental Conditions

This chapter reports the results of another study that investigated the prevalence and pattern of presentation of ocular symptoms related to dryness and/or discomfort reported by contact lens wearers and non-contact lens wearers under different environmental conditions.

Chapter 3

Contact Lens Materials. Part I – Relevant Properties in Clinical Practice

In this chapter we present a review on the more important properties of contact lens polymers, how these properties are important to maintain the ocular surface in a healthy state and which are their clinical implications in the daily contact lens practice. This information helps to choose which contact lens properties could be more important among those that could be investigated according to the facilities present in the laboratories where the experimental work was to be developed.

Chapter 4

Contact Lens Materials. Part II – Ocular Interactions, Deterioration Process and Clinical Impact

This chapter is a complementary part of the previous one. It addresses the main forms of interaction of CL with the ocular surface, the different forms of contact lens deterioration as a consequence of wear, the polymer properties that are primarily involved, and how these changes can affect the clinical tolerance of the contact lens by the eye. Along with the previous one, this chapter summarizes a significant amount of the current knowledge on CL material properties and deterioration in order to guide and discuss the subsequent research.

Chapter 5

Microscopic Observation of Unworn Silicone Hydrogel Soft Contact Lenses by Atomic Force Microscopy

In this chapter I present the results of the topography analysis of silicone-hydrogel contact lens polymers using AFM. This instrument provides an incomparable resolution of surface topography and reliable quantitative information at the nanometric scale about the roughness of the surface in the fully hydrated state under environmental conditions. In the following chapter, data from indentation with the AFM tip in Contact Mode will be used to obtain further quantitative data about the mechanical properties of the contact lens surface.

Chapter 6

Surface Topography and Mechanical Properties of Silicone Hydrogel Soft Contact Lens Materials With AFM

The surface of different soft contact lenses was analyzed with AFM in order to evaluate their topographic appearance according to the procedure presented in the previous chapter and the mechanical response to nanoindentation analysis. Along with the previous one, this chapter provides a nanometric quantification of the contact lens surface properties.

Chapter 7

Refractive Index and Equilibrium Water Content of Conventional and Silicone Hydrogel Contact Lenses

This chapter addresses the question of measurements of EWC and refractive index of soft contact lens polymers used in conventional and silicone hydrogel materials. The information from this work was of value to perform hydration measurements in following chapters. Of particular importance is the previously unknown relationship between EWC and refractive index for silicone hydrogel materials which is significantly different from those previously described for conventional hydrogels. This fact motivates that when the EWC of silicone hydrogel materials is measured with a manual refractometer, we obtain values higher than the actual EWC of the material. This happens because the refractive index of these materials is lower than that of conventional hydrogels of the same EWC.

Chapter 8

Equivalences Between Refractive Index and Equilibrium Water Content of Conventional and Silicone Hydrogel SCL from Automated and Manual Refractometry

In this work statistical relationships between refractive index and EWC were derived from measurements obtained by automatic and manual refractometry. By using these equations, it is possible to interchange values given by both techniques and convert EWC and refractive index into the most appropriate parameter according to the study design and methods to be used. When the refractive index is used to derive the EWC of the material, the EWC obtained for silicone hydrogel materials is not the actual according to the results obtained and additional corrections should be done according to the results presented in chapter 7.

Chapter 9

Determination of the Oxygen Permeability and Other Relevant Physiological Parameters of Soft Contact Lenses Using a Polarographic Method

In this chapter, the instrumental oxygen transmissibility and permeability of different contact lens materials was measured with an electrochemical method. Values obtained were compared against nominal values given by the manufactures. Values of oxygen transmissibility were also used to obtain other parameters that are more representative of the physiological oxygen availability at the anterior corneal surface, namely the partial pressure of oxygen at the contact lens-cornea interface, the biological oxygen transmissibility (BOAT), oxygen flux and the equivalent oxygen percentage (EOP) under open and closed eye conditions.

Chapter 10

Qualitative and Quantitative Characterization of the *In vitro* Dehydration Process of Hydrogel Contact Lenses

The purpose of this chapter was to analyze the process of *in vitro* dehydration of contact lens materials exposed to a controlled atmosphere and to derive qualitative and quantitative parameters that could characterize each material. Results from this work allowed us to conclude that each material has a particular and repeatable dehydration process under *in vitro* conditions. Furthermore, numerous quantitative parameters were obtained that characterize this process. As expected, some of these parameters are strongly correlated with the EWC of the hydrogel.

Chapter 11
Analysis of the Deterioration of Contact Lens Polymers. Part I: Surface Topography

In this chapter AFM in Tapping Mode was used to evaluate the topography of unworn and worn silicone hydrogel materials. We have observed that the surface roughness increases significantly for most of the materials being evaluated. There is an exception with one material whose roughness decreased in some samples analyzed when compared with unworn reference samples of the same material. This is probably due to partial or total filling of the superficial macropores that characterize the topographical appearance of unworn samples of this material.

Chapter 12
Analysis of the Deterioration of Contact Lens Polymers. Part II: Surface Mechanical Properties

In this chapter AFM in Contact Mode was used to evaluate the surface mechanical response of worn and unworn contact lenses with nanoindentation. These values of modulus cannot be used interchangeably with the bulk modulus obtained using other methodologies of mechanical testing, which are the values commonly referred by the manufacturers. However, the mechanical behavior of the material at the surface could be of relevance to understand the interaction of the lens and the ocular surface. There is a general trend towards increase in rigidity of the surface of worn lenses compared to unworn samples of the same materials.

Chapter 13
Analysis of the Deterioration of Contact Lens Polymers. Part III: *In vitro* Dehydration of Contact Lenses

The EWC by refractometry, as well as the in vitro dehydration process using a gravimetric method have been evaluated for worn contact lens materials. Overall, there is a remarkable change in the dehydration profile with a worsening of the initial dehydration descriptors being observed in all worn samples analyzed when compared against unworn samples of the same materials. The EWC of the materials also decreased for most of the lenses after they had been worn.

Chapter 14
General Overview of Results, Conclusions and Future Work

This chapter summarizes and discusses the main findings presented in the previous parts of the Thesis, highlighting the main outcomes of the work, their potential implications in experimental and clinical research, as well as future lines of work that could be developed on the basis of the work carried out in this Thesis.

Chapter 1

Contact Lens Fitting Profile in Portugal: Strategies for First-fits and Re-fits†

1.1. Abstract

Purpose: To evaluate the standards of contact lens practice in Portugal, with particular attention to the characteristics of first fits and refits regarding aspects such as symptoms of dryness, overnight wear, silicone hydrogel (Si-Hi), multifocal prescriptions, and care systems.
Methods: A questionnaire was distributed to 300 contact lens practitioners in Portugal, and they were asked to fill them with the following first 10 fittings (only right eye of each patient). Fifty-six questionnaires were returned to total of 529 fittings.
Results: The mean age of contact lens wearers was 28.1 ± 10.1 years, and 94.4% of the wearers were fitted with soft contact lens (SCL) wearers (67.9% hydrogel lenses, 21.2% Si-Hi lenses, and 5.3% biomimetic SCLs). Sixty percent of patients wore their contact lenses for 9 to 12 hours per day. The lenses were replaced on a monthly basis in 71.0% of cases, and 82.8% of wearers used a multipurpose solution for lens cleaning and disinfection. Significant differences were found between first fits and refits regarding the prevalence of dryness symptoms (higher incidence of frequent symptoms in the evening in the refitting group, $p < 0.01$, χ^2), replacement schedule (lower incidence of monthly disposable lenses in refits compared to first fits, $p < 0.05$, χ^2), and care regime (lower incidence of multipurpose solutions and higher incidence of hydrogen peroxide in refits, $p < 0.01$, χ^2).
Conclusions: Statistical analysis to the current trends in the Portuguese contact lens fitting profile showed that contact lens practitioners in Portugal are receptive to use innovations in contact lens products, such as silicone hydrogel (Si-Hi) and biomimetic materials, and daily-disposable contact lenses to refit patients who have not succeeded with previous lenses. Multifocal lenses also experienced a significant increase in their prevalence among refits and new fits. Rigid gas permeable (RGP) materials maintained and even experienced a slight increase in refits. Conversely, there is still a low incidence of extended-wear prescriptions, most of them being made with low-Dk SCLs.

1.2. Introduction

Several studies have been carried out in recent years to explore the contact lens fitting profile in several parts of the world.[1-6] Those studies have the double advantage of showing how the contact lens market is changing and the level of acceptance of new contact lens materials, wearing schedules, care solutions, and so forth.[7] These habits have generated a

† Gonzalez-Meijome JM, Jorge J, Almeida JB, Parafita MA. Contact lens fitting profile in Portugal in 2005: strategies for firts fits and refits. *Eye Contact Lens.* 2007;32:81-88.

bibliographic basis for yearly follow-up of trends in contact lens practice which is of enormous importance to gauge contact lens habits of prescription as a reflection of the scientific innovations launched by the manufacturers every year.

In recent years, significant innovations have been incorporated to the contact lens practice, particularly on the field of hyper-transmissible contact lenses for continuous wear,[8-11] and biomimetic materials attempting to arrest tear evaporation from the polymeric structure of hydrogels lenses[12-14] showing significant clinical improvements in the ocular surface of symptomatic contact lens wearers.[15] Despite these efforts of the industry to meet the physiological demands of the ocular surface, thus promoting safer and more comfortable wear for longer periods, the contact lens marketplace shows some signs of stagnation in the last years.[16] Contact lens drop-out is pointed as the main factor limiting contact lens growth, with contact lens discomfort considered as one of the main reasons for contact lens wear discontinuation.[17,18]

Currently, there are more than 100 millions contact lens wearers worldwide.[19] In Portugal, it is estimated that 3.5 to 4.0% of the population wears contact lens for cosmetic or therapeutic purposes.[20] Conversely, other countries have a much larger incidence of contact lens wear,[5,21,22] which suggests that there is room for contact lens growth in Portugal. However, this hypothesis will require a full knowledge of the patient profile and the current standards of contact lens prescriptions to identify those aspects that can be improved and to delineate strategies for the future. Nevertheless, little is known about the materials, designs, wearing schedules, overnight wear, care solutions, and the impact of new materials on the habits of contact lens practitioners.

The goal of the this pioneer study in Portugal was to investigate the characteristics of patients presenting more frequently for contact lens fitting or refitting and the prescription strategies of Portuguese contact lens practitioners regarding contact lens materials, designs, and geometries most frequently used; and the care solutions most frequently prescribed. The authors were particularly interested in the standards of contact lens practice in first fits and refits regarding patient symptoms of dryness, high-Dk Si-Hi and biomimetic materials, extended-wear and continuous-wear and multifocal contact lens fitting.

1.3. Material and Methods

A questionnaire was created to obtain relevant information about the fitting profile of the Portuguese population *table 1.1*. Three hundred questionnaires were sent to optometric and ophthalmologic consultants in the country by direct delivery or by e-mail, and the practitioners were asked to complete the form with information only from the right eye of each patient for the 10 consecutive contact lens fittings. The questionnaires were distributed from October 20 to November 30, 2005.

Fifty-six forms were returned, with a total of 529 valid fittings; and thirty-one fittings were not included for further analysis because of missing data. Because of the geographical proximity, most questionnaires were from the north and central part of the country, with 80.0% from Porto, Braga and Lisbon, which are the main metropolitan centers in Portugal. Compared to other studies,[2] the 19.0% response rate in the present study can be considered high, and comparable to other recent studies.[6]

Table 1.1. Parameters to be completed by practitioners and investigators regarding each fitting

	Completed by Practitioners	Completed by Investigator
Patient Data	First fitting / Refitting, Gender Age Ocular Dryness Motivation for contact lens fitting	-
Previous contact lens **Prescribed contact lens**	Brand Manufacturer	Material Geometry Dk EWC (%) FDA group
Contact Lens Power	Sphere Cylinder	-
Wearing time	Hours per day	-
Overnight Wear	Number of nights per week (if any)	-
Care System	Solution(s) prescribed	
Replacement	Replacement schedule	-

Data from the questionnaires were stored in a database, and nominal variables were codified for further statistical analysis. Practitioners were asked to write only the brand and manufacturer of the contact lenses (new lens and previous lens for refits); at the time of data storage, data about material, geometry, oxygen permeability (Dk), equilibrium water content (EWC), and Food and Drug Administration (FDA) group for SCLs were obtained.

It was decided to classify material Dk in three ranges, with low-Dk materials having less than 20 barrers, high-Dk materials having more than 80 barrers, and medium-Dk materials having between 21 and 79 barrers. This is the most logical classification considering the contact lens material availability at present. Similarly, because all SCLs currently in the marketplace are in the range from 20 to 80% of equilibrium water content (EWC),[23] three groups were created instead of the classic classification into low and high water content. These groups were low (<40%), medium (41% - 60%), and high EWC (>61%).

Statistical analysis was processed with SPSS version 14.0. Descriptive statistics were computed. The prevalence of dryness symptoms and other fitting characteristics among first fits and refits was compared by using the Pearson chi-square test.[24] Age differences between first fit and refits were assessed by one-way analysis of variance. The level of statistical significance was established for $\propto$=0.05, although other degrees of significance are also identified herein.

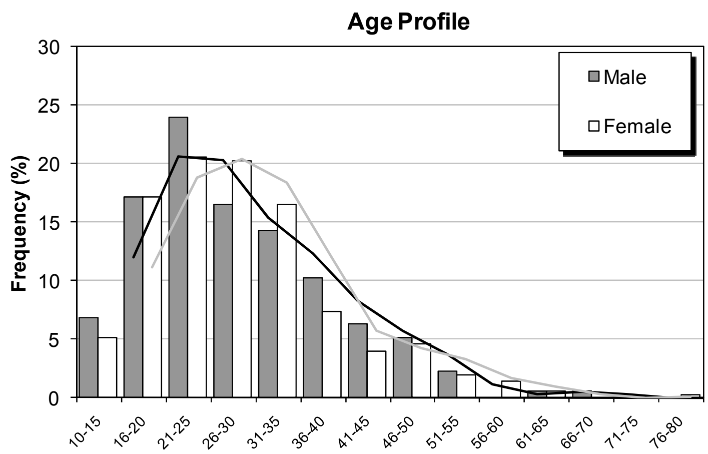

Figure 1.1. Number of fittings for males and females by intervals of 5 years from 10 to 80 years of age.

1.4. Results

From the collected fittings, 352 of the patients were females (66.5%) and 177 were males (33.5%). The mean age was 28.1 ± 10.1 years for females and 28.9 ± 10.4 years for males; differences were not statistically significant (p = 0.379, analysis of variance). For the females, the age range between 18 and 30 years encompasses 50.0% of the fittings. Male and female age profiles are shown in *Figure 1.1*. New fits accounted for 58.4% of the total number of fittings collected.

Figure 1.2 shows the refractive profile of the population for sphere and cylinder components of the prescribed contact lens power. Thirty-eight percent of the contact lenses had an astigmatic correction, and nine (0.02%) patients had a presbyopic add value.

Cosmetic and visual motivations were the main reasons given for contact lens fitting; however, convenience, sport and professional motivation are also important as shown in *figure 1.3*.

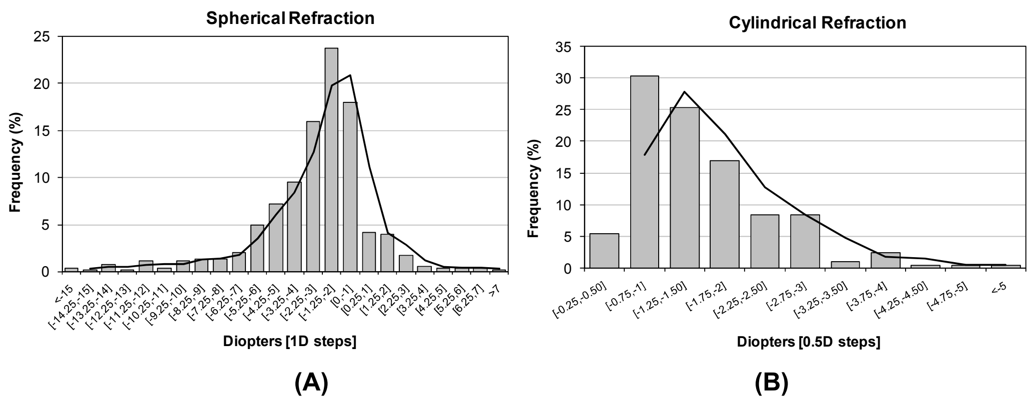

Figure 1.2. Refractive profile as prescribed sphere in 1-diopter steps (A) and prescribed cylinder in 0.50-diopter steps (B) among the study population (n=529 for sphere and n=201 for cylinder).

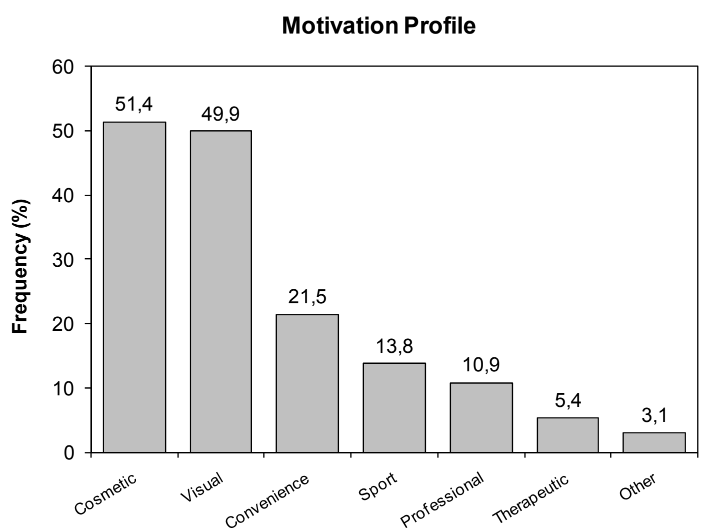

Figure 1.3. Motivations for wear for patients fitted with contact lens.

Figure 1.4 shows the pattern of dryness symptoms for new fits and refits. Although the proportion of the refits who were patients with a history of contact lens discontinuation could not be ensured, refitted patients reported significantly more frequently that they felt dryness symptoms often (p = 0.04, Pearson χ^2), and in the evening (p = 0.002, χ^2) compared to patients in the new fit group. Conversely, the number of subjects reporting that they never felt dryness symptoms was significantly higher in the first fit group (p < 0.001, χ^2). The number of males and females in the first-fit vs refit groups was different. Females represent 63.0% in the first fit group and 71.0% in the refitting group, but this difference was not statistically significant (p = 0.054, χ^2). The age of patients being refitted was significantly higher than those in the first fit group (p < 0.001, analysis of variance).

Figure 1.5 shows a comparison between the characteristics of previous lenses and new lenses fitted to those patients in the refitting group. Details about design, material, Dk, EWC, and Food and Drug Administration (FDA) group for SCLs are provided. A slight, non-statistically significant decrease in the spherical lens group is accompanied by a slight increase in toric and multifocal lenses. There are significant differences between the fitting profile in both groups as a consequence of the higher incidence of refits with Si-Hi materials and the corresponding decrease in the conventional hydrogel group (p < 0.001, χ^2).

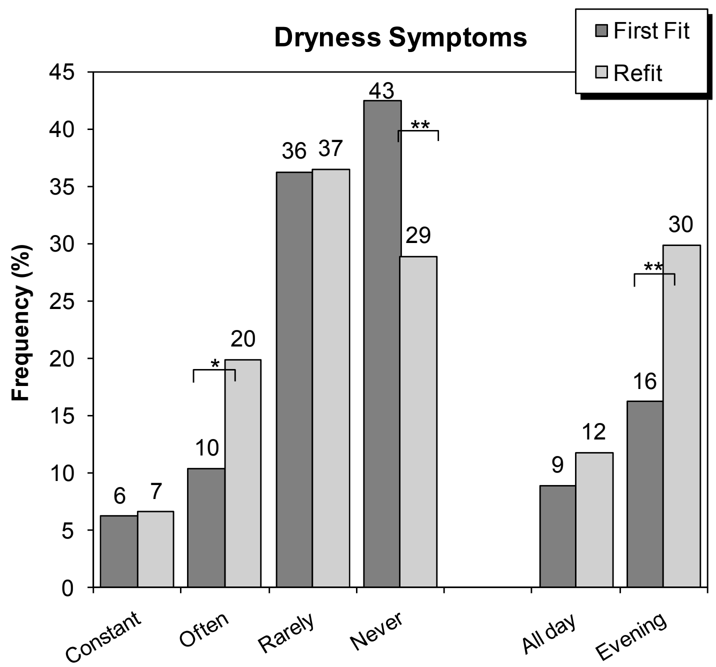

Figure 1.4. Frequency of presentation of some dryness symptoms and when they were cited in the daytime among the study population. Brackets indicate significant differences (*p<0.05; **p<0.01).

This change is accompanied by a significant change in the Dk of new lenses, with an increase in high-Dk contact lenses and a decrease in low-Dk lenses (p < 0.001, χ^2) and a change in soft contact lens EWC, with an increase in materials with a low EWC (p = 0.003, χ^2) and a modest increase in the high EWC, which all together motivate an overall decrease in SCLs with a medium EWC. Finally, there is also a significant change in the FDA group of lenses being fitted compared with the previous patient's lens. The increase of group I, group II, and group III, translates into a significant decrease in group IV contact lenses (p < 0.001, χ^2).

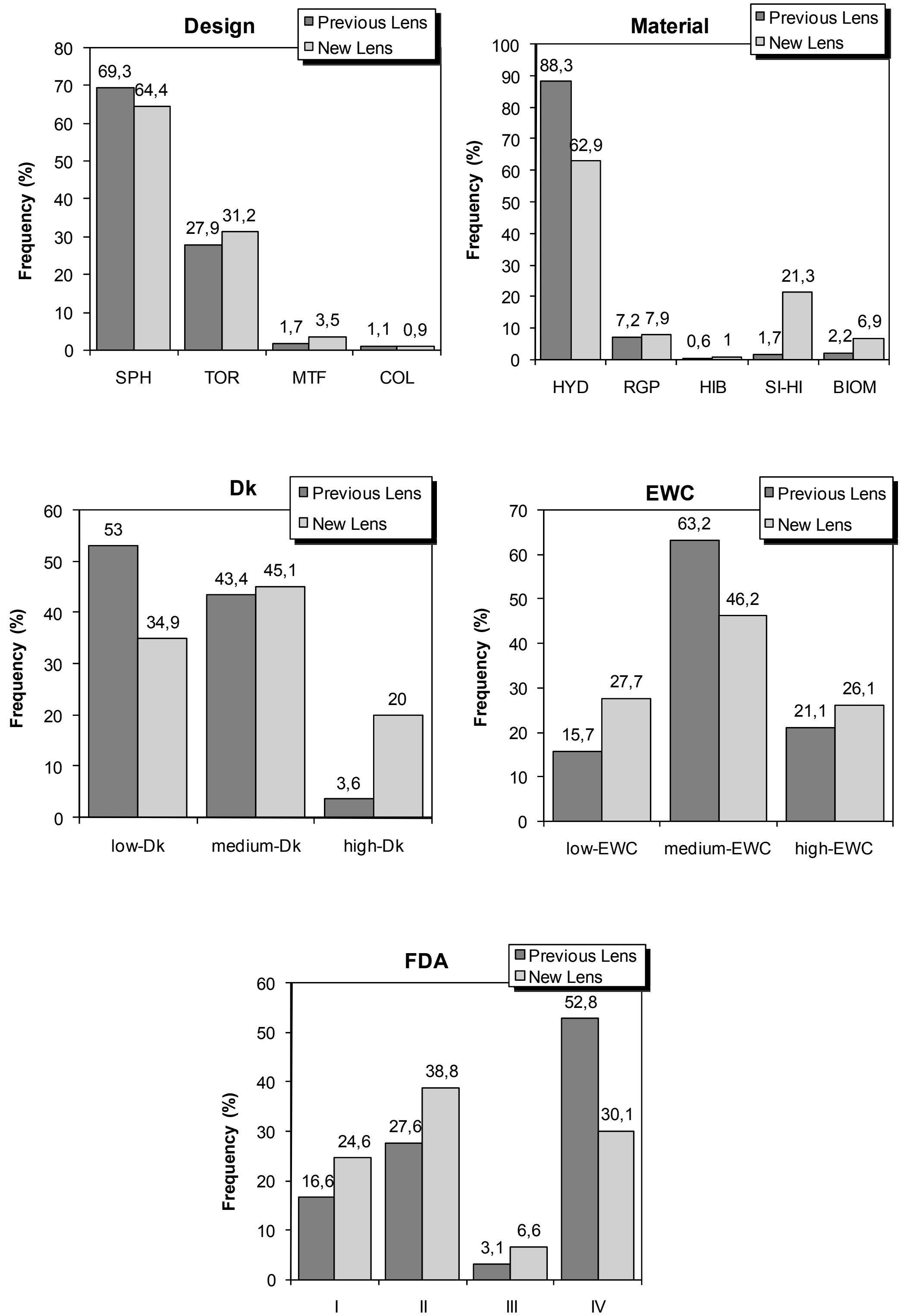

Figure 1.5. Characteristics of previous and new contact lens fitted to those patients in the refitted group (n=220).
SPH: spherical; TOR: toric; MTF: multifocal; COL: color; HYD: conventional hydrogel; RPG: rigid gas permeable; HIB: hybrid; SI-HI: silicone hydrogel; BIOM: biomimetic (omafilcon A, hioxifilcon A, B, C); EWC: equilibrium water content.

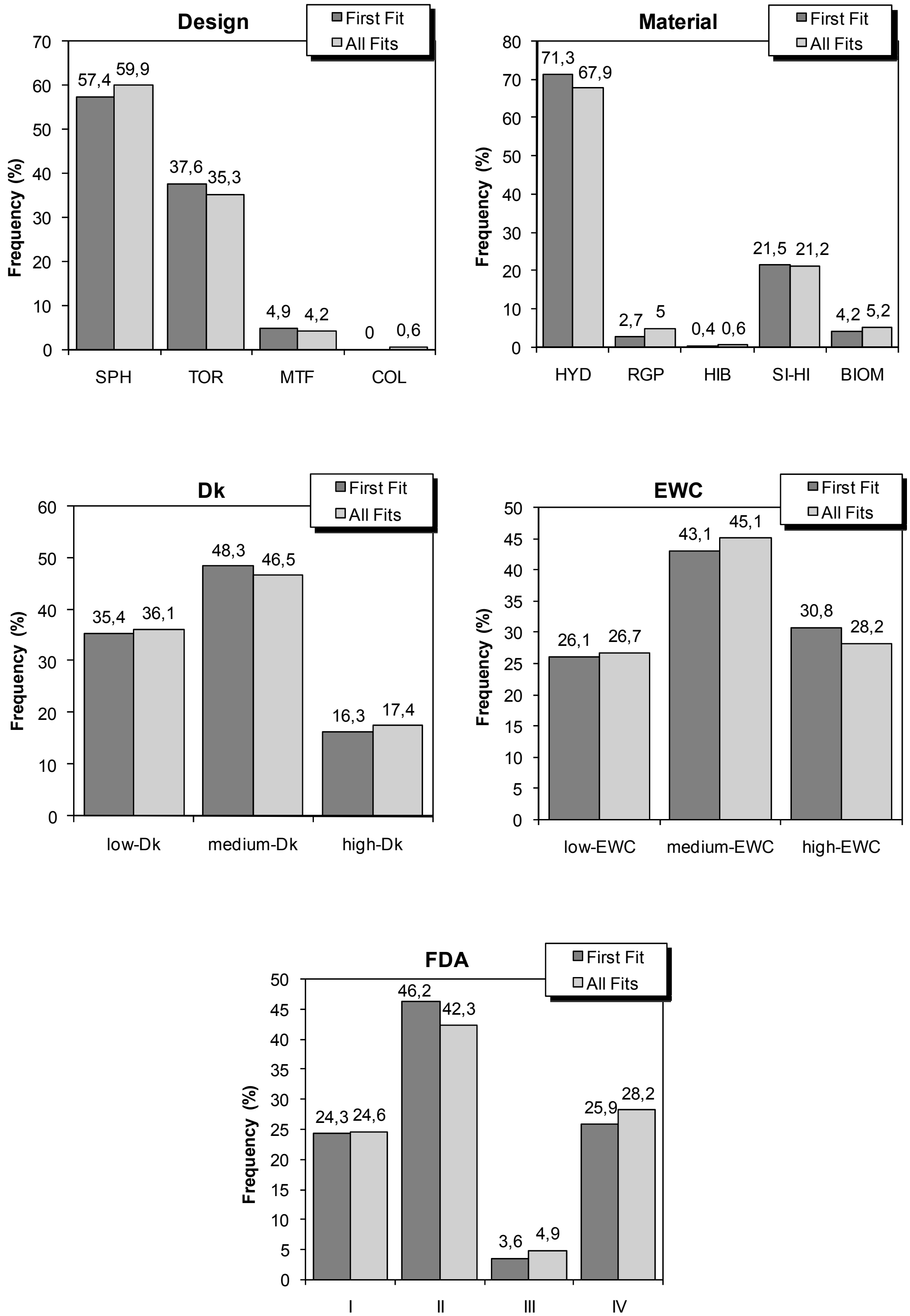

Figure 1.6. Characteristics of new contact lenses fitted to those patients in the first fit group (n=309) compared with the same data for the whole population (n=529).
SPH: spherical; TOR: toric; MTF: multifocal; COL: color; HYD: conventional hydrogel; RPG: rigid gas permeable; HIB: hybrid; SI-HI: silicone hydrogel; BIOM: biomimetic (omafilcon A, hioxifilcon A, B, C); EWC: equilibrium water content.

Figure 1.6 shows the current fitting profile in the study. The characteristics of contact lenses fitted to the whole population are compared against those fitted to patients wearing contact lenses for the first time. No differences were present between both fitting groups for any of the items compared. However the incidence of rigid gas permeable (RGP) lens fitting as first option is half of that observed for the whole population.

Twenty-four patients (4.6%) patients were wearing their contact lenses on an extended-wear basis from 1 to 7 nights a week (45.0% conventional SCLs, 50.0% Si-Hi contact lenses, and 3.7% biocompatible SCLs). Acuvue 2 (etafilcon A, EWC = 58%) (Johnson & Johnson Vision Care, Jacksonville, FL) is still the lens more frequently used for extended wear (35.0%), followed by Focus Night & Day (lotrafilcon A, EWC = 24%) (CIBA Vision, Duluth, GA) for 25.0% of these fittings and other Si-Hi lenses for the other 30.0%.

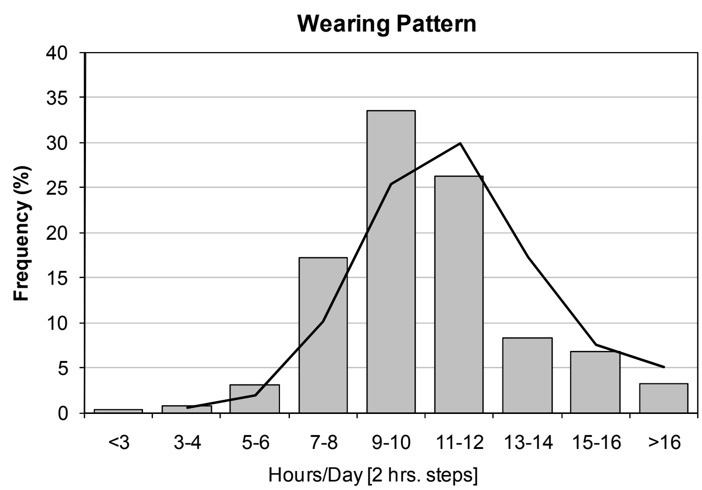

Figure 1.7. Wearing schedule profile in number of hours per day.

Figure 1.7 shows the average number of hours per day of contact lenses wear. Two thirds of patients wore their lenses between 8 and 12 hours per day. The replacement schedule is shown in *figure 1.8* for patients fitted for the first time and refits. In both groups, a monthly schedule represents more than two thirds of all fittings. However, a surprising fact is observed within the refitted group with a significant trend towards decrease in this modality and an increase in yearly replacement lenses.

Among the care systems, *figure 1.9* shows that multipurpose solutions are the most frequently prescribed care systems for new fits and refits. However, a statistically significant difference is found between both groups with multipurpose solutions decreasing and a corresponding increase in the prescription of hydrogen peroxide in patients being refitted.

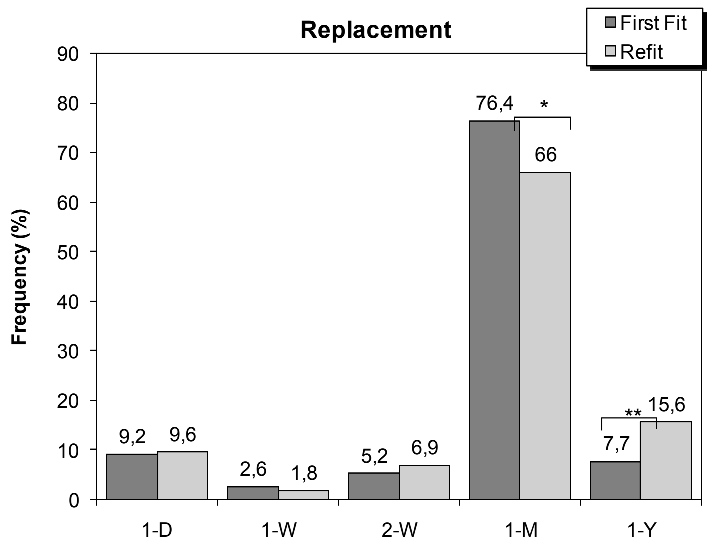

Figure 1.8. Replacement schedule for first fits and refits. Brackets indicate significant differences (*p<0.05; **p<0.01).
1-D: daily replacement; 1-W: weekly replacement; 2-W: biweekly replacement: 1-M: monthly replacement; 1-Y: yearly replacement.

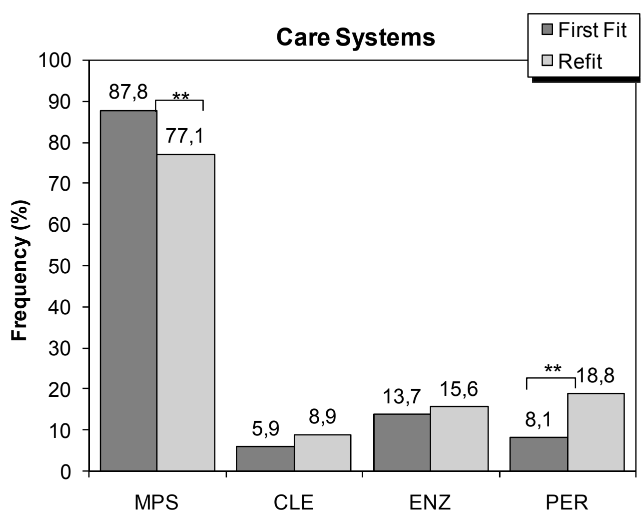

Figure 1.9. Care systems for first fits and refits. Brackets indicate significant differences (*p<0.05; **p<0.01). The association of various care systems makes series exceed 100% (115.5% in the first fit group, 120.4% in the refit group).
MPS: multipurpose solution; CLE: daily cleaner; ENZ: enzymatic cleaner; PER: hydrogen peroxide.

1.5. Discussion

The typical contact lenses candidate and the lens types most frequently used in Portugal (soft vs. RGP) are in agreement with other studies carried out in the United Kingdom and some Australian territories.[2] Women between 18 and 30 years of age, with a cosmetic motivation, are the stereotype of the contact lens wearer in Portugal. Results showed an important prevalence of Si-Hi lenses that exceeds the prevalence reported in the most recent studies carried out in other countries.[3,7] This growth could reflect the success of Si-Hi contact lens prescriptions for daily wear, instead of continuous and extended wear, as the first-generation lenses of this type were intended. This effect was also observed in Australia.[7] Nowadays, with most Si-Hi lenses being delivered to the marketplace for daily wear, it is expected that the proportion of Si-Hi prescriptions as a first choice will increase.

Compared to other countries such as Australia, the current data showed lower incidence of extended wear, a higher incidence of monthly disposable contact lenses, and approximately the same rate of multipurpose solution as the care regimen.[1,2] However, the current results agree with the trends on habits in Europe, at least for the patients that are fitted with contact lenses for the first time.[25]

There is also a clear evidence of the increase in multifocal CL fitting among first fits and refits, which is in agreement with a similar quantitative progression observed by Bowden and Harknett in the United Kingdom,[26] and Woods and Morgan in Australia.[1] However, their prevalence is still clearly lower compared with data from other studies reporting an 8% prevalence of bifocal SCLs in refits.[3,17]

The proportion of first fits and refits supports those data reported by Woods and Morgan for the Australian territories.[2] However, it is not know how many refits had a history of contact lens wear discontinuation or were wearing contact lenses at the time of the refit. It will be necessary to account for this issue in future studies. A closer observation was that patients attending contact lenses clinics for refits have significantly higher incidence of symptoms of dryness being even more frequent towards the end of the day. This is in agreement with most studies analyzing the prevalence of discomfort, which has been considered as a primary factor for contact lenses dropout,[17] and has also been recently evidenced in a university population in the authors' area.[27] Most refits were also made with Si-Hi lenses instead of conventional hydrogel lenses, which is in agreement with the findings reported by other investigators[7]. However, in Portugal, this increase does not reflect an increase in the proportion of extended-wear or continuous-wear contact lens. Furthermore, in the present study, low-Dk SCLs still represent an important portion of the extended-wear prescriptions.

The higher proportion of RGP lenses in the whole population compared to the first fit group suggests that most of the RGP are prescribed to patients who had already been wearing this type of lens. This is also observed when the refitted group was analyzed, with a slightly higher prevalence of RGP materials in previous lenses and new lenses prescribed which shows that RGP lenses are marginally used to solve problems with previous contact lens wear and most were already RGP contact lens wearers refitted with SCLs.

No differences exist between fitting approach for the general population and for those being fitted for the first time. This could indicate that the practitioners fitting approach does not vary significantly in new patients looking for contact lenses for the first time from that followed for the general population. Another hypothesis would be that the strategies followed with refitting patients to solve underlying complications are also incorporated as first options for those patients who want to wear contact lenses for the first time.

According to these findings, it can be concluded that refits with new lenses reflect a change from ionic SCLs with medium or high EWC to high-Dk Si-Hi lenses with a low EWC. Similar findings were documented by Woods and Morgan in Australia.[1] The slight increase in high water content is the result of changes to daily disposable or biomimetic SCLs. Biomimetic lenses have shown to be effective for release symptoms and ocular surface staining in patients with dry eye syndrome.[15] Problems with ocular discomfort and poor physiological responses, among other clinical and commercial concerns, will certainly affect the current trends on refits observed in this sample.

Despite a general preference for monthly SCLs, an increase in yearly replacement lenses was noted among the refits. This has been also noted by Woods and Morgan.[1] This trend may be explained only on the basis of lack of fitting parameters with disposable lenses in certain patients. The reasons could involve poor fitting and unavailable refractive correction with disposable lenses. This is an important issue that the manufacturers should address in the future as the availability of more fitting parameters increased significantly the subjective comfort in patients wearing a disposable Si-Hi contact lens.[28] Regarding daily-disposable lenses, in the current study, a significant proportion of patients in first fits and refits are fitted in this replacement schedule. This value is higher than that reported in Australia,[2] but is still significantly lower than that reported in the United Kingdom.[3]

A recent study showed that candidates to contact lens fitting are now less interested in laser in situ keratomileusis, particularly in those older than 30 years of age.[24] Also, a recent literature review by Foulks, pointed out the preference of patients for extended wear or continuous-wear lenses, with reduced need for handling and cleaning of the lenses; however, the same report showed that only 10% of contact lens practitioners prescribed extended wear lenses for their patients, with a small increase in the predisposition toward this practice after FDA approval of high-Dk Si-Hi for continuous wear.[22]

Because of all this in addition to the recent innovations on contact lens practice such as the new Si-Hi materials, daily-disposable lenses and contact lens corneal reshaping, there is clearly room for the Portuguese contact lens market to grow, which could be extended to many other countries. However, on the view of the current data, it is necessary that contact lens practitioners be less conservative regarding some aspects of contact lens prescribing, such as extended wear and continuous wear and use of proper materials to do so, multifocal lens fitting or RGP fitting for conventional cases, and advanced fitting approaches such as orthokeratology. There is also a matter of concern with the more frequent symptoms described by patients presenting for refits, with significantly more frequent symptoms in the end of the day. The option of most practitioners changing these patients toward SCLs with a low water content seems to be right for patients at risk for dryness symptoms.[29] It is necessary, however, to understand whether this solution is the best one for every patient with different types of contact lens-related ocular discomfort, because other studies did not show significantly different tolerance between contact lenses with a low and high water in patients with tear film deficiency.[30] Furthermore, new biomimetic lens materials made of medium and high water content have shown to be effective on dry eye signs and symptoms[15]. Also, it will be important to encourage the manufacturers to expand the fitting range for their disposable SCLs.

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Chapter 2

Symptoms in a Population of Contact Lens and Non-Contact Lens Wearers under Different Environmental Conditions†

2.1. Abstract

Purpose: To investigate ocular symptoms related to dryness in an adult population of contact lens (CL) and non contact lens (n-CL) wearers using video display terminals (VDT) for different periods of time under different indoor conditions related to air conditioning (AC) and heating units (HU) exposure.
Methods: A questionnaire was distributed to 334 people within a university population of which 258 were part of the n-CL group and 76 of the CL wearers to assess symptoms of ocular discomfort potentially related to dryness. Only soft contact lens (SCL) wearers (n = 71) were included for further statistical analysis because of the reduced number of people wearing other lens types. A 2:1 match by gender group of 142 subjects in the n-CL group was used as a control sample.
Results: There was a marked difference between the prevalence of symptoms and the way they are reported by CL and n-CL wearers. Red eye, itching, and scratchiness are more common among CL wearers, but the difference is statistically significant only for scratchiness ($p < 0.01$, χ^2). The vast majority of subjects who reported symptoms often and at the end of the day are significantly more prevalent among CL wearers ($p < 0.01$, χ^2). Gender differences were also encountered. Female CL wearers reported more scratchiness than males in the n-CL wearing group ($p = 0.029$, χ^2) and in the CL group ($p < 0.008$, χ^2). Females wearing CL reported symptoms of red eye ($p = 0.043$, χ^2) and scratchiness ($p < 0.001$, χ^2) more significantly than those in the n-CL group. Within the CL group, the prevalence of symptoms occurring sometimes or often and at the end of the day was higher among females ($p < 0.001$, χ^2). The use of VDT was associated with a higher level of scratchiness among CL wearers ($p < 0.05$, χ^2). The number of hours working with VDTs seemed to be associated with an increase in the prevalence of burning sensation in the CL group ($p < 0.01$, χ^2), whereas symptoms like red eye and scratchiness also increased significantly among n-CL wearers. Compared to n-CL wearers, all symptoms increase in CL wearers in environments with AC and HU, except excessive tearing. However, these differences are only statistically significant for scratchiness.
Conclusions: Our results show that people who wear soft CL and work with VDTs for longer periods of time are more likely to develop symptoms like eye burning and scratchiness than n-CL wearers. This risk could be higher for women than men. Scratchiness and the appearance of symptoms near the end of the day are typically associated with ocular discomfort during CL wear in this sample, and clinicians should question their patients about these symptoms to anticipate serious discomfort.

† Gonzalez-Meijome JM, Parafita MA, Yebra-Pimentel E, Almeida JB. Symptoms in a population of CL and n-CL wearers under different environmental conditions. *Optom Vis Sci.* 2007;84:e296-e302.

2.2. Introduction

Ocular dryness is one of the most common complaints made to eye care professionals. It has increased considerably in recent years because of the aging of the population, the increase in systemic drug intake, changing environmental conditions and refractive surgery procedures.[1,2] However, treatment is often difficult because of the great variety of factors involved in its aetiology,[3,4] and the relatively low efficacy of current treatments in providing symptom relief.[5,6]

Ocular dryness affects 35.0 to 60.0% of contact lens (CL) wearers and is one of the most important causes of CL discontinuation in the medium and long terms.[7] Women are more prone to suffer from dry eye and they are twice more likely to describe dryness symptoms than men.[8]

Pathologic dry eye seriously affects the patient's quality of life,[9] and is a contraindication for cosmetic CL wear. However, even in mild cases, dryness symptoms can be very challenging for patients wearing CL. Many studies have confirmed an increase in dry eye symptoms associated with CL wear.[10] Previous studies have shown that dryness symptoms in CL wearers are seriously affected by environmental parameters,[11] and a recent study has confirmed that such symptoms could be driven by thinning and instability of the pre-lens tear film in low relative humidity and low temperature environments.[12]

Currently, the aging of the CL wearers in developed countries, along with the increase in the intensive use of video display terminals (VDT) and increased treatment of indoor environments could exacerbate dryness symptoms in CL wearers. The age-related systemic diseases, which are prone to exacerbate dry eye symptoms such as rheumatoid arthritis, and the use of drying medications such as diuretics and antihistaminic drugs are matters of further concern. In addition, the impact of refractive surgery procedures in tear function is well known.[13] So, considering the demographic evolution, the increase in the prescription of SCL in the last 30 years, and the expansion of refractive surgery procedures in the last decade, patients wearing CL will present some of these symptoms more frequently in the future.

The aim of this study was to evaluate the prevalence of ocular symptoms among CL wearers and non contact lens (n-CL) wearers under different environmental conditions and the use of VDT.

2.3. Material and Methods

This is a comparative analysis on the global report of ocular symptoms in an observational, cross-sectional study involving CL and n-CL wearers with 334 people in the academic population of the University of Minho (Braga, Portugal). The data were collected during November 2005. As patients completed the questionnaire, they gave their consent for data to be anonymously processed for this study. One hundred seventy of them were males (50.9%) and 164 were females (49.1%). The mean age was 25.4 ± 7.8 ranging from 18 to 61 years old. To homogenize the sample, five CL wearers were excluded from the sample because of they were using, or have been recently using, other types of lenses different from SCL. Thus, for statistical purposes only 71 CL wearers (22 males, 49 females) and 142 n-CL wearers (44 males, 98 females) in a 2:1 match by gender control group were analyzed.

A questionnaire was completed by 334 people (see sample in section 2.7) regarding symptoms of dry eye ("red eye", "itching", "excessive tearing", "burning" and sand sensation or "scratchiness") and their frequency ("sometimes", "often", "all the time", "early in the morning" and at the "end of the day"). Despite other studies considering ocular discomfort or dryness symptoms, we chose these five symptoms as those are more specifically associated with CL-related dry eye symptoms;[14-16] dryness and discomfort were not questioned directly. Specific questions regarding environmental conditions at work/study place were included in order to obtain information about environmental factors that can potentially affect the prevalence of ocular symptoms. These include the use of VDT, type of VDT (Cathode Ray Tube-CRT or Thin Film Transistor-TFT), their average daily use in hours, and the use of heating units (HU) and air conditioning (AC) units at work/study place.

The statistical analysis was carried out with SPSS v14.0. Descriptive statistics were obtained in order to characterize the sample, the CL wear profile, and the prevalence of symptoms. To compare symptoms among CL and n-CL wearers or those under the environmental conditions quoted above, the Pearson Chi Square (χ^2) test was used.[17] Restrictions applied to this test include <20 elements involved in the comparison, all groups compared had more than one element, and at least 80.0% of the groups had more than five elements. The level of statistical significance was established for $\propto = 0.05$, although other degrees of significance are also identified in tables and graphics throughout the text.

2.4. Results

The distribution between CL and n-CL wearers was 33.3% and 66.7%, respectively. Only SCL wearers were considered for subsequent analysis. Demographic data regarding the patients actually included in the statistical analysis are listed in *table 2.1*. All subjects in the CL group declared they used their lenses on a daily wear schedule. In the group of CL wearers, 28.2% were using or had used artificial tears because of complaints, whereas only 3.5% described this fact in the n-CL wearing group.

Table 2.1. Demographic data for CL and n-CL wear groups

		n-CL group	CL group*
Sample Size		n = 142 (67.7%)	n = 71 (33.3%)
Male:Female Ratio		44:98 (31.0%:69.0%)	22:49 (31.0%:69.0%)
Age	**Mean±SD**	23.65 ± 5.12	24.9 ± 5.47
	Range	18-47	19-38
Wearing Time (years)	**Mean±SD**	-	4.93 ± 4.76
	Range	-	0.1-25

* only soft CL wearers were considered

2.4.1. Symptoms among CL and n-CL wearers

Figure 2.1 presents the prevalence of different symptoms in both groups. CL wearers present a higher prevalence of symptoms of red eye, itching and scratchiness, being statistically significant for red eye (p = 0.009, χ^2), and scratchiness (p < 0.001, χ^2). The opposite trend was found for burning sensation (p = 0.033, χ^2). *Figure 2.2* presents the frequency of those symptoms (sometimes, often, and constantly) and their pattern of appearance (early in the day, end of the day). Almost no subject in either group presented symptoms "constantly" or "early in the day". However, the proportion of CL wearers reporting the symptoms "often" is higher than that of the n-CL group (p = 0.052, χ^2) and the symptoms are more likely to be noticed at the "end of the day" in the CL group (p < 0.001, χ^2). The presence of occasional symptoms as described "sometimes" by the patients does not per se imply contact lens-related dry eye because its incidence is even higher in the n-CL wearing group than in the CL group (p = 0.142, χ^2).

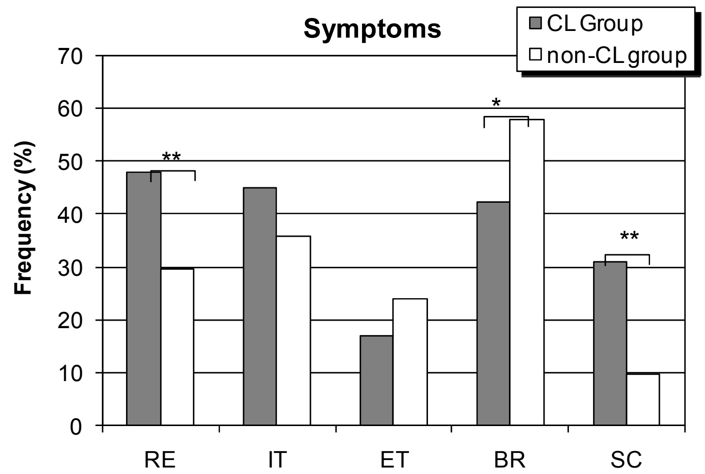

Figure 2.1. Frequency of symptoms of red eye (RE), itching (IT), excessive tearing (ET), burning (BR) and scratchiness (SC) for subjects in the CL wear group (dark bars) and n-CL group (white bars). Brackets indicate significant differences (*$p < 0.05$; ** $p< 0.01$).

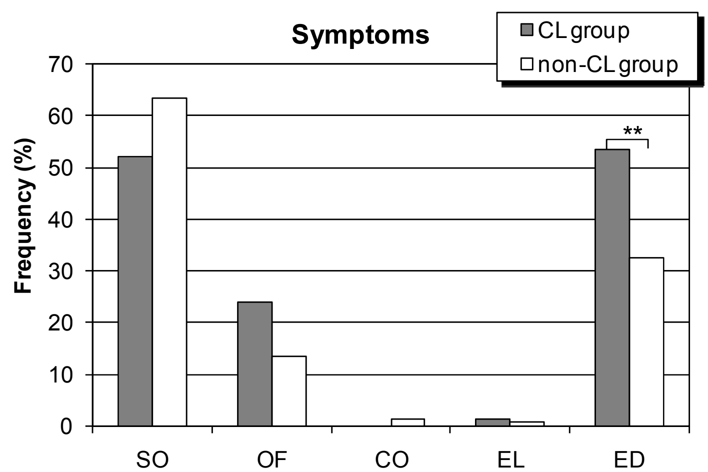

Figure 2.2. Pattern of symptom appearance as being "sometimes" (SO), "often" (OF), "constant" (CO) "early in the day" (EL), and at the "end of the day" (ED) in the CL and n-CL wear groups. Brackets indicate significant differences (*$p < 0.05$; **$p < 0.01$). χ^2 not applicable at CO and EL, because more than 20.0% of the samples have expected count < 5.

2.4.2. Symptoms among male and female CL and n-CL wearers

Table 2.2 shows the prevalence of symptoms for male and female subjects. The prevalence of burning sensation was significantly higher among females in the n-CL group ($p = 0.019$, χ^2), whereas females wearing CL reported a significantly higher prevalence of scratchiness ($p < 0.008$, χ^2) than males. *Table 2.3* shows the pattern of appearance of symptoms for males and females in the CL and n-CL groups. Females are more likely to present symptoms "often" than males in the n-CL and CL groups ($p < 0.05$, χ^2). However in the CL group, females reported more frequently again that they felt the symptoms "often" ($p = 0.049$, χ^2).

Table 2.2. Prevalence of symptoms as a function of gender for CL and n-CL wear groups

		n-CL group (n=142)		CL group (n=71)	
		Cases (%)	χ^2 (sig. *p*)	Cases (%)	χ^2 (sig. *p*)
Red Eye	**Male**	11 (25)	*0.402*	11 (50)	*0.811*
	Female	31 (32)		23 (47)	
Itching	**Male**	11 (25)	*0.069*$^{\psi}$	9 (41)	*0.637*
	Female	40 (41)		13 (47)	
Excessive Tearing	**Male**	10 (23)	*0.820*	2 (9)	¥
	Female	24 (24)		10 (21)	
Burning	**Male**	19 (43)	*0.019**	10 (46)	*0.714*
	Female	63 (64)		20 (41)	
Scratchiness	**Male**	3 (7)	*0.415*	2 (9)	*0.008***
	Female	11 (11)		20 (41)	

$^{\psi}$Statistically significant at 0.1 level
*Statistically significant at 0.05 level
** Statistically significant at 0.01 level
¥ Chi^2 test not applicable because more than 20.0% have expected count < 5 for some group.

Table 2.3. Frequency of symptoms between males and females for CL and n-CL groups

		n-CL group (n=142)		CL group (n=71)	
		Cases (%)	χ^2 (sig. *p*)	Cases (%)	χ^2 (sig. *p*)
Sometimes	**Male**	29 (66)	*0.675*	14 (64)	*0.193*
	Female	61 (62)		23 (47)	
Often	**Male**	2 (5)	*0.038**	2 (9)	*0.049**
	Female	17 (17)		15 (31)	
All the time	**Male**	0 (0)	¥	0 (0)	¥
	Female	2 (2)		0 (0)	
Early in the day	**Male**	1 (2)	¥	0 (0)	¥
	Female	0 (0)		1 (2)	
End of the day	**Male**	6 (14)	*0.001***	10 (45)	*0.361*
	Female	40 (41)		28 (57)	

*Statistically significant at 0.05 level
** Statistically significant at 0.01 level
¥ Chi^2 test not applicable because more than 20.0% have expected count <5 for some group.

2.4.3. Symptoms among CL and n-CL wearers and VDT

Daily use of VDT was reported by 98.5% of people answering the questionnaire. Of those included in the statistical analysis, 49.5% use CRT displays, 43.8% use TFT displays, and 6.7% use both of them, with different daily exposure profiles as observed in *figure 2.3*.

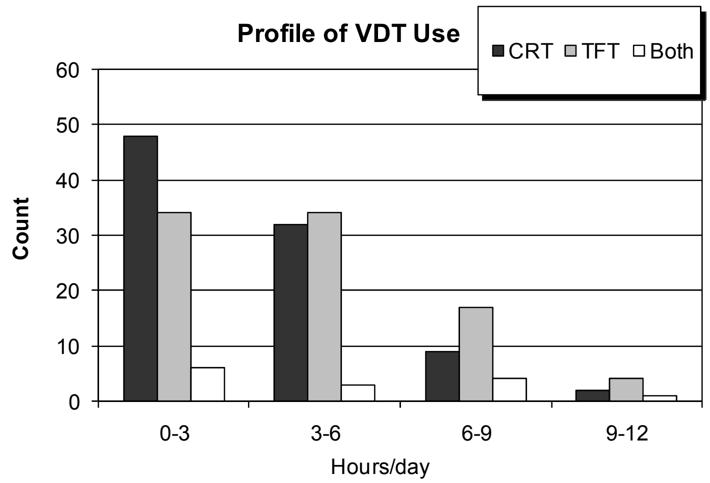

Figure 2.3. Use (hours/day) for different VDT.

When compared with CRT, the proportion of people using TFT displays increases as the number of hours of daily use increases. Although the number of CRT displays is higher for those using them for <3 h/day, TFT displays are more frequent for those using them more than 3 h/day, particularly for the more intensive users (>6 h/day).

Figures 2.4A and *2.4B* depict the pattern of symptoms presentation in CL and n-CL wear groups as a function of the daily exposure to VDTs. Comparative prevalence of symptoms among different VDTs users showed that scratchiness was significantly more frequent in CL wearers using both types of terminals for more than 3 hours.

In the n-CL group, the symptoms were more prevalent as the number of hours spent working with computers increased. Those trends were statistically significant for "itching", "excessive tearing", and "scratchiness". On the other hand, in the CL group, the prevalence of symptoms increased in subjects using VDT 3 to 6 h a day, but not in the group using VDTs 6 to 9 h a day. For those CL wearers using VDTs for <3 h a day the "burning" sensation was significantly lower than for those using them for 3 to 6 h (p = 0.016, χ^2) and for those CL wearers using VDTs 3 to 6 h a day "scratchiness" was significantly higher (p = 0.048, χ^2).

In general, the number of hours using VDTs did not affect the pattern of appearance of the symptoms, except for the response "end of the day" that presented statistically significant differences with increasing hours for n-CL group (p = 0.017, χ^2). For those using VDTs for 3 to 6 h a day, the percentage of patients reporting symptoms at the "end of day" was significantly higher in the CL group (p = 0.006, χ^2). This behavior was also observed for those CL wearers using VDTs for 6 to 9 h a day (p = 0.002, χ^2).

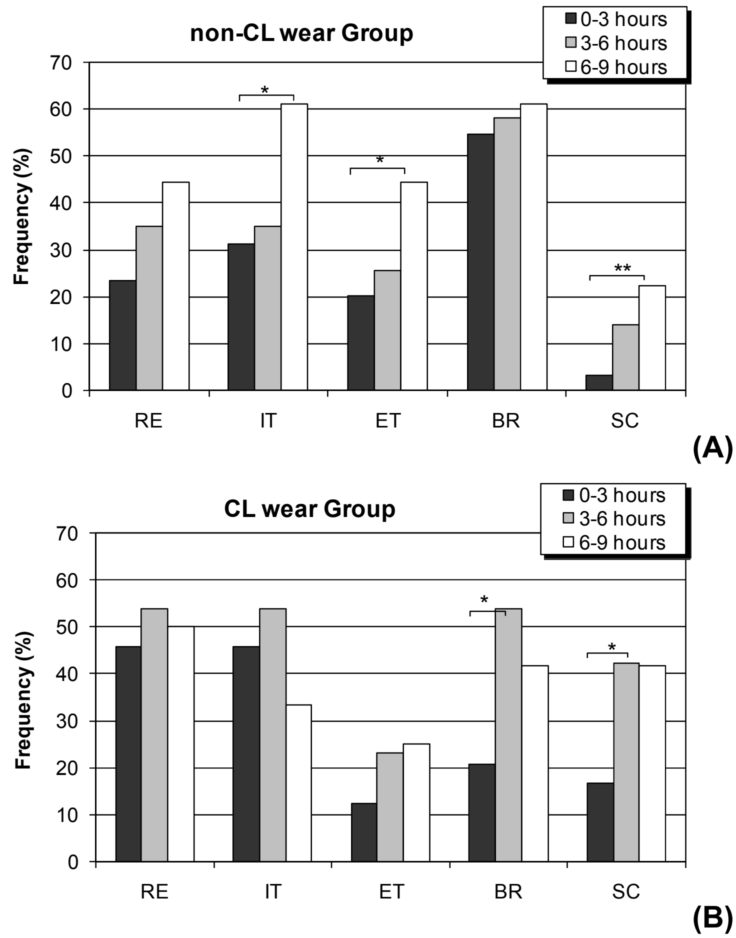

Figure 2.4. Frequency of symptoms of red eye (RE), itching (IT), excessive tearing (ET), burning (BR), and scratchiness (SC) as a function of the number of hours a day using VDT in the n-CL group (A) and CL wear group (B). Brackets indicate significant differences (*$p < 0.05$; **$p < 0.01$).

Overall, the prevalence of most symptoms is more frequent in CL than n-CL wearers as seen in *figures 2.4A* and *2.4B*. A statistical comparison between n-CL and CL wearers has showed that "red eye" ($p = 0.040$, χ^2) and "burning sensation" ($p = 0.005$, χ^2) are significantly more frequent in CL wearers than n-CL wearers using VDTs <3 h/day; for those using VDTs 3 to 6 h/day scratchiness was significantly more prevalent in CL than n-CL wearers ($p = 0.008$, χ^2).

2.4.4. Symptoms among CL and n-CL wearers and indoor environment conditions (AC and HU)

Among those working/studying in AC and HU environments, the prevalence of symptoms increased in CL wearers compared to n-CL wearers except for the burning sensation (*figure 2.5*). Scratchiness was the only symptom with a significantly higher prevalence among CL than n-CL wearers using AC ($p < 0.006$, χ^2) and HU ($p < 0.005$, χ^2).

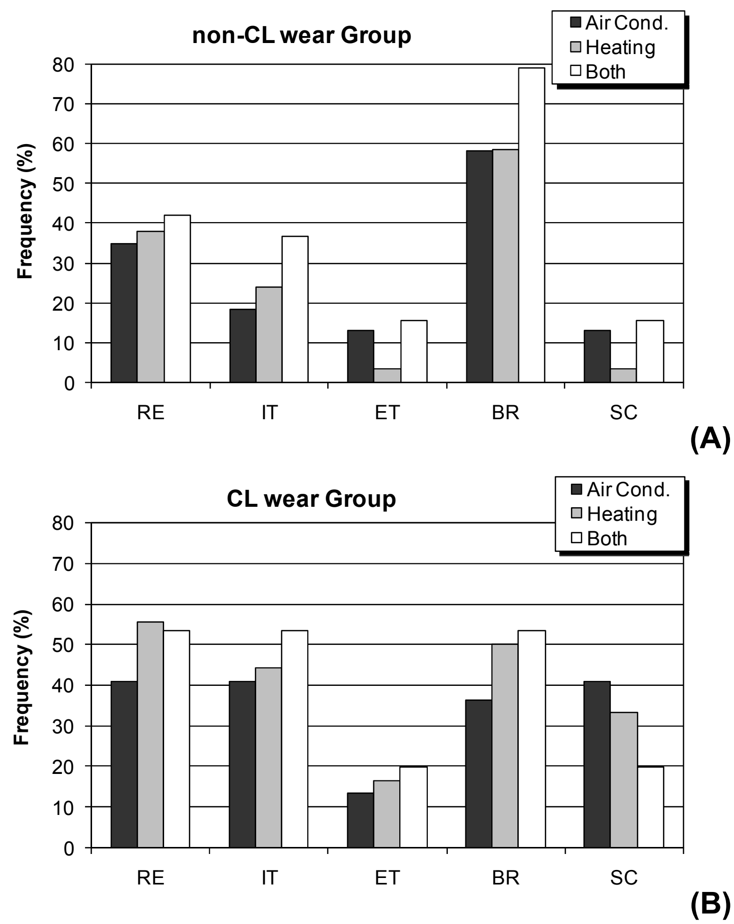

Figure 2.5. Frequency of symptoms of red eye (RE), itching (IT), excessive tearing (ET), burning (BR), and scratchiness (SC) for subjects using AC, heating devices or both in the n-CL group (A) and CL wear group (B).

2.5. Discussion

Ocular dryness and related symptoms continue to be the main complaint among CL wearers and it is believed that this is why CL wearers discontinue their use[18] and opt for other vision correction strategies such as refractive surgery.[19] Discomfort was indicated as the main reason by 51.0% of patients that discontinued CL wear in the UK.[7]

In this study, we have identified a higher prevalence of certain symptoms potentially associated with changes to the ocular surface in the CL wear population. Those who "often" reported symptoms increased significantly in the CL wearing group (24.0%) compared to n-CL wearers (13.0%). This is consistent with the results presented by Fonn *et al.*,[20] who described an almost linear decrease in patient comfort with different types of hydrogel and silicone hydrogel CL during a 7-h period among a group of symptomatic CL wearers. The level of scratchiness was the most significant difference between CL and n-CL wearers. Also, symptoms are more likely reported at the end of the day; 53.5% of CL wearers reported symptoms later in the day, whereas only 32.0% of n-CL wearers reported this.

The main reasons for the presence of these symptoms may be found in the tear stability, or lack of it, over the CL material, which can be adversely affected by environmental conditions of air temperature (AT) and relative humidity (RH).[21-23] It is generally accepted that pre-lens tear stability is significantly affected by low humidity environments. In a recent study, Maruyama *et al.*[12] have concluded that no statistically significant differences in tear volume was detected under different AT (10 to 35º) and RH (10.0 to 50.0%) conditions. However, they found that although noninvasive tear break-up time was independent of the environmental conditions without a CL in place, it decreased significantly as the air became dryer and colder for high and low water content SCL. These findings were associated with an increase of dryness complaints, particularly in high water content SCL.[12] Nichols *et al.*[24] have recently described similarities between the thinning of the pre-lens and pre-corneal tear film involving evaporation, dewetting, and pressure-gradient flows. However, the thinning process was more rapid over the CL material and the authors related more rapid thinning to dewetting processes. This could explain the higher prevalence of symptoms among CL wearers, particularly at the end of the day when the CL surface wettability could be more seriously affected.

For the population in this study, the use of heating devices in the work place might enhance ocular symptoms, which was not the case for those using air conditioner units that seemed to present a weaker correlation with the raising of ocular symptoms.

We noticed that working with VDTs can also influence the frequency of symptoms, particularly for those using TFT displays. However, this was probably related to a more intensive use of these displays rather than to the nature of the VDT. Indeed, for this population, the daily use of VDT was significantly higher than that reported by Begley *et al.* for the general population.[2] Working with computers is a relevant matter of concern when fitting SCL to patients with the VDT exposure pattern reported in the present study. The fact that the most intensive VDT users do not present any severe symptoms suggests that a limited number of hours (perhaps between 3 and 6 h of computer use) might become irritating for CL wearers, and that above that number there is no increased impact on the wearer. However, more specific studies should be carried out in order to confirm this hypothesis.

The proportion of CL wearers reporting symptoms at the end of the day is almost twice as large compared to n-CL group. In a recent study Begley *et al.*[17] have shown that for all symptoms under study, Sjögren's syndrome (SS) and non-Sjögren's syndrome keratoconjunctivitis sicca (non-SS KCS) groups presented an increase in the number of subjects who reported moderate to aggravated symptoms in the evening. For example, 67.0% of subjects with SS and 32.0% of subjects with non-SS KCS reported moderate to severe discomfort in the morning vs. 90.0% in the SS group and 60.0% in the non-SS KCS group in the evening. In the present study, almost no subject reported symptoms early in the day. This suggests that the pattern of appearance of symptoms (morning vs. evening) could be important to differentiate between pathological and marginal CL-related symptoms.

Furthermore, a recent study has shown that clinicians often underestimate the severity of dry eye conditions, particularly as far as older women are concerned[1,25]. In the author's opinion although it is not possible to evaluate a general population directly, this suggests that CL wearers at risk of developing symptoms who cannot be correctly managed might face a risk of CL intolerance in the future, if the clinicians rely only on clinical signs of dry eye to change the fitting/wearing strategy. However, to date, no standard tool has been provided for a proper subjective evaluation of CL related symptoms. Meanwhile, direct questions must be asked to patients wearing CL about their eye sensations and the way that these present themselves. Scratchiness at the end of the day appears to be key points to detect subtle problems in an early stage. This fits with the conclusions drawn in a recent study.[14] Our study shows that this is even more important for females, for intensive VDT users and for subjects who work in indoor heated environments. Strategies such as more frequent lens replacement, more intense cleaning and a reduced wear schedule should be adopted earlier in order to maintain comfortable and safe CL wear.

In general terms, our results suggest that those CL wearers, (particularly young women) that use of VDT for long hours in air conditioned rooms, run a higher risk of presenting certain symptoms (mainly scratchiness) at the end of the day. If not solved, such a condition could lead to the discontinuation of CL wear in the medium term. The at risk group corresponds to the prototype of the most common contact lens wearers in Portugal to be fitted for the first time or refitted. Within this specific populations 66.5% are female and aged 28 ± 10 (whole sample); 20.0% of the patients who are refitted describe frequent symptoms vs. 10.0% of first fits, and 30.0% describe symptoms in the evening against 16.0% in the first fitting group. These differences are statistically significant at $p = 0.05$ and $p = 0.01$ levels, respectively.[26]

In conclusion, current demographic and socioeconomic trends along with the current CL wearer profile could lead to an increasing proportion of CL-related symptoms among the world population of CL wearers. Despite significant improvements in CL materials and palliative treatments that could reduce these problems in the future, clinicians should consider new standards of subjective evaluation. This includes the pre-fitting investigation of risk factors that can potentially affect CL tolerance in the medium and long terms, and a proper follow-up schedule with direct questions that allow early detection of symptoms that can suggest changes in the CL wearing strategy.

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2.7. Appendix

Please, answer the following questions placing ☒ where appropriate.

Preliminary data

- Male ☐ Female ☐ Age [ ] Occupation [ ]

- Do you wear contact lenses?
No, I do not wear contact lenses ☐

Yes ☐ *Soft / Hydrogel* ☐ *Rigid and Rigid Gas Permeable* ☐ *For how long?* [ ] *years/months*

Questionnaire

1. Have you ever used drops for your eyes?
No ☐ *Yes* ☐ *Which kind: Drugs* ☐ *Artificial Tears / Saline* ☐

2. Which kind of symptoms/signs did you feel after a normal day working/studying?
Red eye ☐ *Itching* ☐ *Excessive tearing* ☐ *Scratchiness* ☐ *Burning* ☐

3. How frequently you feel this/these sign(s)/symptom(s)?
Never ☐ *Sometimes* ☐ *Frequently* ☐ *Constantly* ☐

There is a specific part of the day when you feel them more?
Early in the day ☐ *End of the day* ☐

4. Do you use to work/study in closed rooms with some of the following environments?
Air conditioned ☐ *Heating units* ☐ *Dust* ☐ *Chemicals* ☐

5. Do you use frequently computers at your working/studying place?
Yes ☐ *No* ☐

6. Do you feel some irritation after having using a computer for a prolonged period?
Yes ☐ *No* ☐ *I do not use computers* ☐

7. Which kind of screen use your computer?
Conventional (CRT or TV-like) ☐ *Flat screen (TFT, LCD or laptop-like)* ☐

NOTE: This questionnaire is anonymous. By answering this questionnaire you agree that this data would be used with scientific and teaching purposes by staff of the Department of Optometry at the University of Minho.

Signature

Chapter 3

Contact Lens Materials. Part I – Relevant Properties in Clinical Practice

3.1. Abstract

Purpose: Biocompatibility of contact lenses (CLs) relies on several parameters that are characteristic of the materials they are made of. This paper presents a review on the properties of contact lens materials and their clinical relevance for eye care practitioners.
Methods: The relevant literature is critically reviewed, with particular attention to soft contact lenses (SCLs), which are presently the lenses most commonly used worldwide.
Results: After the shake of the contact lens (CL) market between mid 90´s and the beginning of the new millennium, primarily attributed to refractive surgery, recent developments have opened a new promissory future for the field of CLs. However, the relationship between CLs and ocular surface is far from being perfect in terms of biocompatibility. The impact of several CL properties on biocompatibility of these devices is still far from being fully understood. CL research is changing, and much more investigators in multidisciplinary teams are directing their interests towards the study of materials, their properties and their interactions with the ocular surface.
Conclusions: Nowadays we have conquered a relevant knowledge about some of the most important CL properties and the minimum requirements they should meet in order to warrant biocompatibility to avoid ocular compromise. Equilibrium water content (EWC), oxygen permeability and surface wettability are still major concerns within the field of CL research and development. Nevertheless, other parameters as mechanical properties, hydraulic permeability or surface topography are now increasingly investigated to find new answers to the old questions related to CL biocompatibility that will help to limit the negative side effects of CLs in the ocular surface.

3.2. Introduction

Twenty-five years ago, about 20 million people around the world worn CLs; approximately 65% SCLs and 35% rigid and rigid gas permeable (RGP) CLs according to the Menicon-Toyo's 30th Anniversary Special Compilation of Research Reports (Toyo Contact Lens Co, Ltd) published in 1982.[1] Nowadays, there are about 125 million CL wearers worldwide,[2] most of them in the United States of America, Europe and Australia. The Asian population and other emergent economies have an enormous potential to increase the CL market in the next decades. At present, there are many CL designs, made of significantly different materials that can be fitted as the most appropriate solution for each patient. According to the Association of CL Manufacturers in 2005, there were more than 400 different CLs types. Of these about 215 were RGP CLs and almost the same number were hydrogel and silicone hydrogel (Si-Hi) materials with spherical, toric and bifocal correction.[3] Despite the continuous delivery of new CL materials problems related to biocompatibility are still present, and limit the growth of the CL market. Of the 38 million CL wearers in the United States by 2005, about 2.8 million dropped out of CL wear. The 3 million new fits within the same period resulted only in a net increase of 0.5%.[2] Different reasons can be behind the high drop-out rate, but most of them are related with intolerance of CL and care solutions[4-7] that is, due to deficient biocompatibility of the lens and/or care solution on the ocular surface.

Biocompatibility is the suitability of materials for use in CLs and in other medical or surgical devices. The evaluation of biocompatibility of any material for medical or biological application requires tests that must provide a full understanding of the host response.[8]

In earlier times, the adoption of medical materials and devices was made on a trial-and-error basis. Nowadays, the assessment of biocompatibility requires support from multidisciplinary teams using an agreed range of methodologies, the accreditation of participating test laboratories, and the adoption of quality protocols supported by certified reference materials. This is the case in current CL research and development where engineers, chemists, physicians, optometrists, biologists, microbiologists, immunologists, physiologists, and physicists work together to bring up new products, CLs and compatible solutions, for the CL industry. CLs are medical devices that are regulated in the United States of America (USA) by the Food and Drug Administration (FDA) and are intended to be used in close contact with mucosal membrane of the ocular surface for a few hours with daily removal or up to 30 days of continuous wear. According to the biocompatibility standards in the USA, these CLs should be tested for the following biological effects: cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute systemic toxicity and sub chronic toxicity.[8] However, not universal harmonization has been achieved yet. Biocompatibility is based on standards such as ISO 10993 for the Biological Evaluation of Medical Devices. One limitation of these standards is that several tests are described to evaluate different aspects of biocompatibility rather than a specific test for each one of these issues as mentioned by Marlove.[8] In the European Union, two Directives have been issued, the Directive on Active Implantable Medical Device (90/385/EEC) and the Directive on Medical Devices (93/42/EEC). Four main aspects are considered in the evaluation of biocompatibility of medical devices according to these standards: chemical safety, microbiological safety, physical safety and biological safety which specifically refers to the compatibility between the material and the body and comprise all chemical, physical, and microbiological characteristics of the device and its component materials.[9] All these aspects seem to fit quite well to the relationship of CLs with the ocular surface. The equivalent standard to ISO 10993 in the European Union will be represented by the standard or European Norm (EN) created by the European Committee of Standardisation (CEN), that is, EN 30993 concerning the Biological evaluation of medical devices.

The history of polymethylmethacrylate (PMMA) CLs is linked to the first recognition of biocompatibility of synthetic polymers, evident when fragments of PMMA in the eyes of pilots from the canopy of fighter planes during World War II did not cause an inflammatory response. This fact was the stimulant to think about the application of PMMA to manufacture the first commercially available plastic contact and intraocular lenses. Currently we have a significant body of knowledge about the effects of CL on the ocular surface[10-12] as well as the physiological and pathological modifications that affect different corneal layers under different CL wear modalities.[13,14] This has been possible by a better understanding of corneal metabolic demands,[15,16] the mechanisms of CL related corneal infiltration and infection[17,18] and the response of the limbus and conjunctiva to CL wear.[19,20] With CLs the host is primarily the cornea, that ideally should tolerate the lens without any adverse response. However, different factors such us hypoxia, dryness, or mechanical trauma, often limit the ability of a CL to be fully biocompatible with the ocular surface. Because CLs are to be worn on the tear film and not on direct contact with the corneal epithelium, but separated from it by a thin layer of the tears, the biocompatibility of a CL is primarily dependent on the ability of the tear to spread over and under the lens, and to transmit oxygen to the ocular surface, primarily through the lens itself and secondarily by the flux of oxygenated tear film over and under the lens.

Despite significant advances in the clinical use of CLs, some old problems continue to be present at a same or even increased level with the use of some of the new CL materials. This is the case of deposits,[21] microbial adhesion,[18,22-26] mechanical interactions[20,27,28] or dehydration of the ocular surface exacerbated by the presence of the CL.[29-32] As a consequence and considering the potential of the new CL materials, the CL market continues to be under the expectations of manufacturers and practitioners. Undoubtedly, the limitation of the compatibility between the CL and the ocular surface is a major cause to explain the limitation experienced in the CL market. This is supported by the fact that the thousands of people entering or re-entering into the CL market each year are balanced by an almost equal number of patients that discontinue CL wear. Note that many of those patients who opted for refractive surgery procedures were CL wearers, and that the main factor behind their surgical option consisted on CL or care solutions related problems.[5]

Discomfort is the main reason argued by patients to justify CL discontinuation, and dryness is one of the most common causes of discomfort.[7] In addition to patient-related or fitting-related causes of discomfort, material-related properties play also an important role on lens intolerance. In fact, CL biocompatibility of the current generations of CL materials is not as good as should be. So far we have not reached full understanding of the effect of CLs material on lens complications, and this will continue to limit the expansion and success of CLs worldwide.

As far as we know, there is no recent review on peer-reviewed journals that addresses the question of materials properties of current CLs from a physiological point of view. Therefore, the aim of this review is to give an overview of the principal CL materials currently available, their most relevant properties, how they interact with the ocular surface, and to provide an insight on how current and future CL materials could be improved in order to satisfy the needs for higher biocompatibility under different modalities of wear.

3.3. Brief historial overview

Since the early attempts to create an optical element for vision correction in contact with the eye, many materials and designs have been used in order to correct ametropia, protect the cornea as a therapeutic device or correct serious irregularities of the ocular surface for mixed optical and therapeutic effect.

Advances in CL have been linked to advances in materials with good optical properties and biocompatibility with the ocular surface as the main goals. Looking back to the historical background of CL practice, three men in different parts of Europe, August Müller (Kiel, Germany); Eugene Kalt (Paris, France); and Adolf Fick (Zurich, Switzerland) worked simultaneously to establish the scientific basis to build up the CL research and clinical practice.[33] This happened around the year 1888 when opticians as Ernst Abbe, who built the lenses used by Adolf Fick, and Otto Himmler, who develop the lenses for August Müller, also played an important role in the early CL history.

Their initial work was with scleral lenses, the precursor of corneal CLs, was based on the blown glass technology, and almost 50 years will pass until the transition to the field of plastic materials by William Feinbloom who constructed the first hybrid lens (glass and plastic) between 1937 and 1938. At this point, John Mullen, Istvan Gyorrfy and Theodore Obrig fitted the first plastic corneal lenses made entirely from PMMA. Ten years later, 400.000 people only in the United States of America were wearing PMMA corneal CLs, thanks to the rapid growth of the CL industry. The American Academy of Optometry in 1945 recognized the CL practice as a subspecialty within optometry.

About a dozen years later, the idea for a more comfortable, oxygen-permeable, and biocompatible material motivated the invention in 1956 of a soft hydrogel material made of poly(hydroxyethyl methacrylate), abbreviated HEMA, by Otto Wichterle and Dravoslav Lim at the Czech Academy of Sciences, (Prague, then Czechoslovakia). The first hydrogel CLs manufactured was reported in 1960 by Wichterle and Lim.[34] With 38.6% hydration, this material was soft enough to improve the comfort. However, although the permeability to oxygen, carbon dioxide and metabolites was assumed there was no reliable data to support it. The first fitting experience with the soft HEMA hydrogel CLs was carried out by a check ophthalmologist Maximillian Dreifus. These early soft lenses were manufactured in Czechoslovakia by an innovative method called spin casting. The lenses were thicker and of larger diameter than those made later in the USA. The Wichterle and Lim patent was acquired by Bausch & Lomb in 1967 and hydrogel CLs rapidly gained an important place in the CL market. The Food and Drug Administration (FDA) in the USA, when the rapid expansion of the commercialization of HEMA and other hydrogel CLs, and some reports of clinical complications from the use of these lenses, decided to give all new CLs the category of health products submitting them to strict controls prior to commercialization.[10] The second patent in this field should also be highlighted because it was registered in the United States as a different approach to that of Wichterle's because the new lens did not used HEMA. Refojo and Korb made hydrogels copolymerizing methyl methacrylate and glyceryl methacrylate (2,3-dihydroxypropyl methacrylate) or P(GMA/MMA). This material was given the name crofilcon A by USAN. This lens could be manufactured in a thinner design and also demonstrated to have higher resistance to deposit formation[35] and bacterial attachment[36] than HEMA hydrogels. Lower protein penetration was evidenced by optical microscopy, and this fact was attributed by the authors to the lower porosity of this hydrogel compared to HEMA hydrogels of similar EWC.[37] Despite low EWC of this material, the possibility to make ultrathin designs made possible to use this material in aphakic SCLs in order to satisfy oxygen needs for daily wear.[38]

With the availability of the soft hydrogel lenses, more comfortable and easier to fit that the rigid PMMA lenses, came a substantial increase of CLs wearers and fitters, mainly optometrists, ophthalmologists, and depending of the local laws opticians and other technicians. However, fitters with good experience of the optical performance the PMMA lenses, but lack of oxygen permeability, realized that many patients could be better served with a RGP lens than with a hydrogel lens. From this need, rose a new generation of oxygen permeable CL materials starting with the polymerization of PMMA with methacryloxypropyl tris(trimethylsiloxy)silane, also known as TRIS by Norman Gaylord, a chemist. After that a series of RGP lenses of the same family of materials were made with TRIS or similar siloxane acrylates. The higher oxygen permeability, less direct contact with the ocular surface, and better tear exchange between the lens and the corneal surface compared with the conventional hydrogel lenses accounts for a safer mode of vision correction with the RGP than with the hydrogel lenses. A second generation of RGP lenses includes in its formulation perfluoroalkylmethacrylate monomers that contribute to improve the mechanical and physiological performance of the lenses.

The next goal of the CL industry was to produce high oxygen permeable hydrogel lenses for extended wear (day and night) during up to several weeks or months. The high oxygen permeability of these materials was achieved by using silicone macromers, consisting of silicone polymers (polydimethylsiloxane) terminated at both molecular extremes with hydrophilic radicals ended with acrylate moieties. Other oxygen permeable monomers used in these materials are TRIS or TRIS-like monomers containing siloxane radicals. For hydration, HEMA or other hydrophilic monomers, such as acrylamide derivatives, vinylpyrrolidone (VP) and/or methacrylic acid (MA) were copolymerized with the above mentioned hydrophobic siloxane rich macromers and/or monomers.

Aware that the tear film was the source of the principal deposits on CLs along with the common thought that lens handling was a main source of CL related infections, the industry introduced by the middle 80's the concept of disposable or frequent replacement SCLs. This could be considered as the second revolution on the hydrogel CL field, after the launch at industrial scale of the first HEMA based SCLs. Nevertheless, far from solving all the problems and concerns surrounding daily and extended wear CL complications, the following two decades have been devoted to an intense research activity for CL materials which could overcome the growing episodes of ocular infections and physiological complications resulting from CL wear, and particularly for overnight CL wear.[39]

The third revolution in the hydrogel CLs industry come twenty years later with the invention of the silicone hydrogel SCLs that, by improvement in oxygen permeability to increase the levels of biocompatibility, renewed the interest of continuous and extended wear modality.[40]

Consequently, all these developments provided the basis for a rapid expansion of CL wear during the last 30 years. Currently, the biocompatibility of CLs has improved, particularly by the use of disposable lenses that allow the patients to wear new lenses each day with no need for care solutions, at a reasonable cost. These developments have reduced significantly the incidence of CL-related adverse events.[41] However, even the newest disposable and Si-Hi lenses cannot be considered as fully biocompatible devices because they still cause significant interaction with the anterior surface of the eye as demonstrate in several recent studies.[21,25,42-44]

3.4. Main monomers for current contact lens formulations

Monomers used for the production of CL polymers are usually made of some combination of carbon (C), hydrogen (H), oxygen (O), nitrogen (N), silicon (Si) and fluorine (Fl), arranged to form molecules. The composition and arrangement of the individual links (monomers) in the polymer chain will determine most of its characteristics, and small changes in chain design and link composition can dramatically alter the material's properties. The composition can be very simple by repeating the sequence of links using only one kind of monomer as PMMA or can be made more complex by adding other monomers. The result is a homopolymer or a copolymer, respectively.

Current Si-Hi, in addition to silicone polydimethylsiloxane (PDMS) moieties used in the elastomeric silicone CLs, contains TRIS or TRIS-like monomers used in RGP. On the other hand, some of the main monomers used in the manufacture of conventional hydrogel lenses are included in the formulation of Si-Hi lenses. The main monomers used in the manufacture of CLs include:

- Methylmethacrylate (MMA) imparts rigidity, impermeability to oxygen, good optical quality, is used in rigid PMMA lenses, as component in some copolymers used in RGP lenses, and in some hydrogel soft lenses to improve mechanical strength.
- Hydroxyethylmethacrylate (HEMA) also known as 2-hydroxy-ethyl methacrylate, with the same polymer backbone as MMA, but substituting the hydrophobic methyl (CH3) ester side radical by a hydrophilic hydroxyethyl radical ($-CH_2CH_2OH$). The HEMA polymer (PHEMA) swells in water to form the original HEMA hydrogel (polymacon) invented by Wichterle and Lim, has an EWC of 38.6% and an oxygen permeability of about 9 barrer. HEMA also forms part of several copolymers used in other hydrogel SCLs.
- Methacrylic acid (MA) also related chemically to MMA and HEMA but with a carboxyl group (organic acid –COOH), is widely used in FDA group IV, ionic materials. Is highly hidrophilic and ionizable (COO^- and H^+). Methacrylic acid is also used in RGP lens to improve wetability.
- Glyceryl methacrylate (GMA) also a methacrylate derivative, with two nonionizable hydrophilic groups (OH) versus one in HEMA, is highly hydrophilic and was originally used copolymerized with MMA in the ultrathin CSI hydrogel lenses. GMA is used now copolymerized with HEMA in a family of materials that claim to reduce the CLs dehydration.
- Ethylene glycol dimethacrylate (EGDMA) also known as ethylene dimethacrylate (EDMA) – is a cross-linking agent that adds stability and stiffness to the polymer. Is

used in small proportions to the other monomers in the polymer, but depending in the amount used, may reduce hydration and gas permeability in hydrogels. Cross-linking agents such as EGDMA and similar dimethacrylates or divinyl monomers are used in all kind of CL materials.

- N-vinyl pyrrolidone (NVP), also known as vinyl pyrrolidone (VP), is a very hydrophilic nonionic cyclic lactam (-$NCOCH_2$-) and is used in hydrogel CLs copolymerized with HEMA or MMA in high EWC materials of FDA group II. NVP is also used in some Si-Hi materials. The presence of vinyl pyrrolidone in SCLs has been reported to be related with lipid deposits.
- Methacryloxypropyl tris(trimethylsiloxy)silane (TRIS) was one of the most important constituents in the early RGP lens materials. Currently is used in both RGP and Si-Hi materials. Different modifications in the molecular structure of TRIS have been used to improve its compatibility with hydrophilic monomers in the Si-Hi lenses. TRIS contains the element silicon in the form of siloxane radicals (-Si-O-$Si(CH_3)_3$) that after polymerization have a carbon to carbon polymer backbone with the siloxane moieties on the side. Thus, chemically speaking, TRIS and similar compounds are not members of the silicone family (such as polydimethylsiloxane used in elastomeric CLs), where the siloxane radicals are the links forming the backbone of the polymer chain.
- Silicone. The most common silicone polymer is polydimethylsiloxane used to produce silicone rubber CLs. Silicone rubber is a cross-linked network of polysiloxanes with high oxygen permeability (about 600 barrer). Much work was done in the development and clinical testing of this high oxygen permeable silicone rubber CLs, including procedures to make their surface hydrophilic. However, due, among other causes, to their tendency to adhere to the cornea, these lenses were not successful. However, silicone polymers linked at both ends to hydrophilic moieties terminated acrylate moieties (like all cross-linking monomers) are the macromers (macro monomers) that copolymerized with hydrophilic monomers produce the highly successful Si-Hi CLs of high oxygen permeability and RGP lenses.
- Fluoromethacrylates were first used to increase the free volume fraction of TRIS copolymers used in RGP lenses, thus increasing their oxygen permeability. Nowadays, fluorinated moieties linked to silicone are used in some Si-Hi materials. Fluorinated compound as well as silicone, and TRIS are very hydrophobic, and even when linked to hydrophilic monomers in the Si-Hi that have a substantial amount of bulk water,

the surfaces remain hydrophobic, and have to be treated to make the lens surface hydrophilic and tolerable in the eye.

All current materials are copolymers, and their formulations also include monomers that balance the principal characteristics of CL materials, as water content (in conventional hydrogels and Si-Hi materials), oxygen permeability, surface properties and mechanical strength.

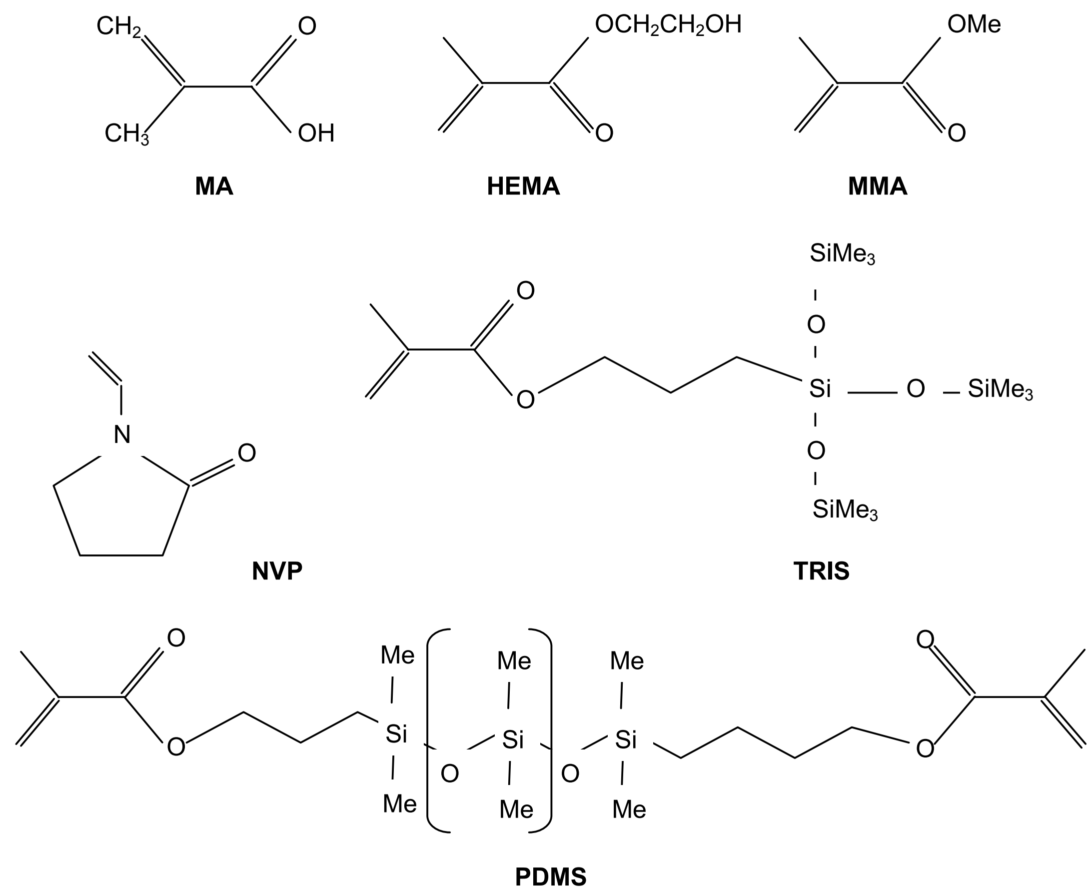


Figure 3.1. Different monomers used in current contact lens production (Me is CH_3).

Information about patents and formulations for CLs can be obtained at the specific patent documents and several reviews available in the literature about SCLs and Si-Hi,[45,46] rigid and RGP CL,[47] rigid and RGP CL, and current Si-Hi materials.[48] Additional updated information can be obtained from two recent papers that mention the main monomers of several conventional hydrogel and silicone hydrogel materials.[49,50]

3.5. Polymerization and manufacturing technologies

A CL polymer is a complex structure that consists of molecules with high molecular weight (>10.000) cross-linked in a three dimensional amorphous network. If we can imagine polymer molecules as pieces of string loosely entangled, their interaction and entanglement governs the polymer's characteristic physical properties. The first step in the manufacture of CLs is the polymerization of the material. Polymerization is the process by which monomers are combined in the presence of cross-linkers and initiators in order to create a stable structure. It can be done by different methods not relevant to this review.

The CL polymers obtained from the polymerization are named according to the criteria of the United States Adopted Names Council (USAN). A CL generic name has a unique prefix attached to a common suffix, "filcon" for hydrogel materials and "focon" for RGP materials. The only exception is polymacon, the first soft CL material, patented before the USAN guidelines for CL materials were created. In the USA, USAN only regulates the generic names of the CL materials, while FDA regulates the CL as medical devices.

Three manufacturing technologies used to produce CLs are lathe cutting, spin casting and cast molding. The polymerization process is different depending on the manufacturing procedure. For lathe cutting, the material is first polymerized as solid rods that then are cut into buttons for further processing in computerized lathes to produce the lenses. In spin casting the monomer preparation is placed on a rotating mold and polymerization occurs during mold's rotation to define the shape of the finished lens. Changing mold's shape and rotation speed, different lenses are obtained. In cast molding the polymerization also occurs by injecting the monomer mixture between convex and concave molds that will define posterior and anterior surfaces of the finished lens. Cast molding is the principal method used today as it produces high amount and high quality CL lenses for daily and continuous wear, and particularly of disposable and frequent replacement CLs. Although not many lenses are produced today by spin cast, this system deserves a special place on CL history as it was the revolutionary method invented by Otto Wichterle and developed by Bausch & Lomb, making possible mass production of CLs at reduced costs, thus expanding CL wear to millions of people all around the world in just a few years. In spite of improvements through computer assisted control, lathe-cut technology is the most expensive method and is now used only to manufacture a limited amount of special SCLs, but it is still used for the manufacture of almost all rigid and RGP CLs. Dry production and lathe cut of soft CL materials requires a precise knowledge of the linear expansion of the polymer in order to know the exact shape of the finished lens after full hydration (see section 3.6.2.2). Even most of cast molding lenses are produced in dry state and then hydrated.

Table 3.1. Nominal parameters of some CLs. All lenses are produced with cast-molding technology except lenses made in Hioxifilcon A, B and P(GMA)+HEMA+MA copolymer, produced by lathe-cut. Some of the principal monomers included in each material are also quoted along with the main monomeric chain

	Brand	USAN Generic name	Material (main monomers)	EWC (%)	Ionic (FDA)	Dk (barrer)	ST	CT (mm)
Silicone Hydrogels	Air Optix Night & Day	Lotrafilcon A	TRIS+DMA+siloxane monomer	24	No(I)	140	Plasma coating	0.08
	Purevision	Balafilcon A	TRIS+NVP+TPVC +NCVE+PBVC	36	Yes(III)	99	Plasma oxidation	0.09
	Air Optix	Lotrafilcon B	TRIS+DMA+siloxane monomer	33	No(I)	110	Plasma coating	0.08
	Acuvue Advance	Galyfilcon A	HEMA+PDMS +DMA+PVP	47	No(I)	60	No	0.07
	Acuvue Oasys	Senofilcon A	HEMA+PDMS+ DMA+PVP	38	No(I)	103	No	0.07
	Biofinity	Comfilcon A	-	48	No(I)	128	No	0.08
Conventional Hydrogels	Soflens 38	Polymacon	HEMA	38.6	No(I)	8.5	No	0.065
	Equis 60	Hioxifilcon A	HEMA+GMA	59	No(II)	24	No	0.13
	Acuvue 2	Etafilcon A	HEMA+MA	58	Yes(IV)	28	No	0.084
	SPH4UV	Hioxifilcon B	HEMA+GMA	49	No(I)	15	No	
	Proclear	Omafilcon A	HEMA+PC	62	No(II)	32	No	0.065
	Osmo 2	-	p(GMA)+ HEMA+MA	72	Yes(IV)	45	No	0.14
	Actifresh 400	Lidofilcon A	MMA+VP	73	No(II)	36	No	0.12
	PrecisionUV	Vasurfilcon A	MMA + VP	74	No(II)	39	No	0.14

USAN: United States Adopted Names Council; EWC: equilibrium water content; Dk: oxygen permeability; ST: surface treatment; TD: total diameter; BCR: base curve radius; CT: central thickness. Dk measurement units (x 10^{-11} (cm^2/sec)[ml O_2/(ml x mm Hg)]). DMA: *N,N*-dimethyl acrylamide; GMA: glycerol methacrylate; HEMA: 2-hydroxyethyl methacrylate; MA: methacrylic acid; MMA: methyl methacrylate; NCVE: (*N*-carboxyvinyl ester); PC: phosphorylcholine; TRIS: 3-methacryloxy-2-hydroxypropyloxy propylbis(trimethylsiloxy)methylsilane; TPVC (tris-(trimethylsiloxysilyl) propylvinyl carbamate); PBVC (poly[dimethysiloxy] di [silylbutanol] bis[vinyl carbamate]); VP: *N*-vinyl pyrrolidone

Grobe demonstrated that SCLs produced by cast-mold presented smoother surfaces than those produced by lathe-cut,[51] conversely Maldonado-Codina and Efron reported poorer clinical performance of spin-casting HEMA lenses when compared with lenses made of the same material using by other technologies. They reported that spin casting CLs induced more limbal and conjunctival hyperemia, dehydrated more, had less on-eye movement and provided poorer low contrast sensitivity, but adhered less proteins.[52]

For Si-Hi and RGP CLs of high oxygen permeability part of manufacturing technologies is surface treatment needed to overcome the poor wettability and tolerance due to surface hydrophobicity. This is the case with all siloxane (TRIS-like and silicone moieties) containing materials that are highly hydrophobic because of siloxane migration to the surface of the lens. The hydrophobic nature of siloxane moieties increases the risk of lipid deposition. The use of polyethylene glycol methacrylate grafting on the CL surface, polymerization in polar molds to force charges to migrate to the surface of the lens, and addition of surfactants have been used in the past to overcome the hydrophobic nature of silicone containing lenses. The use of hydrophilic monomers failed to solve the problem because of phase separation during polymerization. Nowadays, plasma (highly ionized gas by electrical discharge) treatment, allows to create Si-Hi and RGP materials with surfaces that wet well by tear and are well tolerated by the ocular surface.

3.6. Main properties affecting the compatibility of contact lenses

The relevant characteristics for a material intended to be used as a CL are those related to the surface wettability, electrostatic charge, surface topography, bulk matrix, hydration, and oxygen permeability, properties related to the mechanical behavior, elastic modulus, flexure and hardness, and hydraulic and ionic permeability. These properties are important for the CL wearer, for comfort and convenience of use for prolonged periods of time, sometimes overnight for several days or weeks without removal or care.

3.6.1. Surface properties

The surface properties of the biomaterials for CL manufacture are important to evaluate their biocompatibility, particularly regarding their smoothness or roughness, the dryness or wettability of the lens surface related to the structural and functional groups interaction with each other and with their surrounding environment. The main points of interest in a surface arise from the fact that surfaces in contact with biological tissues are potentially reactive, are different from the bulk, and are readily contaminated. Apart from the chemical interaction, surface roughness of devices contacting living systems will influence their biological reactivity. The relationship between surfaces is especially critical in CL practice as the polymer should interfere as less as possible with the epithelial surface of the cornea and with the palpebral conjunctiva.

A smooth surface is essential to promote biocompatibility between CL and the ocular surface. SCLs made of conventional hydrogel materials promote optimum mechanical interaction with ocular surface and lids through the moisture on their surfaces. However, with the advent of silicone hydrogel (Si-Hi) materials, and the need for surface treatments to improve wettability along with the fact that these materials are more rigid than conventional hydrogels, the mechanical interaction between the CL surface and the ocular surface became an important issue.

Table 3.2. Properties of the six Si-Hi materials currently available

	Air Optix Night & Day	Purevision	Acuvue Advance	Air Optix	Acuvue OASYS	Biofinity
Material	Lotrafilcon A	Balafilcon A	Galyfilcon A	Lotrafilcon B	Senofilcon A	Comfilcon A
Manufacturer	CIBA Vision	Bausch & Lomb	J&J Vision Care	CIBA Vision	J&J Vision Care	Cooper-vision
Dk	140	99	60	110	103	128
Thickness @-3.00 D (mm)	0.08	0.09	0.07	0.08	0.07	0.08
Dk/t (barrer/cm)	175	110	86	138	147	160
EWC (%)	24%	36%	47%	33%	38%	48%
FDA	I	III	I	I	I	I
Surface treatment	25 µm plasma polymerization	Plasma oxydation	No	25 µm plasma polymerization	No	No
Elastic modulus (Mpa)	1.4	1.1	0.4	1.2	0.6	0.8
Tensional modulus (psi/MPa) (**)	238/1.64	148/1.02	65/0.45	190/1.31	92/0.63	105/0.72[§]
Elastic/Viscous Component (KPa) (,§)**	58/18	44/5	28/8	42/7	36/8	-/40
Elastic/Viscous Ratio	3.17	8.8	3.5	6	4.5	-
Friction coefficient(**)	≅0.07	≅0.06	≅0.015	≅0.03	≅0.011	-
Contact Angle(º)	80	95	65	78	68	-
Initial relative dehydration (%)	1	1.9	2.4	1.5	1.9	2.3[§]

FDA: Food & Drug Administration
Pa: pascal; MPa: megapascal; psi: pounds per square inch
1Pa = 1 N/m^2; 1 kPpa = 10^3 N/m^2 1 MPa = 10^6 N/m^2 = 100 N/cm^2 = 145 psi
Sources:
- Manufacturers.
- Ross G *et al*. Silicon hydrogels: trends in products and properties.[53]
(**)Values of the elastic and viscous components as well as the ratio derived from them are approximate values obtained visually from graphs on the correscponding communication so they should be interpreted as orientative rather than exact values.
- (§)Tighe B. Trends and developments in silicon hydrogel materials.[54]

The surfaces of first generation Si-Hi materials because of the siloxane moieties migrating to the surface are hydrophobic, are naturally non-wettable by tears and hence poorly tolerated. Therefore, the lenses are finished with treatments to obtain wettable surfaces by plasma oxidation in Purevision[48] and plasma polymerization of a mixture of trimethylsilane, oxygen (air) and methane in Air Optix Night&Day.[55] Plasma polymerization is also used in Air Optix. Conversely, as quoted by the manufacturer, Acuvue Advance and

Acuvue Oasys do not need surface treatment to warrant wettability. Absence of surface treatment is also claimed for Biofinity.

3.6.1.1. Wettability

Surface wettability is one of the main parameters defining CL biocompatibility as it relates to comfort, ocular surface interaction, gas permeability and spoilage by tear deposits. Wettability depends on the surface energy of the CL and the surface tension of tears. A wettable CL depends of a lens surface with high surface energy, which is a hydrophilic surface, and a low surface tension of the tear film. Some authors have defined this as the necessity of creating a material that the water can love even more than itself. Wetting agents applied to the surface of a CL act as surfactants that by dissolving in the tears lower their surface tension allowing the 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 wettable as the day goes on. Therefore, the best solution would be to aim to increase the surface energy of the lens surface to promote o low interfacial tension between the lens and the tear film. This is one of the main problems to resolve by the scientific community as CL related dryness and discomfort can account for the majority of CL wear drop-out world wide.[5,7]

Optimal wettability is still a serious challenge even with modern plasma treated Si-Hi CLs. The oxygen-permeable components of these lens materials are the highly hydrophobic silicone, siloxysilane (TRIS) and perfluoro moietiess that adversely affect the wettability of the lenses.

Multiple strategies have emerged recently and in the past decades to create lens surfaces that are chemically similar to natural human tissue, a practice referred to as biomimesis. This is the case of so-called biomimetic materials used in several medical applications including CLs. Such materials contain phosphatidilcholine (PC), a molecule found in the lipid layers of a cell membrane that gives the membrane a relatively neutral electrical charge, and the ability to bind water. It is said that CL polymers with phosphatidilcholine moieties, called “biocompatible”, minimize deposit formation and dehydration. Court *et al.*[56] applied this method to PDMS SCLs and significantly reduced the water contact angle on the surface and the protein uptake of the lens -the lowest the water contact angle on a surface, the highest is its wettablility. Another similar approach was the polymerization of poly(ethylene glycol) onto RGP CLs. Using this strategy, Sato *et al.*[57] found that the hydrophobic surface of the RGP CLs changed to a hydrophilic surface, reducing significantly the contact angle, as well as lipid and protein uptake. While contact angle did not change significantly with addition of more than 5 units of poly(ethylene glycol) per lens, protein and lipid uptake was reduced exponentially as a function of ethylene glycol units on the surface.

Other strategies consist on modifications of the polymer surface to limit interaction with surrounding materials instead of to imitate biological tissues. These include the use of sulfoxide chemical groups, which retain water while resisting protein deposits, and the use of electrically charged molds in the production of CLs to create polar surface charges, that can attract water but not other contaminant materials. The development of Si-Hi has brought out and older approach in promoting surface wettability by exposing the finished lenses to an electrically charged plasma gas, which chemically transforms the hydrophobic silicone components on the lens surface into more hydrophilic silicate compounds that wet well and resist deposits without decreasing oxygen permeability. The use of selenium in CLs is also a promising method to reduce bacterial adhesion to CL materials, and is already being tested in animal models.[58]

3.6.1.2. Electrostatic charge (ionicity)

Depending on the monomers used, SCL polymers can be ionic or non-ionic, with and without electrostatic charges, respectively at the CL surface. An ionic hydrogel is defined as one containing more than 0.2% ionic constituents. The FDA created its Classification of Lens Groups for hydrogels based on EWC and electrostatic charge (ionicity) of the polymer, assuming that different hydrophilic lenses with similar water content and electrical charge would respond in a similar manner to the surrounding environment. Certain monomers used in CL manufacture almost invariably confer some degree of ionicity to the CL material, as is the case of methacrylic acid (MA). From the clinical perspective, this property is directly related to the level of protein (mainly lysozyme) adhesion, which is significantly higher in ionic materials as demonstrated by numerous studies, while lipid attraction was found independent of the ionicity of the material.[59]

3.6.1.3. Viscosity and friction

Friction coefficient is important in CL fitting as the movement of the CL riding the ocular surface relies strongly on this parameter and is closely correlated with surface energy and wettability. Problems with frictional behavior arise because of progressive surface dehydration during lens wear. In hydrogel lenses friction depends on hydration. Thus, Kim *et al.*[60] have demonstrated that the surface friction and adhesive force of the hydrated CL were significantly reduced compared to those measured in partially dehydrated surfaces. Different approaches have been proposed to improve this property. Sato *et al.*[57] demonstrated that

RGP lens surface viscosity, increased linearly with the number of poly(ethylene glycol) units deposited over a CL surface.

Friction is clinically relevant as it controls the interaction between the CL and the surrounding tissues: cornea, bulbar and tarsal conjunctiva. As the lens dehydrates during the day or weeks of lens wear, because of exposure to dry environments and/or deposit formation, friction will increase and could be responsible for end of day discomfort, and palpebral reaction in the form of papillary conjunctivitis.[48]

Other parameter that has been used in the literature, is lubricity and it is defined as the ability of a material to resist friction, expressed as the force required to move a known load across a surface at a given speed.[61] In CLs, surface lubricity relates most closely to the ability of the eyelid to travel smoothly across the surface of the lens without irritation. Coefficient of friction, a measure of the lubricant properties, represents the amount of friction created at the lens surface from a load roughly equal to eyelid forces and oscillated at frequencies to mimic the normal blink. Values are then adjusted for hydrogel materials deformation and the fluid interface when measuring a wet lens.[62] Hence, lubricity and friction, are closely related.

3.6.1.4. Surface topography

Several techniques have been recently applied to CL microscopic examination with different purposes; these include X-rays photoemission spectroscopy (XPS),[63] atomic force microscopy (AFM)[64] or scanning electron microscopy (SEM).[65] Gonzalez-Meijome *et al.*[66,67] evaluated three Si-Hi CLs using AFM microscopy in Tapping™ Mode scanning areas ranged from 0.25 to 400 μm^2. Mean roughness (*Ra*), root-mean-square roughness (*Rms*) and maximum roughness (*Rmax*) in nanometers (nm) were obtained for the three lens materials at different magnifications. The three CLs showed significantly different surface topography. Roughness values expressed in nm were dependent of the surface area to be analyzed. Statistics revealed a significantly more irregular surface of balafilcon A (*Ra* = 6.44 nm; *Rms* = 8.30 nm; *Rmax* = 96.82 nm) compared with lotrafilcon A (*Ra* = 2.40 nm; *Rms* = 3.19 nm; *Rmax* = 40.89 nm) and galyfilcon A (*Ra* = 1.40 nm; *Rms* = 1.79 nm; *Rmax* = 15.33 nm). Ra and *Rms* were the most consistent parameters, with *Rmax* presenting more variability for larger surface areas. The higher roughness of balafilcon A was attributed to the plasma oxidation treatment used to improve wettability. Conversely, galyfilcon A displays a smoother surface. These observations could have implications in clinical aspects of Si-Hi CL wear such as lens degradation, resistance to bacterial adhesion or mechanical interaction with the ocular surface. *Figure 3.2* illustrates the surface of five Si-Hi CL observed with AFM.

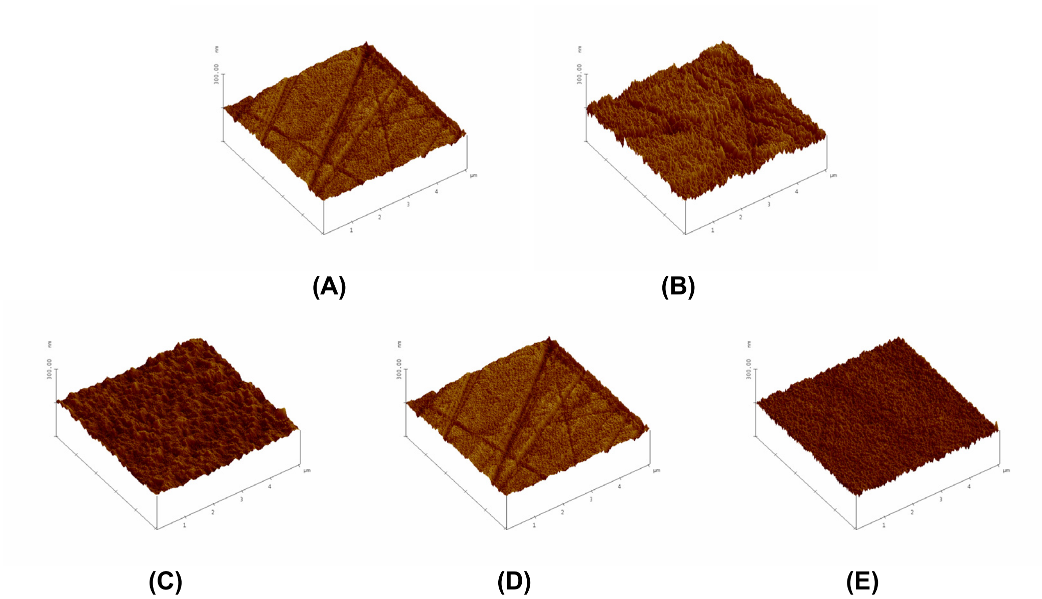


Figure 3.2. Surface appearance of five Si-Hi materials: lotrafilcon A (A), balfilcon A (B), galyfilcon A (C), lotrafilcon B (D) and senofilcon A (E) with the atomic force microscope (AFM).

Bagget *et al.*[68] calculated mean roughness (Ra) using a home-made software, within a range of 4.9nm for a 78% water content cast molded P(MMA/NVP) hydrogel lens, to 16.98 nm for a 55% water content, lathe-cut P(HEMA/MAA) hydrogel lens, for a scanning range of 19 μm.[68] They attributed some responsibility for the higher roughness to the presence of methacrylic acid (MA) in the 55% water content lathe-cut lens. Conversely, they found a smoother surface on the 78% water content lens with NVP made by cast-molding. This agrees with the smooth structure of galyfilcon A that has a significant content of polyvinylpyrrolidone (PVP). Grobe[51] reported that SCLs produced by cast-molding presented smoother surfaces that those produced by lathe-cut.

Among other properties of the CL surface, such as hydrophobicity and atomic composition, Bruinsma *et al.*[23] demonstrated that surface roughness was one of the mayor determinants of *Pseudomonas aeruginosa* adhesion to etafilcon A [P(HEMA/MAA)] SCLs. Also Baguet *et al.*[69] used AFM to monitor deposit formation on SCL surfaces and showed that as the surface roughness increased also increased the deposits on the lens.

3.6.2. Bulk properties

3.6.2.1. Equilibrium water content

This parameter is specific of hydrogel materials and represents the ability of the material to bind water and it's perhaps the most important property defining their clinical behavior. This affinity is determined by the rate of hydrophilic to hydrophobic radicals and the density of cross-links in the polymer network that governs the EWC of hydrogels, and their physical properties. However, this ability to hydrate does not mean hydrogel lenses polymer network are totally hydrophilic. In fact, they have both hydrophilic and hydrophobic portions, which are particularly important in Si-Hi materials. In hydrogels, the polymer network is filled with free water and bound water. In the free water the water molecules are bound to each other and to hydrophilic radical in the network. On the other hand, bound water molecules are more strongly attached to themselves and to the polymer network by both hydrogen and so-called hydrophobic bonds. Free water, moves easily within and out the polymer network, is easy to vaporize and is a good solvent for substances like some solutes in tears as sodium chloride, some medication in eye drops, etc. The solubility of compounds (i.e. ions, drugs, metabolites, etc.) in a hydrogel is a function of the content of free water. Conversely, bound water is strongly attached to the polymer network but in the right conditions can also evaporated from the hydrogel but at a slower rate that the free water. A third type of water is described by some authors, called the intermediate water as shows physicochemical properties somewhat between free and bound water because its molecular motion in the molecular space of the polymer shows behavior similar to that of bound water at lower temperatures and to that of free water with increasing temperature. This type of water is found loosely bound to hydrophobic groups or around the bound water molecules. Free and bound water are also known as freezing and non-freezing water.[56]

The proportion of bound water ranged from 8.2 to 14.5% in soft lenses on the range from 32.7 to 60.2% EWC. The same study concluded that although the material with NVP presented a slightly higher proportion of bound water, a correlation was not found between EWC and bound water except for those lenses where main constituent was HEMA with no additional comonomers.[70]

The proportions of bound and free water control the adsorption and desorption processes as lens dehydration, drug delivery, gas permeability in conventional hydrogels and hydraulic and ionic permeability. Adsorption of bound water and desorption of free water showed approximately an inverse relationship, especially for the glycerol methacrylate (GMA) group which showed easy water uptake and slower water release. On the other hand, NVP shows a more difficult water uptake and easy release as shown by Yamada and Iwata, 1982 (referred by Kanome).[70]

Directly related to these properties is the so-called water balance, proposed by Benz as an objective measure of the approximate on-eye performance of a lens. Water balance is measured as the ratio of the time it takes, *in vitro*, for a lens of constant thickness (approximately 0.10 mm) to loss 10% of its water weight and the time it takes to return to

EWC. This parameter is reported in relative values compared to p-HEMA, considered as the standard reference.

Figure 3.3 presents examples of the dehydration process of three SCLs. Initial dehydration rate (DR) is similar for different materials, however, medium and high EWC lenses, maintain or even increase the DR for longer periods while low EWC lens starts to decrease its DR faster. More details about this methodology of evaluating CL material dehydration under *in vitro* conditions will be given in chapter 10.

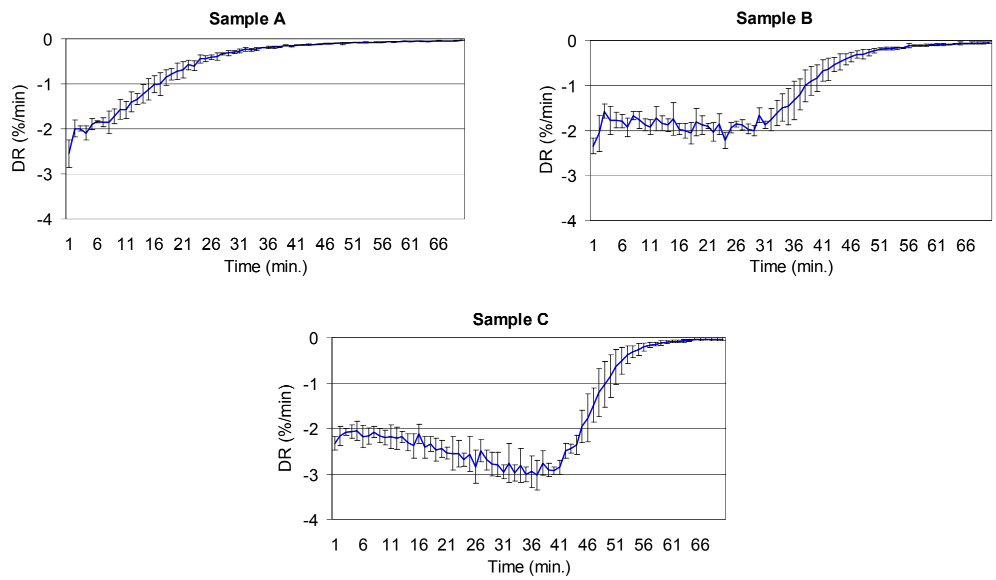


Figure 3.3. Dehydration curves representing dehydration rates (DR) during a period of 70 minutes for samples of three materials: sample A (low EWC), sample B (medium EWC) and sample C (high EWC).

Several factors affect the *in vivo* EWC of SCL including nominal EWC, lens thickness, pre-lens tear break-up time, ocular surface temperature, osmolarity, pH, relative humidity, wearing schedules, hydrogel material, blinking abnormalities, and cleaning regime.[71]

Hydrogels EWC also influences the design of CLs. For example, lens thickness depends on the EWC in such a way that high water content lenses must be produced with higher thickness in order to maintain physical properties and allow handling. Then, this is also related to the oxygen transmissibility (Dk/t) of conventional hydrogels that increases with EWC but decreases with thicker designs. As a result, high water content materials failed to satisfy oxygen needs for extended wear. Moreover, high EWC hydrogels have several handicaps, due to poor mechanical properties, higher interaction with components of tears and care solutions, and higher desiccation of the ocular surface. Benjamin[72] concluded that the most efficient combination between EWC, lens thickness and Dk/t is in medium EWC hydrogels. These hydrogels gained a great relevance in the field of disposable SCLs from mid 80's till present, some of them being widely prescribed for extended wear before the advent of Si-Hi CLs.

The close relationship between EWC and oxygen permeability in conventional hydrogels (non Si-Hi) is a result of the mechanism of gas diffusion through the aqueous phase within the matrix of these materials instead of through the solid polymer itself. Equation 3.1 presents the relationship derived by Morgan and Efron.[73]

$$Dk = 1.67 \cdot e^{0.038 \cdot EWC} \qquad \text{(Equation 3.1)}$$

However, this relationship is no longer valid for modern Si-Hi containing siloxane and fluorinated moieties. In these materials the solid phase instead of its liquid phase, is the most important contributor to oxygen permeability. This fact has made possible that CLs with near the softness and comfort of conventional hydrogels are available that can deliver all needed oxygen to the cornea, that has not been possible with conventional hydrogels CLs. Now, Si-Hi lenses with significantly lower water content than the conventional hydrogels provide significantly higher oxygen flux to the cornea.[48,48,74-77] Furthermore, as the Dk of conventional hydrogels decreases as EWC decreases (i.e. dehydration),[78] the opposite is true for Si-Hi SCLs.[79]

The EWC of hydrogel CL also depends on the solution used to hydrate the material. For example, Refojo[80] has shown that EWC in distilled water is about 1.03 to 1.08 higher than in 0.9% saline solution. Now, there are ISO international guidelines regarding the type of solution that most be used in SCL tests procedures.[81]

3.6.2.2. Linear expansion

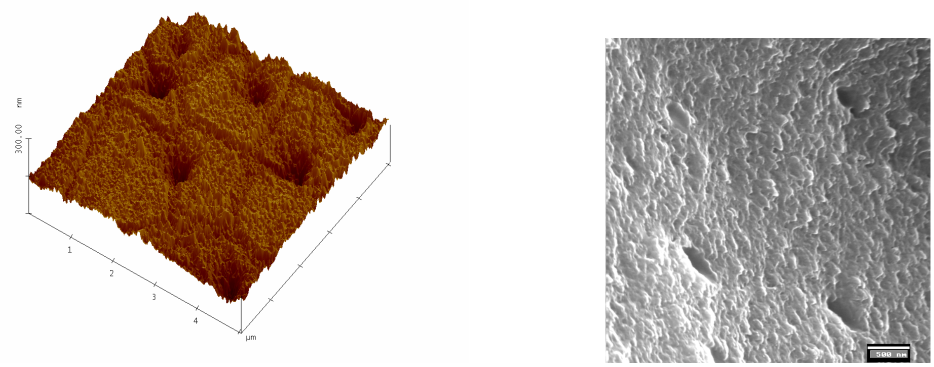
This parameter defines the difference between the dimensions of the polymer in the dry state and in the fully hydrated state. Percentage linear expansion (%LE) of hydrogel CL materials is represented according to the data of Refojo[80] by a linear relationship for materials with EWC ≤ 50% (low hydration) as described by equation 3.2. For materials with EWC above this value, the linearity is lost and the %LE increases exponentially as a function of EWC.

$$\%LE = -0.9 + 0.5 \cdot EWC \qquad \text{(Equation 3.2)}$$

This is a relevant parameter because it will affect the degree of parameter change (diameter, thickness and base curve radius) when the lens dehydrates during wear.

3.6.2.3. Pore size

The molecular arrangement of hydrogels creates pores that can potentially facilitate the diffusion of solutes and water across the lens. In order to be used as a SCL, the polymer should warrant a certain quantity of fluid to pass through the lens. Porosity is usually achieved by different methods of polymerization.[82] Pore morphology, density and size are usually controlled by the amount of NaCl present during the polymerization process.[82,83] As NaCl particles in the solution increase, the porosity of the hydrogel also increases.[82] Current literature differentiates between macro-porous hydrogels[82] and super-porous hydrogels.[84] Hydrogels used in CL manufacturing correspond with the macro-porous definition,[65] and these pores are only seen under high resolution macroscopy, without interference on the transparency of the material. We won't expand the discussion to other porous structures not suitable for optical applications.



(A) (B)

Figure 3.4. Macropores in the surface of a Si-Hi CL analyzed with Atomic Force Microscopy -AFM- (A) and scanning electron microscopy -SEM- (B).

A non-desirable result of the porosity of hydrogel CLs is the ability of some proteins, some lipids and other soiling entities from the tears to penetrate within the polymer meshwork.[37,85,86] In fact, one procedure to determine the pore size of polymers has been to determine the ability of entities of different molecular weight to penetrate the surface of the CL. Using dextrans of different molecular weights and molecular shape, lysozyme and serum albumin, Refojo and Leong[37] determined the pore size of different hydrogels. They concluded that the pore size should range from at least 19 angstrom (Å) for poly(glyceryl methacrylate-co-methyl methacrylate) [P(GMA/MMA)] of 41.5% EWC to at least 50 Å for hydrogels obtained from redox polymerization of aqueous solutions of glyceryl methacrylate (PGMA) with 76-85% of EWC. The presence of macropores, observable under specific microscopy techniques is not usual. However, larger structures similar to macropores have been observed in the Si-Hi CL Purevision (balafilcon A) using scanning electron microscopy,[65] and atomic force microscopy[67,87] shown in *figure 3.4*.

3.6.2.4. Oxygen permeability, transmissibility and related parameters

Oxygen flux through CLs has been one of the most important parameters investigated in CL research. According to the definition of Fatt,[88] oxygen permeability is the ability of oxygen molecules to move within a polymeric material. This property defined as "Dk" is specific for each material and can be obtained by multiplying the coefficient of diffusion "D" that is related to the circulation of oxygen molecules through the CL, and coefficient of solubility "k" that describes how many oxygen molecules are dissolved in the CL. Due to the complexity of terms involved, units of oxygen permeability are better known as barrer† or Fatt units. Tighe (2002) claims attention for the current change in Dk and Dk/t units as international community is changing the expression of pressure from mmHg for Pascal or hectopascal (hPa).[46]

The ability of any material to allow oxygen transport is specific of each material, per unit thickness (1 cm). However, if we want to know the actual amount of oxygen reaching the cornea through a given CL we have to consider the thickness of that specific lens. We obtain the oxygen transmissibility for a given CL by dividing the oxygen permeability of the material (Dk) by the average thickness of the given CL (L or t_{av}). This is a more representative parameter of the actual oxygen flux into the cornea, which is symbolized as "j" and is given by Fick's first law (equation 3.3) as a function of partial pressure of oxygen at the front of the lens (P_2 in mmHg) and at the lens-corneal interface (P_1).

$$j = \left(\frac{Dk}{L}\right)_{app} \cdot (P_2 - P_1) \qquad \text{(Equation 3.3)}$$

Oxygen transport is different in different CL materials. In conventional hydrogel whatever they have low or high water content, oxygen delivery to the ocular surface takes place mainly through the water phase, so the higher the water content, the higher the permeability. In these hydrogels EWC and Dk are correlated.[89,90] For the Si-Hi oxygen permeation occurs mainly through the silicone-siloxysilane portions of the solid phase in the hydrogel. Nevertheless, the water also contributes to the gas transport thought the Si-Hi as demonstrated by Compañ *et al.*[77] that found a slightly higher Dk value for the hydrated Si-Hi materials that for their xerogel (dry state).

† Barrer are 10^{-11} (cm^2/sec)[ml O_2/(ml x mm Hg)])

In the RGP lenses the oxygen transport occurs mainly through the voids created in the polymer network by the bulky TRIS moieties and through the TRIS radicals themselves, and a smaller amount through the portions of network rich in perfluoro radicals (organic entities where all the hydrogen atoms are substituted by fluorine atoms).

Gaseous (oxygen and carbon dioxide) exchange is of vital importance for the maintenance of normal ocular surface homeostasis and particularly cornea's physiology.[10] However, the insufficient oxygen transport to the cornea through conventional hydrogel CLs was a handicap for continuous (day and night) lens wear. The main breakthroughs in the CL industry were closely linked to the invention of materials with increasing oxygen permeability. It was the case in the sixties with hydrogels, in the seventies with RGP and high water content hydrogel SCLs, and in the late nineties with Si-Hi and high Dk RGP materials. The efforts of many investigators in academy and in industry were directed to an important goal of CL practice, which is to provide a day and night, safe and comfortable mean of vision correction with CLs (extended and continuous wear).

The oxygen transmissibility of a CL to satisfy the needs of the cornea was first provided by the Holden and Mertz's criterion,[16] which established minimums Dk/t of 24 barrer/cm to prevent corneal edema with hydrogel CL daily wear, and 87 to limit corneal edema under overnight CL wear to a level equal to the edema that occurs after overnight sleeping without CLs. More recently this criterion was revised and corrected by Harvitt and Bonanno,[15] so that the Dk/t target to limit overnight corneal edema to the normal physiological levels should be modified to values higher than 35 and to 125 Dk/t units for open and closed eyes respectively. Such numbers are so high that approach the normal conditions of corneal edema and limbal redness without CL on the eye.[91-93]

Three methods are most commonly used to measure oxygen Dk/t of CLs: polarographic, coulometric and gas-to-gas techniques, each one having advantages and disadvantages.[72,79,94] The polarographic methods was modified and used recently by Wichterlova *et al.*.[95] Also, an apparently simpler device was reported by Hadassah and Sehgal in 2006.[96]

Nevertheless, both Dk and Dk/L are only descriptors of CLs performance under specific and controlled conditions that provide an idea of the corneal needs for oxygen in ideal conditions, but in reality the amounts of oxygen required by the cornea varies from patient to patient and their environmental conditions. Therefore, new parameters to describe corneal oxygen performance were derived from the flux of oxygen onto the cornea under a CL, including equivalent oxygen percentage (EOP), biological oxygen apparent transmissibility (BOAT) and oxygen flux (j). In order to calculate these parameters, it is necessary to know the partial pressure of oxygen at the cornea-CL interface.[76]

Because direct measures of the concentration of oxygen at the surface of the cornea under a CL are difficult to obtain, it is estimated indirectly by the EOP, that represents the equivalent percentage of oxygen that will induce a certain hypoxic stress on the corneal surface. The most common approach to evaluate the EOP is to measure the oxygen uptake rate of the anterior cornea from a reservoir after the cornea has been exposed to known concentrations of oxygen.[97,98] Then, the amount of oxygen uptake by the cornea from the reservoir immediately after a CL was removed from the eye is correlated to the previously obtained EOP to find the actual oxygen concentration behind the CL. This approach assumes that the deficit of oxygen in the cornea during hypoxic stress with a CL is equivalent to that obtained from air with lower than 21% oxygen (at equivalent atmospheric pressure). Calibrated curves allow the conversion from depletion rates into EOP values ranging from EOP = 0 to EOP = 20.9% corresponding to the oxygen percentage in fresh air at sea level under standard pressure and temperature conditions. According with existent classifications, low, medium and high EOP values under CLs are considered for values lower than 6%, 6 to 11% and higher than 11%, respectively.[72] The main advantage of this parameter over Dk/t is that EOP determinations are not adversely affected by boundary layer and edge effects of CL materials and reflect more accurately the level of oxygen available at the corneal surface under CLs or whatever other hypoxic stimulus. According to data from Benjamin,[99] EOP and Dk/t are related by the logarithmic relationship expressed in equation 3.4 and shows that above Dk/t values of 140 barrer/cm, the curve tends to be asymptotic without significant improvements in EOP as CL Dk/t increases. Similar relationship has been obtained by Compañ *et al.* in a recent study and equation 3.5 represents the relationship found between EOP and Dk/t.[76]

$$EOP = 14.139 \cdot \log_{10}(Dk/t) - 8.960 \qquad \text{(Equation 3.4)}$$

$$EOP = 13.062 \cdot \log_{10}(Dk/t) - 9.0056 \qquad \text{(Equation 3.5)}$$

The biological apparent oxygen transmissibility (BOAT) concept arises from the need to reduce the scale of oxygen flux to the anterior corneal surface to the maximum of 5 μl/cm^2/hr, currently accepted as the maximum corneal oxygen consumption in the absence of any physiological barrier, at sea level. BOAT has been described by Fatt as the oxygen transmissibility measured for a sample modified by the biological properties of the cornea, which multiplied by the oxygen tension in air, gives the oxygen flux into the cornea. BOAT is expressed in the same units as the Dk/t, but their values depart from each other as the transmissibility of the material increases.[76,88] Two different equations have been derived by

Fatt for materials with Dk/t values below 25 barrer/t (equation 3.6) and materials with Dk/t between 25 and 60 barrer (equation 3.7).

$$Dk/t_{BOAT} = 7.70 + 0.158 \cdot Dk/t \qquad \text{(Equation 3.6)}$$

$$Dk/t_{BOAT} = 11.14 + 0.0305 \cdot Dk/t \qquad \text{(Equation 3.7)}$$

The "physiologically effective Dk/t" and "physiologically effective Dk" were also introduced by Hill[100] as predictors of CL performance and safety. While EOP is calculated from the "oxygen depletion rate" or "oxygen shortfall units", these two parameters are derived from the "hypoxic stress units" but the meaning is essentially the same.

Finally, recent research is being directed towards the computation of total corneal oxygen consumption as an index for describing corneal oxygenation. The point is to know how and where oxygen is consumed, more than solely consider the flux of oxygen into the cornea (j).[76,101]

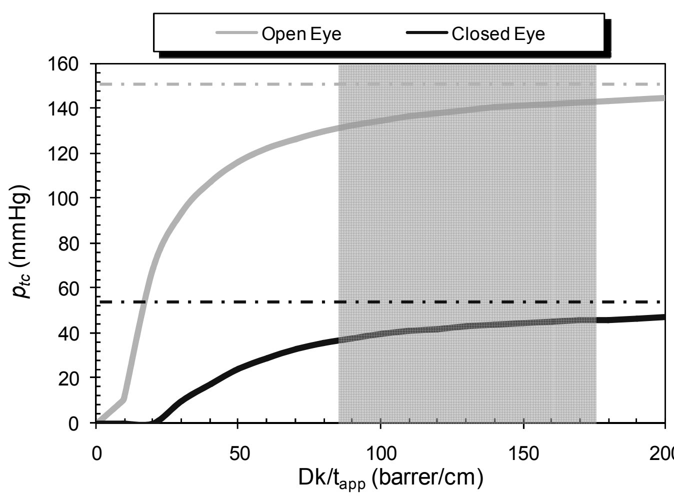


Figure 3.5. Partial pressure of oxygen under CLs (p_{tc}) of different Dk/t under open (light line) and closed eye conditions (dark line). Modified from Compan *et al.*[76] Shaded area corresponds to the range of Dk/t values for Si-Hi materials.

Brennan[102] reported that values of Dk/t of 15 and 50 barrer/cm will be enough for the cornea to satisfy 96% of its normal oxygen consumption under daily wear and overnight wear conditions respectively. The findings of Compan *et al.*[76] showed that CLs with oxygen transmissibility higher than 100 barrer/cm provide the lens-cornea interface with enough oxygen tension to substantially reduce additional oxygen flux onto the cornea. According to their results, in lenses with Dk/t>70 barrer/cm, partial pressure of oxygen only reflects modest increase despite significant increase in Dk/t.

3.6.2.5. Hydraulic and ionic permeability

Until mid nineties, the main properties considered to evaluate CL compatibility were oxygen permeability, wettability, resistance to deposits and to a lesser extent, mechanical properties. It was from a patent that the question of ionic and hydraulic permeability arose as a key question for on-eye Si-Hi CL behavior.[48] Ion and hydraulic permeability are described together as ion transport can only happen dissolved in water. Nowadays, it is accepted by the clinicians and researchers that ion permeability in Si-Hi is essential to warrant lens movement on the eye, which is essential for all CL compatibility with the ocular surface. Some researchers agree that a certain level of ion permeability is necessary to avoid Si-Hi lens binding, but above that level, further permeability does not warrant an increase on the lens movement. However, although ion permeability and Si-Hi lens movement are related, there is not scientific proof to justify this dependence. It is clear that a tear layer behind the lens is essential to facilitate lens movement, but lens thickness seems to be less important.[45] In conventional hydrogels, water permeability follows a similar behavior that oxygen permeability because of their similar molecular size. Also, ions such as sodium and chloride diffuse though the aqueous phase of hydrogels, following similar relationship. According to Tighe, the minimum EWC to warrant ion and water permeability in a CL is 20%.[103] The diffusion of small ions as sodium and chloride increase as the EWC of the hydrogel increases. Therefore, the diffusion of these ions in a 20% EWC hydrogel would be substantially smaller than that of 50% EWC hydrogels. In the Si-H, the higher the Dk, the lower is the EWC, so one would think that the lower EWC in these materials the lower would be their water and ion permeability. On the other hand, the polymer network of the Si-Hi consists of two localized phases, one rich in siloxane moieties somewhat segregated from a hydrophilic phase swollen in water. Such a structure leads to a higher porosity than that of the conventional hydrogels, and hence more permeable to water and ions than a conventional hydrogel of similar hydration. At difference from earlier Si-Hi CLs, a new Si-Hi lens (Biofinity, Coopervision) shares a high Dk (128 barrer) with the highest EWC (48%) for this kind of materials. The benefits and handicaps of this new combination of properties is still to be shown.

Liquid water can move across a membrane through two mechanisms called *bulk flow* and *diffusion*. Water movement through hydrogels is usually considered as diffusion, where water molecules move independently of each other driven by a concentration gradient. Bulk flow present in porous membranes consists on the movement of water molecules driven together through the pores by a gradient in hydrostatic pressure. Diffusion of water vapor is governed by vapor pressure gradient, thermodynamic activity, which depends on the difference of vapour pressure (activity) of water at both sides of the membrane. In the inner side of the membrane could be water vapor and liquid water, but only water vapor in the outside. Diffusive permeability is responsible, for example, for liquid water pervaporation through silicone rubber membranes or CLs. Pervaporation is a phenomenon of clinical significance in CL wear. During pervaporation of tear fluid through CLs, the water reservoir present behind the CL permeates though the material and evaporates at the front lens surface when the water saturation of air is below 100% relative humidity.[104] This effect is usually related to two other relatively common complications of SCLs, lens binding and punctuate staining.[105] An osmotic mechanism could explain these two situations which could be particularly serious under overnight CL wear because in the absence of tear evaporation a hypotonic tear environment surrounds the CL. This situation has proved to be associated with depletion of the post-lens tear film.[106]

In addition, under open eye conditions, if the front surface of a hydrogel CL dehydrates, the difference on swelling pressure between the anterior dryer portion and the wet post-lens increases the diffusion of water from the post-lens space to the front lens surface where continues evaporating at rates depending on the environmental conditions. This could be particularly important not only in lenses made of silicone rubber, presenting a high water vapor permeability but also with SCL, particularly those with thinner designs and high EWC.[104] Ultra-thin, hydrogel content lenses were associated by Little and Bruce to higher pervaporation resulting in corneal staining under open eye conditions.[105] Thus, pervaporation explains the thinning of the post-lens tear film and supports the mechanism of lens binding and punctuate keratitis seen in SCL wearers.

Recent research conducted by Weinmuller *et al.*[107] reported that water vapor diffusion coefficient (D) increases significantly with water concentration for polymacon (38% EWC) and hilafilcon A (70% EWC) (from approximately $0.3 \cdot 10^{-8}$ to $4.0 \cdot 10^{-8}$ cm^2/s) because of augmented free volume related to higher EWC, whereas a more complex composition dependence was observed for alphafilcon A (66% EWC) and balafilcon A (36% EWC) probably as consequence of a combined effect of polymer relaxation, plasticization, and water clustering. Balafilcon A shows the highest diffusivities at given water weight fraction ($3.5 \cdot 10^{-8}$ to $8.0 \cdot 10^{-8}$ cm^2/s). This effect has been attributed by the authors to the great water-vapor diffusion coefficient of PDMS in the SiHi lenses. This agrees with the results reported by Tighe[48] for the two first available Si-Hi materials. This author quoted a value of ionic permeability for lotrafilcon A and balafilcon A as being twice the ionic permeability of PHEMA (polymacon). The higher hydraulic permeability of these materials could be related with some degree of separation of hydrophobic and hydrophilic portions of the network.

The other clinical area of interest is hydraulic and ionic flow of tears (tear exchange) between the interface lens-cornea and the pre-lens tear film, as lens movement on the eye depends on the ability of tears to be pumped in and out of the lens-cornea interface, particularly to prevent CL binding. These tear exchange is even more important for lenses that are to be worn day and night. During sleeping there is not only the lack of blinking needed for tear pumping under the lens, but also lower volume of tears on the eye, and increasing post-lens tear thinning by lid pressure and osmotic absorption into the cornea. The removal of debris at the interface lens-cornea upon blinking is also important.[108] Those considerations are of special interest in SCLs because of their large diameter and close-fitting to the anterior ocular surface that limits CL movement.

Hydrogel materials hold water and expand its polymer network. Ions and molecules, when are soluble in water have the potential to enter into the hydrogel network depending on their molecular size and shape, as well as the pore size in the hydrogel. The pore size of low-water content lenses is about 0.5 μm and may be as high as 3.5 μm with high-water lenses.[109] Recent observations of Si-Hi materials support the existence of macropores in the balafilcon A material.[65]

Refojo[110] reported that the self-diffusion coefficient of water molecules in pure water was 2.8 x 10^{-5} cm^2/sec at 25º C in poly-HEMA 38.7% water content. However, Yamada and Iwata[111] reported a diffusion coefficient of 5.7 x 10^{-5} cm^2/sec at 25º C for the sorption process of water in poly-HEMA. These differences in the diffusion coefficient of water in hydrogels was explained by Kanome[70] as a result of the retarded water movement induced by the hydrogen bonds between the polymer and water once this has been adsorbed. Under open-eye conditions, and particularly under certain environments, a higher hydraulic permeability would not be desirable as it will increase the so-called evaporative–dehydration process.[112] If the water loss rate from the lens is sufficiently high, the post-lens tear film may be depleted leading to corneal desiccation[113,114] and lens adherence to the cornea.[115]

Different strategies have been considered to increase CL hydraulic permeability. Fenestration was the commonest assayed with PMMA impermeable hard lenses in the seventies.[33] The same approach was also followed with a new thick SCL for keratoconus with two fenestrations or pressure balancing holes (PBH) of which primary goal was to avoid negative pressure and to increase tear mixing under the CL. More recently Miller *et al.*[116] performed 40 fenestrations 100 μm in diameter in Si-Hi CLs, obtaining a significant improvement in tear mixing under the CLs.

Recent studies demonstrate that ophthalmic solutions have pH values that vary within a wide range.[117] Such conditions could affect the EWC of hydrogels CLs. Gemeinhart *et al.*[118] demonstrated that superporous hydrogels are sensible to pH variations. Also, hydrogel CLs that contain ionic moieties and high EWC hydrogels are more affected by the environmental conditions than nonionic hydrogels and lower EWC. Refojo (1976)[119] showed that pH sensitive hydrogels used in CL manufacture can change their EWC from 58% to 43% with small changes in pH of the solution from 6.75 to 6.20, respectively. Of course this facts have implications on the dynamics of drug release from hydrogel CLs as demonstrated by Hiratani and Alvarez-Lorenzo,[120] that modulated the composition of the lenses to adapt the drug loading and release behavior for the treatment of specific pathological processes.

3.6.2.6. Density

Density, or specific gravity of all CLs depends on the polymeric composition, and, of course, for hydrogels on their EWC. Typical density of SCLs ranges from 1.16 g/cm^3 for polymacon (38%) and 1.05 g/cm^3 for a hydrogel of higher EWC (75%) at 20º. For current RGP, typical values of density are within a narrow interval from 1.1 to 1.2 g/cm^3. Refojo and Leong[121] demonstrated the strong relationship between material composition and density and developed a method to identify the early RGP CLs, that at that time did not contain perfluoro moieties.

Clinical implications of RGP material density are stronger than for SCL as the smaller diameter and inability to conform the ocular surface of those lenses gives gravitational force a higher role on lens movement and centration, mainly in inter-palpebral lens fitting. Increased lens mass is associated with lower lens position, which should increase the incidence of 3 and 9 o'clock staining in corneal lenses.[122]

3.6.3. Mechanical properties

An adequate mechanical behavior is essential for CLs to promote a good interaction with the ocular surface. However, it is necessary to reach a balance between strength to avoid tearing, scratching and allow ease of handling and, on the other hand, a CL should be being as soft and flexible as possible to be comfortable on the eye.[120] Different parameters are related with the mechanical behavior of a polymeric material: strength, toughness (tensile, compressional, flexural, torsional, impact), elastic modulus, and elongation to break.

The important mechanical properties for RGP materials are those that affect their stability, mainly resistance to flexure and to temporal or permanently deformation. Some of these properties are also important to SCL, but tensile strength and resistance to fracture are more important.

Polymer stability is determined by the incorporation of cross-linking agents that usually represent around 1% of the mixture. Lens flexure has been identified as a principal source of on-eye aberration of current CLs. The effectiveness of future aberration-free CLs will rely strongly on the ability of materials to maintain their parameters.[123,124] The stability of the RGP lens topography depends on the polymer composition and thickness of the lens.

Thinner RGP lenses and lenses with higher proportions of siloxane and fluorinated monomers, instead of PMMA, because of lens flexure, have high risk of inducing astigmatism.[125,126] It is generally accepted that RGP lenses should have a center thickness above 0.12-0.15 mm to avoid flexure.[127]

Mechanical tests on CLs are carried out using instruments that measure the amount of deformation per unit of force.[128,129] For example, clamping each end of a sample, and measuring the length stretched while measures the force that it is exerting. In compression tests, an indenter compresses the sample. The displacement of the machine while is stretching or compressing the sample, represents the strain that the sample suffers in response to the stress exerted. The stress-strain curves are used to derive the mechanical properties of the sample. It can be also measured at a nanometric scale using nano-indentation with AFM.[64,130] It is necessary, however, to differentiate between bulk and surface elastic properties.[131] As SCLs are prone to dehydrate while on the eye, surface modulus could be higher than bulk modulus, due to surface dehydration. Instruments used to compress a sample or to pull both extremes of a sample are useful to evaluate bulk properties of materials, ignoring or minimizing the surface properties. On the other hand, nanoindenttion with AFM reflects a more reliable measure of surface modulus, and should be potentially more directly implicated in the clinical behavior of the CL on the eye and more representative of the mechanical interaction with the ocular surface.

3.6.3.1. Elastic and plastic deformation of materials

Deformation of materials in response to stress is a form of energy dissipation to avoid break. This is a desirable behavior in CLs that are subjected to stress during handling and under the eyelid pressure. However, deformation can be transitory or definitive depending on the properties of the material.

When a material is subjected to stress, there is a part of the induced deformation (strain) that is not permanent, so that the material can completely recover to its original state without permanent deformation; this is called elastic deformation. Conversely, the part of the strain that cannot be recovered after ceasing the stress is called plastic or viscous deformation. The higher the elastic component of a material means that the material will easily recover after removing the stress. The higher the viscous component the most likely is that stress will produce an irreversible change. An example of almost ideal elastic material is silicone rubber (elastomer) which can be stressed with an almost immediate total recovery after the stress has ceased. On the other hand, a strip of parafilm, used in laboratory preparations can be considered as a viscous material, as when you stretch the sample to elongate it, this elongation (deformation) is permanent even after you have ceased the stress.

Similarly, if one compress or indent the sample, a permanent deformation will occur as a result.

However, CL materials different from silicone rubber CLs, are not ideal elastic or ideal viscous materials and they are not desired to do so. Usually, when we submit hydrogel materials under a force, the material reacts first in a linear manner so that the strain is linearly proportional to the stress. This is the elastic component of the material and the part of the stress-strain curve used to compute elastic modulus, also known as Young modulus. After a certain point called yield point, the material becomes less resistant to stress so that strain increases continuously with small changes or even with the same amount of stress. Finally, when de material cannot dissipate more energy, the sample breaks and the test is over. *Table 3.2* provides values of elastic and viscous components for different Si-Hi materials as reported by different authors. It is clear that first generation and the first lens of the second generation Si-Hi materials present the highest elastic modulus, elastic component and friction coefficients.

3.6.3.2. Strength

There are different forms to measure the strength of a polymer. Tensile strength is important for materials that are subjected to longitudinal stress. Compressional strength is important for materials that have to support weight, so it represents the resistance of a material to support transversal stress. Flexural strength is the resistance of a material to bend. Torsional strength is the resistance to suffer strain (deformation) when one tries to twist an object. Impact strength is the resistance of a material to a sudden hit.

The designation "tensile properties" is sometimes used in the literature of CLs to quote several mechanical properties as tensile strength, Young modulus and elongation at break. Tranoudis and Efron[128] evaluated these properties in copolymers of HEMA or HEMA+VP (EWC 40%), HEMA+MA, HEMA+MMA or HEMA+VP(EWC 55%) and HEMA+VP, HEMA+MA or VP+MMA (EWC, 70%). Despite the intuitive idea that tensile properties will depend primarily on EWC, no relationship between EWC and the three parameters under study was observed by these authors. As a general summary, they found that VP conferred higher tensile strength, high elongation to break and moderate to low Young's modulus. Conversely, the incorporation of MA in the polymer composition, even at very low proportions (less than 5% of dry weight) resulted in a weaker overall mechanical strength.

3.6.3.3. Elastic modulus

Elastic modulus or Young modulus represents the stress (force per unit of area) required to produce a unit of recoverable strain (elastic deformation) in a material. In other words, elastic modulus is a measure of how well a material resists reversible deformation. It is defined by others as the force per unit area required to compress the material by a given amount.[61] Units are MPa (MegaPascal or 10^6 N/m^2) and this material property has received increasing attention in the CL literature since the advent of Si-Hi materials.

It is the great molecular length of polymers in relation to their cross-sectional diameter that gives them the property of elasticity. SCLs have a modulus of elasticity much lower than RGP CLs (≈1800 MPa), particularly those based on HEMA, also called as conventional hydrogels (≈0.3 MPa). First generation Si-Hi have a higher modulus (1.1-1.4 MPa) than conventional hydrogels and some of second generation Si-Hi (0.4-1.2 MPa).

Although necessary, excessive elasticity of CLs can cause problems to the ocular surface under blinking conditions as the lens squeezes the surface damaging the epithelium. Along with the relatively hydrophobic nature of Si-Hi materials, the tear film behind the lens is likely to be absent and the friction increases or the lens can bind over the ocular surface. First generation Si-Hi, were found to induce mechanical changes in both cornea and conjunctiva, resulting in conjunctival indentation,[132] trace central corneal flattening,[133] and superior epithelial arcuate lesions.[134] Epithelial indentation is observed after removal of these high-Dk/t materials and is presumably related to the increased incidence of spherical post-lens debris, which has been termed “mucin balls” or “lipid plugs”.[44,135] The incidence of spherical debris behind the lens are probably linked to a higher modulus of Si-Hi CLs.[48]

The new generation of Si-Hi CLs started with Acuvue Advance (Johnson & Johnson, Jacksonville, FL). One of the aims of this material was to provide a lower modulus of elasticity (comparable to that of the mid-water content conventional hydrogels CL) than that of the original Si-Hi lenses and at the same time to keep the Dk at higher values.[62] Such characteristics are attributed to the incorporation of PVP in the polymer for hydration and flexibility. This component gives the CL a satisfactory surface wettability without surface coating or special treatments. More recently, four new materials have been released and all of them have a lower modulus than the first generation of silicone- hydrogel CLs; the newest material in this group is Biofinity. The properties of the six Si-Hi materials currently available are displayed in *table 3.2*.

Overall, modulus is in some way related to EWC in hydrogel CLs, and the higher the EWC the lower the modulus. A clinical consequence of this is that increasing water content reduces resistance to tearing. The elongation to break of an early experimental Si-Hi CL was estimated between 200% (% representing the elongation at break) and 250%.[56]

The other extreme of mechanical properties of CLs is that of the RGP lenses. In this case, excessive flexibility could lead to lens flexure and visual distortion. Ostrem *et al.*[136] reported modulus of elasticity from 1300 to 2200 MPa for RGP and rigid PMMA lenses with Dk/t values ranging from 127 to 0.02 barrer/cm, respectively. The higher proportion of siloxane and fluorine moieties within the polymer the lower the rigidity.

3.6.3.4. Hardness

Hardness represents the resistance of a material to indentation when a known load is applied. It can be calculated according to Meyer as the quotient of the maximum load by the contact area between the tip and the material. This property is not widely used to characterize SCLs, and is usually applied to RGP CLs. Different methods and scales have been created to quantify hardness. Shore and Rockwell scales are the most commonly used to characterize RGP materials. In such materials, hardness decreases in high-Dk materials containing TRIS siloxane and perfluroacrylate moieties (Shore ≈ 80-85; Rockwell ≈ 110-115) versus RGP materials without the perfluoro radicals (Shore ≈ 85-90; Rockwell ≈ 115-120).

3.6.4. Optical properties

3.6.4.1. Transmittance and absorption

Transparency is an essential property of materials for whatever optical element, including CLs. All CLs with refractive purposes are made of transparent materials. The first attempts to obtain biphasic materials combining hydrophilic polymers with siloxane moieties resulted in non transparent materials because of separation of phases with sizes that exceeded the wavelength of visible light (≈500 nm) which induced light scattering and opalescence.

Transmittance and absorption of light along with reflection and diffusion are related to the quality of image obtained through a given optical device. Some of them incorporate UV blocking filters for eye protection and special tints for a better visibility with handling purposes as the reactive dye #4 incorporated in the formulation of some recent CLs. Because of the increasing emphasis on the hazards of excessive exposure to the sun's harmful rays,[137,138] some CLs incorporate UV-blocking capabilities.[139-141] Protection against UV is recommended for all patients and specially aphakic patients, those who participate in prolonged outdoor activities, and patients taken photosensibilizating drugs. Wearing UV-blocking CLs in association with other forms of eye protection offers the maximum protection. Acuvue Advance is the first Si-Hi lens to incorporate UV blocking and the first SCLs marketed to meet the strictest standards for Class I UV blocking. The lenses block more than 90 per cent of UV-A rays and over 99 per cent of UV-B rays, and offer the highest protection of any soft lens. A recent CL polymer with such a property is Acuvue Oasys, (senofilcon A), which incorporates benzotriazole as UV absorbing monomer. This warrants less than 1% transmission in UVB region (280-315 nm) and less than 10% in UVA region (316-380 nm). This superior UV-blocking capability has the benefit of extra reassurance for patients concerned about the hazards of excessive UV.[62]

3.6.4.2. Refractive index

As the refractive index (RI) is a specific characteristic of each monomer, RI of CLs is directly related to material composition and the EWC in SCLs (water RI = 1.33). In fact, the method most commonly used for the measurement of water content consists on the determination of the RI with a refractometer.[142] This is possible because of the close relationship between EWC and the RI of the polymer. Thus, for hydrophilic lenses, higher hydrated materials have a lower RI and materials with lower water content, have a higher RI.[143]

Measurement of RI can be obtained with Abbe refractometers,[144] manual refractometers[31] and modern automatic refractometers.[145] Despite most of them were not intended for the determination of water content on CL materials, hand-held refractometers have been widely used for the last decades demonstrating acceptable levels of accuracy and repeatability for clinical and experimental research.[31,146-149] Nowadays, it is possible to obtain higher levels of accuracy with automatic refractometers.[145] Results from both hand-held manual and automated refractometers can be used interchangeably using the statistical equivalences between EWC as measured with a hand-held refractometer and RI measured with an automated refractometer determined by our group.[150]

RI of CLs is an important parameter from the optical perspective, particularly in back toric RGP lens fitting, as this parameter governs the amount of astigmatism induced by the posterior toric surface. Among other relevant interactions, in CL practice, RI affects optical power and design of CLs, induced astigmatism with rigid toric lenses or lens flexure. For RGP, RI ranges from 1.42 to 1.46 for fluorosilicone acrylates (FSA) materials and 1.46 to 1.48 for silicone acrylates (SA) materials. RI of PMMA is about 1.49. Tranoudis and Efron, measured a wide range of RPG CLs, concluding that values ranged from 1.430 to 1.485. Their results suggested that as a general rule, lenses with refractive indices lower than 1.458 are made from FSA; lenses with refractive indices in the range of 1.458 to 1.469 are made from either fluorosilicone acrylate or SA; and lenses with refractive indices greater than 1.469 are made from silicone acrylates.[146] Those results did not differ greatly from the classification established by Hodur *et al.*[151] who classified as fluorosilicone acrylates those lenses whose RI were below 1.460 and silicone acrylates those lenses whose RI were above this value.

Furthermore, recent developments in the compensation of wavefront aberrations through CLs use different principles, but all of them try to compensate the advance of retard in the local wavefront by shortening or enlarging the optical pathway by changing curvature, RI or thickness.[152,153]

In SCLs, RI is also important because of its relationship with EWC that allows to objectively measuring this important parameter with simple and low cost devices.[143] RI has been used to estimate the water content of new lenses[142] as well as dehydration of worn lenses.[147] Common values for hydrogel CLs range from 1.38-1.41 for high EWC lenses and 1.42 to 1.44 for low and medium EWC lenses and Si-Hi materials. However, clinicians and researchers attempting the systematic determination of EWC or RI of current SCLs must be aware of the different relationships between these two parameters in Si-Hi materials when compared with conventional materials.

The estimation of the RI of hydrogel materials can be achieved by refractometry to obtain direct[145] or indirect[71] measurements. In refractometry, the water content is determined by measuring the RI of the CL relative to the RI of the prism used in the refractometer.[143] Refractometers can either measure percent water or solid content in a solution or hydrogel material.

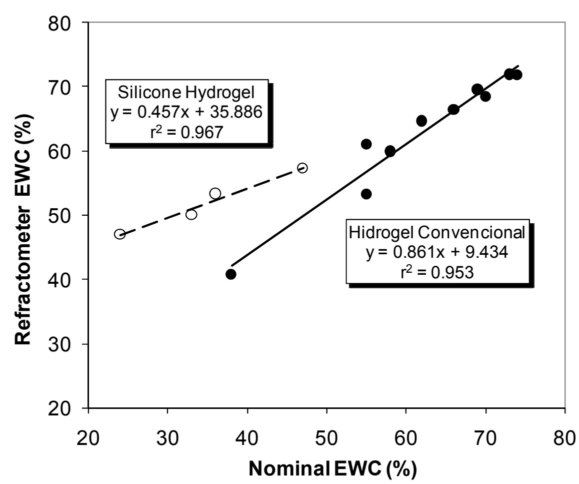


Figure 3.6. Relationship between nominal EWC and EWC measured with a manual refractometer for conventional hydrogel and Si-Hi CLs.

The Atago N-2E (Atago, Ltd. Tokyo, Japan), is a hand-held refractometer that measures the percentage of sucrose in a solution (Brix scale‡) within a range of 28 to 62%. This means that water contents ranging from 38 to72% can be measured with this device. This instrument has also been used to measure the water content of hydrogel lenses.[71] This

‡ Brix scale represents the number of sucrose grams in 100 g of sucrose solution

instrument provides indirect measures as the scale reads the percentage that represents the solid part of the polymer, which then can be converted to percentage values of hydration. Finally, by applying statistical relationships, RI can be determined for conventional HEMA-based hydrogels.[142]

On the other hand, the CLR 12-70 provides direct RI readings with minimal influence of operators hand, and has demonstrated excellent within and between-operators reliability.[145] Conversely, to obtain EWC, the same statistical relationships previously quoted should be applied.

However, modern Si-Hi CLs do not follow the same relationships between RI and hydration, what should be taken into account for clinical and experimental evaluation of both parameters in this kind of materials. This seems to be due to the lower RI of siloxane when compared with conventional hydrogel materials. As a consequence, lenses with lower water content as Focus Night & Day (lotrafilcon A – 24%) display a lower RI than expected simulating a higher content of water than they actually have. However, these kinds of materials follow their particular linear relationships that have been recently elucidated. As a result, EWC of Si-Hi materials measured with a refractometer does not provide the actual value, because these materials do not follow the relationship between Brix values and RI. *Figure 3.6* illustrates the different relationship between nominal EWC and EWC obtained with a refractometer by measuring the RI of the polymer. This subject will be expanded in more detail in chapters 7 and 8.

3.7. Current developments

In the last 30 years we have assisted to a revolutionary change in the field of CL materials, with important developments in the last 5 to10 years as it was the case for the so-called biomimetic or biocompatible materials (omafilcon A, hioxifilcon family), first generation Si-Hi (balafilcon A, lotrafilcon A) and second generation Si-Hi (galyfilcon A, lotrafilcon B, senofilcon A and comfilcon A). The second generation Si-Hi have higher water content (33 to 48%) and lower Young modulus than the first generation materials, and hence better mechanical interaction with the ocular surface. The most recent CL incorporation to this group is comfilcon A which represents the most significant evolution in this field, with 48% water content, no surface treatment and high oxygen transmissibility (160 barrer/cm) for standard thickness. Si-Hi CLs already represent a large proportion of new fittings and re-fits in certain markets. Their application for daily wear, because an overall improved environment to the ocular surface is expected to reduce the incidence of serious complications observed with previously used extended wear lenses.

Other innovation in CL materials is represented by tinted lenses Maxsight (Bausch & Lomb) intended to improve visual performance in outdoor sports. To date, no clinical reports have been published on the objective performance of these lenses, but when compared with clear lenses made of the same material, apparently they do not affects the visual ability of human subjects to detect a flicker light as measured with an instrument to detect the internal light scattering of the ocular media (*unpublished data from* Cerviño and González-Méijome).

Table 3.3. Names assigned by the USAN to hydrophilic CLs for the last 10 years in chronological order[154]

USAN Name	Year	Manufacturer	Trademark
balafilcon A	1994	Bausch & Lomb	PureVision
bisfilcon A	1994	Vistakon J&J	-
siloxyfilcon A	1994	Permeable Technologies	LifeStyle MultiSoft
abafilcon A	1995	Pilkinton Barnes Hind	-
hioxifilcon A	1995	Benz Research	Benz 55G
hioxifilcon B	1995	Benz Research	Benz-G45
omafilcon A	1995	Biocompatibles International Inc.	Proclear
genfilcon A	1996	Vistakon J&J	-
lotrafilcon A	1996	CIBA Vision	Night & Day
nelfilcon A	1996	CIBA Vision	Focus Daylies
epsifilcon A	1997	CooperVision, Inc.	-
hilafilcon A	1997	Bausch & Lomb	Award
hilafilcon B	1999	Bausch & Lomb	Award
acofilcon A	2002	Contamac, Ltd	Contaflex GM3 58% (Soft K67-Soflex)
acquafilcon A	2002	Vistakon J&J	-
galyfilcon A	2002	Vistakon J&J	Acuvue® Advance
hioxifilcon C	2003	Benz Research	Benz-G® 10x
senofilcon A	2003	Vistakon J&J	-
comfilcon A	2005	Coopervision	Biofinity

[a]: approval for 1-7 days extended wear; [b]: approval for 30 days continuous wear

Tables 3.3 and *3.4* summarize the new CLs names assigned by the USAN since the year 1994.[154,155] Despite some concerns about the future of RGP CLs,[156] we can see that the industry, for the last 10 years, has introduced new RGP CL materials almost at double the rate that hydrogel CLs (27 new RGP against 18 new hydrogel CLs). This trend is more evident in the last 5 years, with 10 new RGP CLs against the 6 new hydrogel CLs. With the new RGP lenses, the novelty was not only in materials, but also new geometries, so that these lenses have caused higher impact on the market than the new hydrogel Cls in we exclude the case of Si-Hi CLs. The search for high Dk materials with complex geometries for use in overnight orthokeratology has stimulated their development, and created renewed interest for a type of lenses (RGP) whose fitting is at its lowest level since their invention in the seventies.

In the area of design and optics, the improvements of current multifocal soft and RGP CLs, and the hope on future improvements, make CL practitioners to be confident of the future of CL practice, not only for CL industry and CL fitters, but as a convenient solution to the millions of presbyopes that will need optical correction in the next few years, particularly in those countries where CLs are now widely used by people in their 30's.

Table 3.4. Names assigned by the USAN to RGP and hybrid CLs for the last 10 years in chronological order[155]

USAN Name	Year	Manufacturer	Trademark
enflufocon A	1994	Polymer Technology	Boston® 7/30
lotifocon B	1994	Stellar Contact Lens, Inc	OP-2
lotifocon C	1994	Stellar Contact Lens, Inc	OP-6
pemufocon A	1994	Innovision Inc.	AccuCon
satafocon A	1994	Polymer Technology	Boston VII
sterafocon A	1995	Optical Polymer Research	PERM30-O
wilofocon A	1995	Futuristic Drug Design	Flosi
crilfocon A	1996	G.T. Laboratories	Sil-O-Flex IV
crilfocon B	1996	G.T. Laboratories	Sil-O-Flex II
flusilfocon E	1996	G.T. Laboratories	Fluorex 600
carbosilfocon A	1997	Specialty UltraVision	UltraCon; Epicon
enflofocon B	1997	Polymer Technology	-
hexafocon A	1997	Wilmington Partners L.P Polymer Technology	Quantum II
itabisfluorofocon A	1997	Wilmington Partners L.P Polymer Technology	Boston® RXD
itafluorofocon A	1997	Wilmington Partners L.P Polymer Technology	Boston® RXD
oprifocon A	1997	Polymer Technology	Boston Equalens II
paflufocon E	1998	Paragon Vision Sciences	PVS Basics
hofocon A	2000	BioMed Devices Co.	-
onsifocon A	2001	The Lagado Corporation	-
paflufocon F	2001	Paragon Vision Sciences	-
sulfocon B	2001	Progressive Optical Research, Ltd.	The Alberta Lens™ SM2
onsifocon A	2001	The Lagado Corporation	-
paflufocon F	2001	Paragon Vision Sciences	-
sulfocon B	2001	Progressive Optical Research, Ltd	The Alberta LensTM SM2
migafocon A	2002	Paragon Vision Sciences	-
hybufocon A	2002	Contamac Ltd.	Hybrid FS

A new hybrid CL with an optical portion made of a high Dk RGP material has been also recently introduced to the CL market to correct myopia and hyperopia. However, the use of this lens on keratoconus corneas is one of the most interesting applications [FDA Package Insert, SynergEyes® A and SynergEyes® KC for keratoconus (paflufocon D – hem-iberfilcon A)]. This material provides the finest optics of RGP CLs along with the centration and comfort of SCLs. The high Dk of the center (optical) portion of this hybrid RGP CL provides better oxygenation to the cornea than previous hybrid CLs. Nevertheless, large clinical studies reporting the tolerance of this lens are still to be done.

Also of important is the treatment of CL surfaces with selenium to improve resistance to bacterial adhesion. Currently these CLs are being tested in animals with some success. However, their use in humans without local and/or systemic side effects has not yet been demonstrated.[58]

Other area of great activity in relation to CL has to do with new CL care solutions, and devices to improve the easiness and effectiveness of CL disinfection procedures without side effects.[157] The interaction of CL treated with specific CL solutions, with the ocular surface, particularly in Si-Hi CL wearers, is also a subject that is getting much attention because of the episodes of recurrent superficial keratitis associated with these conditions.

Currently we are getting a deeper knowledge of the properties of CL materials, particularly of new Si-Hi, and how they interact with the ocular surface, cleaning solutions, bacterial adhesion, and deposit formation, of major importance to overcome problems of biocompatibility and long-term tolerance of CLs.

3.8. Conclusions

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

While the high oxygen permeable CLs have solved many hypoxia-related clinical problems, complications related to inflammation, infection and mechanical insult to the cornea still occur with current CLs. The first Si-Hi CL of relatively high water content galyfilcon A (Acuvue Advance, Johnson & Johnson) has significant lower oxygen permeability. The exception is comfilcon A (Biofinity, Coopervision). These lenses, which have been just launched to the marketplace and the next generations of CLs should improve their resistance to dehydration, tear deposits, bacterial adhesion and deposit formation. They should also have less interaction with the ocular surface in terms of mechanical stress, and no absorption of preservatives used in lens care solutions.

The production of high-volume of Si-Hi CLs at lower costs will be very important for the use of these lenses as daily disposable, an excellent option for daily wear CLs. This strategy should be very important to reduce the incidence of deposits and superficial keratitis, and eliminate the problems related to lens care solutions, as occurred with the use of actual Si-Hi CLs.

Finally, the CLs that will be safe for continuous wear for periods longer than thirty days are still to be developed. Again, true resistance of the materials to lens deposits, bacterial attachment and dehydration will be key factors for success. Regarding the RGP CLs, despite their use is diminishing in most countries, they are still necessary for use in keratoconus, orthokeratology, and post-surgical fitting among other applications. Furthermore, for the rebirth of RGP CLs further research and development is crucial to improve their short-term comfort where surface properties, back surface and edge design are probable the key factors to be improved.

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Chapter 4

Contact Lens Materials. Part II – Ocular Interactions, Deterioration Process and Clinical Impact

4.1. Abstract

Purpose: Contact lens (CL) materials are not inert while on the eye, showing significant changes in their properties that cause or exacerbate physiological and pathological changes on the ocular surface.
Methods: An extensive review has been done on the changes experienced by CL while they are in the eye as well as some clinically relevant consequences of interactions between the CL and the ocular surface. Particular emphasis is given to silicone hydrogel (Si-Hi) materials because of their potential and actual growth according to current CL market trends.
Results: Changes at the CL surface level are extensively described in the vast literature available. These changes are particularly associated with deposit formation. Other changes with a major role in the decrease of CL tolerance during wear are associated with the water behavior within the polymer and the dehydration processes. Conversely, changes in oxygen permeability seem to have minor impact on CL tolerance. However, full knowledge of other sources of CL material deterioration requires the investigation of potential changes in other important issues such as surface topography, bacterial adhesion, mechanical properties of the polymers or hydraulic transmissibility.
Conclusions: It is widely accepted that SCL experience significant changes in their physic-chemical characteristics as a consequence of deterioration. Current research attempts to fully describe the deterioration process of CL materials at the surface, but also within the polymer bulk, in order to minimize their effects on ocular physiology, thus prolonging CL tolerance and reduce drop-outs, the more challenging aspect of current CL practice.

4.2. Introduction

To be satisfactorily tolerated, CL materials must be able to keep surface wettability and bulk hydration in hydrogels and Si-Hi, have oxygen permeability to maintain normal corneal metabolism, being permeable to ions and tear components to allow lens movement and avoid lens binding, resist deposit formation, and allow the tear film to spread continuously over the CL surface and the ocular surface not covered by the CL. These demands require the material to have certain bulk and surface properties and keep them during the wearing time and repeated removals, care procedures and insertions.

For a biomaterial to become fully biocompatible, it would be required not to cause changes to the ocular surface (host) and not to suffer from deterioration as a consequence of the interaction with the host. In the ocular context, and more precisely in the field of CL, full biocompatibility will require the CL material do not cause adverse reactions or physiological changes to the ocular surface, and do not suffer significant deterioration as a consequence of the interaction with the ocular tissues and surrounding fluids, particularly the tear film. However, these two aspects of negative interaction between biomaterial and ocular surface are still present, and as a consequence we cannot describe current CL materials as fully biocompatible devices.

Deterioration, deterioration, spoliation, spoilation, spoilage, ageing, deterioration or contamination are words that have been used in the scientific and academic literature to describe the processes of adverse changes in the CL properties that can compromise their ocular tolerance. Spoilation is not appropriate in this field; deterioration will not be used as it will imply a break in the chemical structure of the polymer, which is not presently accepted as a relevant source of contact lens deterioration. In this chapter, the terms deterioration or spoilation would be preferred because they are the most commonly used in the CL field.

Deterioration of medical devices and materials is a very important question and it is covered by parts 13 to 16 of ISO 10993 and CEN 30993 standards concerning the "Biological evaluation of medical devices".[1,2]

Classical implications of CL deterioration almost consider solely the impact of deposit formation and microbial adhesion[3-5] and high quality extended reviews on this subject have been published.[6,7] However, modern CL practice rely essentially in disposable CL,[8,9] of which modern Si-Hi represent a growing part of the disposable CL practice[10] so gross deposit build-up is rarely a serious problem.

Deterioration of CL polymers has been widely studied,[11] but for many times those studies failed to correlate the presence of CL intolerance and material deterioration. Apart from other forms of lens deterioration as scratching or tearing during manipulation, nowadays CL material deterioration is understood as a combination of processes that affect both bulk and surface structure increasing the risk of material dehydration,[11] deposit formation,[6] and bacterial adhesion.[12-14] All of these processes lead finally to lens intolerance in the form of dryness and discomfort,[15] recurrent ocular inflammation, giant papillary conjunctivitis,[16] hyperemia,[17,18] and, less frequently, infection and other adverse events.[19,20]

Drop-out rates among CL wearers vary from 26 to 40% depending on the study,[21,22] being a serious limitation for the growth of CL industry.[23] Discomfort is the main reason pointed out by patients to have ceased lens wear, being responsible for almost 50% of CL discontinuation[22,24] and refractive surgery procedures.[25]

Among CL related factors to explain CL wear discontinuation, surface related changes are common to RGP and SCL.[12] Internal dehydration and deposit formation are also major problems with SCL that could negatively affect oxygen performance,[26] mechanical properties,[27] recurrent epithelial desiccation[28,29] and physical fitting.[30]

The physicochemical basis for most of these changes are now being understood and should be further investigated in the future to develop new materials that improve biocompatibility to promote comfort, long-term tolerance and ocular health under daily, extended or continuous wear modalities.

In the present review we will analyze the interactions of the CL materials with the ocular surface, different forms of material deterioration and the impact of CL wear on the ocular surface. Ocular changes, can also be due to the deterioration of the materials or to the solely use of the device, even before significant levels of deterioration are present. Hydrogel materials are particularly prone to deterioration because of their close interaction with the ocular tear film on the surface and within the bulk of the material. Furthermore, Si-Hi materials have been introduced in the market during the last 7 years, reaching over 20% of new fits in some countries. For these reasons, special attention will be paid to these materials regarding some particular forms of interaction with the ocular surface and how to avoid or minimize them.

4.3. Contact lens interactions with the ocular surface

All artificial materials to be used on the human body are potentially harmful because of lack of compatibility at different levels. Similar to other devices, CL interact with body fluids being potentially subjected to spoilation by components of these fluids. However, the case of CL is significantly different from other devices because CL are not within the body but at the ocular surface. As a result, and because the atmospheric oxygen is the primary source of oxygenation for the anterior cornea, CL must be permeable to oxygen. Furthermore, they are subjected to repeated drying and rewetting and lenses are frequently removed for care and storage in artificial solutions. The interaction of CL with the ocular surface is therefore a complex issue, involving immune and bacteriological interaction, mechanical interaction, metabolic stress and chemical aggressions by the components of care solutions. Because different CL polymers are different in their chemical composition and physical properties, they may react differently to changes in pH, osmolarity, temperature and the components of the various lens care products. The interaction of CL with the tear film is also one of the main problems to be solved in current CL practice. Moreover, interindividual variations in ocular surface shape and biological or metabolic needs would certainly account for different reactions to the same lens materials.

4.3.1. Immune and bacteriological interactions

CLs affect the balance in the biological environment of the ocular surface, disturbing the normal relationship between the ocular surface and the lids, introducing microorganisms that are not normally present, decreasing the oxygen availability and increasing the retention of metabolic debris and tear evaporation rates. Sources of microbial contamination include poor hygiene during lens handling as well as contamination of the lens cases and care solutions.[31] Moreover, the presence of the CL affects the concentration and activity of immunological components of the ocular surface.[32] Also, CL surfaces can increase the chance of bacteria attaching to the material, remaining for longer periods in contact with the ocular surface. These situations altogether place the eye at a higher risk of infection if lens care and handling is not appropriate. The most threatening condition during CL wear is microbial keratitis (MK), and although CL wear is a risk factor for this condition, particularly when low-Dk lenses are worn overnight, its incidence is relatively rare with RGP, hydrogel lenses under daily wear conditions and Si-Hi lenses according to Morgan *et al.*[33] whose results are summarized in *table 4.1*. Other less severe complications as symptomatic and asymptomatic infiltrative keratitis, acute red eye and sterile ulcers[34] are also believed to be driven by immune and bacteriological interaction between CL and the ocular surface and probably other sources of interaction, mainly mechanical interaction and hypoxia.[20] Proper CL handling and care, compliance with wearing and lens replacement schedules, and making an adequate choice of lens material and fitting are the best way to minimize the risk for the ocular health arising from immune and bacteriological interaction. Different aspects of bacterial adhesion to CL will be discussed in later sections related with the surface properties of CL.

Table 4.1. Incidence (cases per 10.000 CL wearers) and relative risk (compared to daily wear of hydrogel CLs -non daily disposable-) of non-severe and severe keratitis (MK) for different types of CL under daily and extender wear regimes[33]

	Daily Wear		Extended Wear	
	Non-severe keratitis	***Severe keratitis***	***Non-severe keratitis***	***Severe keratitis***
RGP	5.7 (0.4)	2.9 (0.5)	0 (0)	0 (0)
Hydrogel (daily disposable)	9.1 (0.7)	4.9 (0.8)	n.a	n.a
Hydrogel (non-daily disposable)	14.1 (1.0)	6.4 (1.0)	48.2 (3.4)	96.4 (15.2)
Silicone hydrogel	55.9 (4.0)	0 (0)	98.8 (7.0)	19.8 (3.1)

n.a: not applicable

4.3.2. Mechanical interactions

With the introduction in the marketplace of the first generation Si-Hi materials, mechanical interaction of CL with the ocular surface has gained increased relevance. These materials have low EWC with significant proportions of siloxane moieties, which results in a higher elastic modulus. As a result, the ocular surface, particularly the corneal and conjunctival epithelium, is under a stronger mechanical stress because of lens movement during repeated blinking. Mechanical interaction is usually associated with micro erosions in the corneal epithelium and, despite usually being of moderate degree, they can increase the risk of infection providing more chances for bacterial attachment and access for bacteria to break the epithelial barrier. More severe epithelial lesions can also be present in the form of superior epithelial arcuate lesions,[35,36] or conjunctival indentations. Flattening of corneal curvature[37,38] and epithelial indentation from post-lens debris[39] have also been linked to the higher modulus of these materials. Second generation Si-Hi materials have a lower modulus of elasticity what could contribute to reduce this interaction.

The mechanical interaction of CL on the ocular surface has also been suggested as a cause for the increase of Langerhans cells in the epithelium of guinea pigs, a sign of inflammatory response,[40] as well as loss of keratocyte density in the corneal stroma.[41,42]

4.3.3. Metabolic interactions

Metabolic interactions between CL and ocular surface are particularly important at the level of oxygen transport through the CL material. Contrary to early CL materials, most of the current high oxygen permeability (Dk) RGP and Si-Hi materials provide enough oxygen flux to the corneal surface to warrant a close-to-normal metabolic function. However, the vast majority of hydrogel materials currently available in the market are of low oxygen permeability (Dk<50 barrer) compared to the permeability of Si-Hi (Dk = 60-140 barrer). These materials, when used overnight, induce significant changes in the ocular surface and the inner corneal structure as it will be analyzed later in section 4.7.1. For these reasons low Dk hydrogel CL are not suitable for extended wear. The physiological consequences of hypoxia and hypercapnia affect several parameters of the corneal and conjunctival tissues and will be covered in more detail in the end of this chapter.

4.3.4. Interaction with tears

It is well known that CL disturb the environment of the ocular surface, and the tear film is, in the short-term, the most affected element. After the lens is placed onto the ocular surface, the normal layered structure of the tear film is broken. Furthermore, on certain areas where a closer relationship exists between the ocular surface and the CL the tear film is squeezed while the tear exchange is minimized and oxygen supply is limited. The immediate effect of CL on the tear function affects therefore the distribution of the tear film, along with a thinning of the pre-lens tear film that increases the evaporation and dehydration rate of the CL. Finally, the secretion of tears is also affected in the medium and long term, particularly with SCL inducing hypo-secretor dry eye. Deposit formation can be considered as another way of interaction between CL and tear components and these will be discussed in detail in section 4.6.1.3 of this chapter.

4.3.5. Chemical interaction with CL care solutions

Chemicals causing potential reactions in the ocular surface may come from the CL or from the care solutions. Some monomers that are compatible with the eye while polymerized in the bulk of the CL can be toxic for the eye when released from the bulk of the material as monomeric entities. In fact, this is one of the reasons for the need to wash finished CLs once polymerized in modern cast-molding chain processes. Despite poly(vinyl alcohol) from SCL is currently being used as a form to extend CL comfort though the day by continuous release,[43] there is no report of adverse effects from spontaneous release of monomeric entities into the tear film with current CLs. The effect of material release from polymer components and the potential subsequent sensitization of the eye is not well known at present. Thus, chemical interactions between CL and the ocular surface are caused primarily by contact sensitization by chemical compounds from the care solutions, in the short or long term. Some of the products used in CL care induce immediate reaction in the ocular surface and therefore cannot be used in direct contact with the eye. Other components, mainly preservative agents, despite being used at very low concentrations can induce medium or long term hypersensitivity, when the concentration of the absorbed chemical reaches a threshold level within the CL material. For this reason, preservatives such as thymerosal are no longer used in lens care solutions. Benzalkonium chloride (BAK) is still used in some care solutions for RGP CL, but not with SCL solutions because of the risk of sensitization from material uptake.

The most common clinical expression of the chemical interaction between CL solutions and ocular surface is a diffuse keratitis, different to the localized keratitis typical of other etiological factors as mechanical interaction or lens dehydration. A characteristic pattern of more intensive staining towards the limbus has been identified with Si-Hi CL, particularly when polyhexamethylene biguanide (PHMB) preserved care solutions are used (*figure 4.1*). It has been observed that Si-Hi materials when used with care systems containing PHMB as a preservative are associated to higher corneal toxicity than other products that do not use this molecule.[44] Similar results were found by Garofalo *et al.*[45] with Si-Hi and FDA group II hydrogel SCL, particularly within the first two hours of wear. However, other recent studies do not support the association between PHMB and toxic keratitis.[46]

A recent study has evidenced the benefits of the application of an artificial tear containing carboxymethylcellulose (CMC) to improve the compatibility of Si-Hi materials with the ocular surface with a decrease in the incidence of superficial staining. The authors explain this finding by the potential neutralization effect of the cationic disinfecting agent by the CMC.[47]

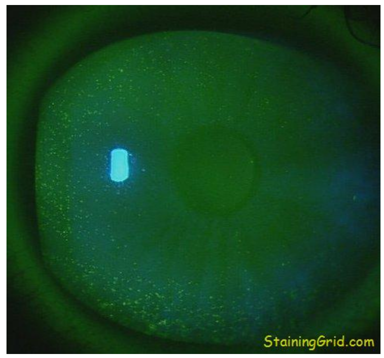


Figure 4.1. Diffuse keratitis seen during Si-Hi CL wear along with PHMB preserved multipurpose solution. Reproduced from Andrasko (www.staininggrid.com) with permission.

4.4. Chemistry of polymer deterioration

Polymers are, in general, stable materials, with low reactivity against external reagents and low intra-molecular reactivity as well. Intra-molecular reactions show various characteristics depending on the three-dimensional molecular configuration of the network. According to Kanome,[48] the factors related to the reactivity of polymers in a polymer reaction are: Affinity, polymer field, 3-dimensional structure and neighboring group effect. Reactivity modes can be classified in the following groups, some of them can be considered constructive as the polymerization process itself, while others are directly implicated in its deterioration process:

- Reaction with external agents – this includes the interaction of material's molecules with the ocular and exogenous environment and is the most relevant form of reactivity between CLs and the ocular surface;
- Intra-molecular reaction;
- Inter-molecular reaction – is a cross linking reaction which is initiated by adding a cross linking agent with reactive group or metal ion, by heating, or by radiation. This property has a predominant role in polymer production;

- Deterioration of polymer – occurs by exposure to heat, light, or oxidation. There are a variety of mechanisms for deterioration (e.g., deterioration of the main chain, deterioration of the side chain, chain deterioration and unchain deterioration). Kanome further identified the probable sources of polymer deterioration in CLs as being:[48]
    - Thermal deterioration from boiling for sterilization, which is not common in current CL practice;
    - Oxidative deterioration from chemical disinfection or auto oxidation by contact with oxygen;
    - Mechanical deterioration by repeated mechanical stress upon wearing and removing lenses and cleaning procedures.

Over the last decades many scientific studies reported the chemical composition of the CL as one of the most important factors governing polymer deterioration by the adhesion of deposits of different nature. In particular, the presence of certain ionizable radicals and the porous nature of the polymers seem to be directly implicated on the higher incidence of certain deposits on ionic and high water content CL that will be analyzed in more detail in this chapter.

4.5. Sources and factors affecting contact lens deterioration

The sources of CL deterioration have been described early in the clinical and basic science literature. Thipathi *et al.*[49] concluded that the main sources and factors surrounding lens deterioration are ocular secretions, finger dirt, cosmetics, disinfecting and cleaning products and procedures, environmental factors, manufacture defects and polymer impurities. In another work, Tripathi *et al.*[5] identified the following factors predisposing to deposit formation and deterioration including: Type of lens and polymer, lens-care system, patient hygiene, ocular and systemic conditions, length of wear, working environment and living environment.[4] Despite their review focused on deterioration due to deposit formation, they also recognized polymer deterioration itself as a source of CL deterioration. The clinical manifestations of CL deterioration were described by Bowers and Tighe who identified the following factors: lens coatings, microbial deposits and extrinsic factors.

Water content is perhaps the most important parameter limiting SCL durability. An increase in water content usually reduces durability, particularly their resistance to tearing and deposit affinity. Two molecular processes are involved in these two sources of deterioration: The first one is within the polymeric structure and causes a decrease in the elastic modulus by the higher water content, that leaves less space for cross-linking monomers that support material stability; the second one is on the surface of the material and is related to the hydrophilic groups that interact with tear proteins, lipids and other substances that may potentially form deposits over the lens surface and within the bulk. The former mechanism has the ability to cause a change on surface wettability as hydrophilic groups usually in contact with tears rotate inside the polymer bulk as the environment-material interface becomes hydrophobic as a consequence of deposit formation. This is a deterioration mechanism that feeds back by promoting a dynamic rotation of molecules as a consequence of a passive surface dehydration process.

Among the patient-related factors that can accelerate polymer deterioration we recognize non-compliance with care systems, lens replacement or recommended wearing schedule. For these reasons, deterioration of CL materials is a highly subject-dependent process.[50] However, material properties are also of primary importance to identify the risk of different forms of material deterioration in the form of deposit build-up as it will be seen in following section 4.6 of this chapter.

4.6. Contact lens properties and deterioration processes

Deterioration processes in CL are related primarily to the material they are made of, particularly, their polymeric structure, hidrophilicity, wearing schedule and replacement schedule. In addition, environmental factors and inter-subject variability also interfere on these ageing processes. Because of their different nature and clinical meaning, the aspects of polymer deterioration will be discussed separately for hydrophilic soft and hydrophobic RGP CL.

4.6.1. Deterioration of soft contact lenses

Hydrophilic polymers for CL are particularly prone to deterioration with use. This is due to three major facts: 1) The properties of the surface of these materials that facilitate the interaction with biochemical elements present on the ocular surface, particularly in partial hydrophobic surfaces (lipid deposits) and ionic surfaces (protein deposits); 2) Their porous structure and ability to absorb and release water and solutes from the tears and the environment in and out the polymer bulk and 3) Their relatively fragile structure, particularly in medium and high EWC materials.

Since their introduction in the CL industry during the seventies, SCL have allowed a great diffusion of the CL, thus creating the necessity for more in depth studies about their physicochemical behavior and interaction with the ocular surface. For these reason, most of the scientific literature on this subject has been directed towards SCL materials.

Furthermore, the advent of Si-Hi materials in the last years has attracted a renewed interest on the polymeric deterioration of hydrophilic materials for SCLs, particularly regarding their affinity for deposits. The forms in which SCL polymers change their properties in a reversible or irreversible process are primarily related to dehydration, lost of surface hydrophilicity, deposit formation, microbial adhesion, changes in the mechanical properties and dimensional changes. The following sections will be devoted to these aspects of SCL deterioration.

4.6.1.1. Dehydration

On-eye dehydration of CL is one of the main problems of lens-related lack of biocompatibility. In SCLs, any phenomenon that causes a change in water content will cause a change in lens dimensions, increase surface deposits and potentially affect mechanical properties, thus compromising patient's tolerance to CL. Different factors affect the ability of the CL to sustain *in vivo* hydration: 1) Patient-related factors include tear secretion and stability, ocular surface temperature and blinking; 2) Lens-related factors are also very important including EWC, lens thickness, ionicity and monomeric composition[29,51-54] and 3) External factors seriously affect the water content as relative humidity, temperature, wearing schedule, lens cleaning regime or the application of artificial humectants.[55,56]

Clinical consequences of dehydration include changes in lens parameters and fitting characteristics,[57] decrease of Dk of conventional hydrogels[26] and increase of Dk in silicone hydrogels,[58] decrease of comfort and wearing time,[53] denaturizing of proteins and deposit build up.

The dehydration process of a CL begins immediately after placement in the ocular surface until a new EWC is reached. The way each material behaves is different however. In a study conducted by Morgan and Efron,[11] SCL showed lower EWC after removal in the end of the day than before insertion. Furthermore, a trend towards lower EWC was also found during 28 days wear for some materials. This was particularly evident for etafilcon A material. Overall, this material showed a difference between pre-insertion and post-removal EWC of 6%, and decrease in pre-insertion and post-removal EWC at the end of the 28 days of 5%.[11]

Environmental factors seriously affect SCL tolerance, and this could be directly related to changes in CL wettability and hydration.[59] Working with computers in rooms with heating units and air conditioning increases the prevalence of certain symptoms of CL intolerance.[60] All this facts are probably due to a higher rate of CL dehydration. However, there are other factors such as minor changes in temperature, solution osmolarity or pH that affect CL hydration in a material-dependent manner. This could be considered as another source of CL deterioration or material stress.

Dehydration of hydrogel CL occurs naturally as a consequence of thermodynamic interactions between water and functional groups. The ability of an hydrogel to hydrate decreases at about 40ºC (eye temperature is 35ºC), and as a consequence water content frequently drops significantly between average room temperature (about 25ºC) and eye temperature. This effect is less important for group I materials and highly significant for group IV materials. However, this effect disappears rapidly as the lens reaches its EWC and is different from the dehydration process that CL wearers suffer over time. The dehydration is directly related with the EWC of the lens.[59]

Regarding osmolarity, it's well known that water content decreases when the lens moves from water to a saline solution and vice versa. This effect is experienced by wearers when they swim in seawater or chlorinated swimming pools as lenses dehydrate becoming tighter and causing more sensation on blinking and difficulties to remove them. Under these conditions pH of water can have a role on CL discomfort. As a consequence of material susceptibility to pH changes, group IV materials react more to changes in solution pH. This is also a matter of concern with some ophthalmic drugs with pH values outside the physiological pH range.[61] According to Lum *et al.* Osmolality and buffering agents influence lens parameters. Packaging solutions can vary the parameters of some lens types from their nominal value to outside the tolerance range set by ISO.[62] The dependence of polymer properties with pH is used in some kind of hydrogels to modulate drug delivery. Gemeinhart *et al.*[63,64] demonstrate how porosity and EWC diminishes as the pH value decreases in this kind of materials. At a different scale something different could be expected to happen with CL materials.

Dehydration may affect CL parameters and fitting characteristics such as oxygen permeability, power, base curve, and diameter; this, in turn, may lead to the ocular surface desiccation and issues with lens comfort during wear.[26,29,51,52,65-70] However, several studies conducted did not confirm a relation between CL-related dry eye symptoms and material lens dehydration.[53,57]

4.6.1.2. Hydrophobicity

The compatibility between tissues and polymeric materials implanted or inserted in the human body depends strongly on the surface properties of the material. Compatibility depends particularly on the ability of the polymer surface to induce conformation changes or denaturizing of proteins adsorbed. This is extremely important in CL materials as they are exposed to air between blinks. Even with little changes in EWC of the polymer bulk, the surface of SCL can suffer important changes in the mechanical properties as a consequence of dehydration. Opdahl *et al.*[27] used AFM to demonstrate that the outer surface of p-HEMA based SCLs dehydrated at a higher rate in low relative humidity (RH) environments (40-50%) while the polymer bulk could still remain hydrated.

CLs disrupt the natural application of the tear film on the ocular surface increasing the evaporation rate and decreasing tear thinning time.[71] More recently, Maruyama *et al.* demonstrated in vivo that as air temperature and relative humidity decreased, the tear film on the SCL became thinner, NIBUT became shorter, and dryness symptoms increased. Dryness was more pronounced in patients wearing high EWC SCL.[59] In vitro studies conducted by the authors also support higher rates of initial dehydration as the EWC of hydrogels and Si-Hi materials increase.[72] This effects could be even more pronounced on worn CL because of different forms of deterioration of CL surface limiting their ability to hydrate (scratches, deposits, lower wettability,…).[73] Furthermore, certain environments and/or activities could also exacerbate the significance of ocular dryness as air conditioning, airplane cabins, higher altitudes (above 3.000 to 4.000 feet), low temperature, low humidity and windy or breeze environments.[74] Some activities potentially associated with higher levels of dryness include computer work, reading, TV and console, driving automobile or practicing winter sports. In a recent study, we were able to correlate computer work under air conditioning environments with a higher prevalence and severity of dryness symptoms in SCL wearers.[60]

Dehydration, deposit formation and hydrophobicity are closely linked in soft and RGP lens materials and these effects are seen in *figure 4.2,* that shows the rapid dehydration of a SCL surface contaminated with deposits, thus strengthening the binding of more deposits.

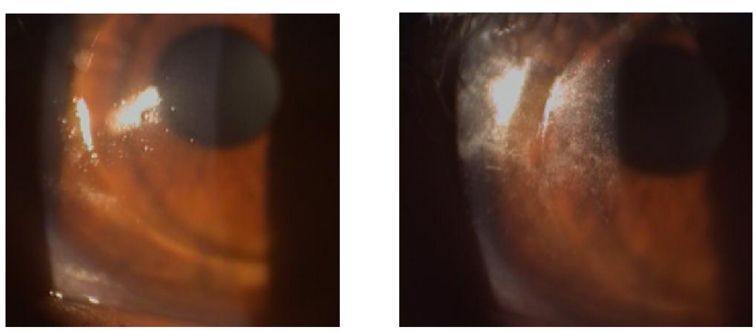


Figure 4.2. Rapid on-eye dehydration in the front surface of a SCL after blinking.

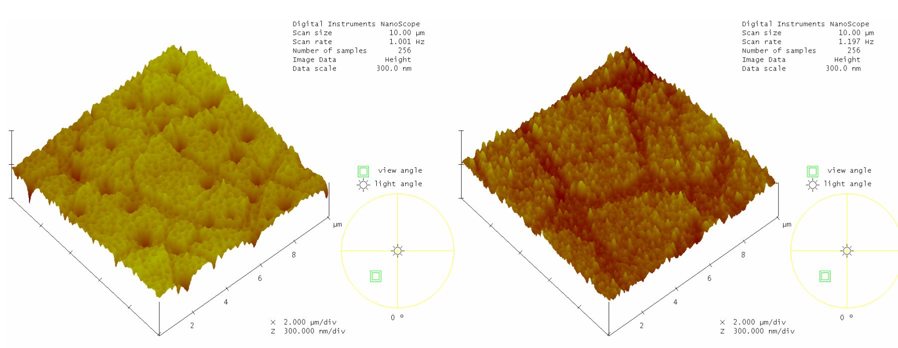
Changes in surface hydration and perhaps other changes in the surface of the CL with time of lens wear are a logical consequence of deposit formation. However, wettability of CL surfaces of first generation Si-Hi did not change significantly after being worn.[75] In fact, in the short-term, some tear components adhered to the CL surface could even improve wettability of Si-Hi materials.[76,77] Other authors have documented a continuous change in the CL wettability, with an increase immediately after the lens was placed on the eye for the first 30 minutes of wear.[78] Differences in the wetting angle of two different CL were reduced after both lenses were worn[77] indicating some normalization effect induced by tear components. However as deposit formation become more important, a reduction of wettability is the most likely effect.

In summary, deposit formation on CL does not mean immediate problems of tolerance; instead, a small amount of tear components onto the CL surfaces, can help to increase the biocompatibility in the short term. However, as these deposits grow-up and some of their components get denaturized, serious biocompatibility problems can arise.

4.6.1.3. Deposits on soft contact lenses

Among other factors, surface roughness of devices contacting living systems will influence their biological reactivity. The relationship between surfaces is particularly critical in CL practice as the polymer should interfere as little as possible with the epithelial surface of the cornea and conjunctiva. This is important in order to maintain corneal transparency, superficial epithelial cell integrity and ocular surface health. However, after the polymer is exposed to the biological fluids (e.g. tears), the adsorption of components begins, contributing to the increase of irregularities on the CL surface. CL deposits are of different types, can affect either the surface or the bulk of the polymer and cause symptoms that affect patient tolerance. They have been conveniently reviewed in several literature reviews.[4,6]

Several characteristics of polymers affect their interaction with tear contaminants, particularly, the electrostatic charge, surface wettability and EWC. The electrostatic charge of the polymer surface and the EWC of the bulk depend on the monomers included, and this is essential to understand the formation of deposits of different nature in SCL polymers. In the case of FDA group IV materials, the presence of methacrylic acid (MA) in most of them is the major factor contributing to the anionic nature of the lens surface.[79]



(A) (B)

Figure 4.3. Microtopographic image of the surface of both unworn and worn SCL. Despite the worn lens presents a more uniform surface in terms of topographic descriptors, the worn lens presents a more contaminated surface, and the typical macropores usually observed are not observed.

The chemical configuration of other monomers as N-vinyl pyrrolidone (NVP) have been also associated with a higher incidence of lipoid deposits in FDA group II CL.[80] As a consequence, and despite the patient-dependent variability in CL deterioration, the nature of the CL material is fundamental to understand the deterioration processes in the form of deposit formation and adverse ocular interactions. In fact, Jones *et al.*[50] observed that once lens material is taken into account, protein deposits display a small inter- and intra-subject variation. Conversely, the same study showed that lipid deposits display a higher patient-related variability.

Goldberg, Bathia and Enns,[81,82] observed significant changes in the surface of worn CL with electron and atomic force microscopy. In *figure 4.3* these changes are evident for unworn and worn samples of the same CL material.

In the following two sections we will give special emphasis to protein and lipid deposits, the most common sources of lens deterioration in current disposable SCLs. Some strategies to minimize their impact will be also discussed.

4.6.1.3.1. Proteins

Proteins are important elements of tears with an active role in the control of microbiological colonies in the ocular surface. However, they are at the forefront of the etiological causes of CL deterioration, particularly lysozyme.

Protein deposition on SCL is a material dependent process.[83] The ionic nature of FDA group IV containing MA significantly adhere more proteins (particularly lisozyme) than copolymers of HEMA with NVP or acrylamide.[84] The most commonly accepted mechanism for lysozyme binding in group IV CL materials is the electrostatic affinity between the anionic material and the positively charged lysozyme at physiological pH.[79] Furthermore, the level of ionicity in the CL surface seems to be related with the amount of proteins deposited.[85] Surprisingly, the higher incidence of lysozyme deposits on ionic materials compared to Si-Hi materials was associated with a lower incidence of denaturation.[86] Despite lower deposits of protein in Si-Hi materials, the higher proportion of denaturized entities, could also add some support to the etiology of increased papillary reaction seen with Si-Hi, primarily associated with the higher modulus of first generation Si-Hi.[87]

The EWC of materials is usually considered as a risk for lens contamination, with higher water content materials being more subjected to spoilation with use because these materials use to have looser chains of polymers which are considered easier to be spoiled by proteins and lipids. However, a study that compared the protein deposition in four ionic group IV SCLs found that the lens with the higher EWC material was that with a lower level of protein deposits.[88]

But spoilation by proteins is not only restricted to the CL surface. Because of its reduced molecular weight, lysozyme is able to penetrate within the polymeric bulk of the material as have been demonstrated in several studies.[89,90]

There are other types of proteins that adhered to the CL surface as albumin or lactoferrin, whose mechanism of adhesion seems to be different from lysozyme. However, because of the large molecular weight of albumin compared to lysozyme, this protein only form deposits on the lens surface without penetration into the lens matrix.[91] Quantities of proteins recovered from worn CL are on the order of <50 μg per lens for non ionic materials to more than 500 μg per lens for ionic group IV materials.[50,92]

Protein deposition on CL could be more significant during overnight wear because some tear film protein levels increase during eye closure. However, those proteins more commonly associated with deposit formation (lysozyme, albumin, lactoferrin) do not increase.[93] Sack *et al.*[94] found considerable higher lysozyme deposits in daily wear than extended wear lenses.

4.6.1.3.2. Lipids

While proteins have a great affinity for ionic materials, lipids have been associated to a higher extent to non-ionic high EWC CL materials.[79,80,95] Those studies comparing directly the level of protein and lipid deposits are conclusive that while ionic group IV materials have a high affinity for protein deposits, high water content non-ionic group II materials present a high affinity for lipids.[92] Several authors agree that the presence of N-vynil pyrrolidone in FDA group II CL materials is a primary factor determining the higher levels of lipid deposits in these lenses.[80,85] Furthermore, the amount of NVP included in the formulation, seems to have an effect on the amount of lipid deposits. If protein deposits on ionic materials are driven by electrostatic interactions, a small level of lipid repulsion by the anionic surface of group IV lenses has also been considered as preventable effect for lipid deposits in this material,[50] thus explaining the lower rates of lipid deposits in these ionic materials.

Lipid deposits have received increased attention recently because there are evidences that that Si-Hi CL are more sensitive to build-up this kind of deposits,[75,86] while other authors did not found such a clear relationship between Si-Hi materials and lipid deposits.[96] Nichols[97] has demonstrated the effectivity of a hydrogen peroxide disinfection associated with surfactant rub step in reducing the level of deposits in a Si-Hi CL.

Larger inter-subject variability regarding lipid deposit formation[50] agrees with the clinical finding of large variability in the front surface wettability of worn CLs.[3] Group I materials demonstrated less inter-subject variability than group IV lenses regarding lipid deposition. The authors explained this finding by the less polar sites available to bind lipids in the group I lens material, which would produce a higher competition for lipoid elements, thus not allowing inter-subject variations to be evident. However, in group IV material, with larger availability for lipid binding, the inter-subject differences will have a chance to become evident.[83]

Bontempo and Rapp[80] found an association between higher water content and higher levels of lipid deposits. They also believe that ionicity has also a significant role in lipid deposit formation. Recently, these authors documented how the material and subject characteristics can affect the type of lipid deposits adhered to the lens surface. According to their results, deposits of larger lipids are more material dependent while deposits of smallest lipids are less material-dependent, displaying more subject-related variability.[83]

Quantities of lipids adsorbed to CLs are on the order of <50 μg per lens.[83] Other authors provide values in arbitrary units of fluorescence intensity instead of absolute quantities. In general, the amount of lipids adhered to non-ionic group II CLs is 1.5 to 2 times greater than those adhered to ionic group IV CLs.[50] Quantification of different lipids adhered to CLs are contradictory, but values ranged from 20 to 100 μg/lens for cholesterol, <1 to 600 μg/lens for oleic acid and <1 to >200 μg/lens for oleic acid methyl ester.

4.6.1.3.3. Wearing time and lipid/protein deposit formation

Another concern with deposits on CLs is change over time. This is important in order to evaluate how wearing schedules can be altered to minimize the impact of deposits on CL biocompatibility.

Protein deposition begins immediately after lens placement on the eye.[98] However, different materials have presented different response in the amounts of protein adhered to their surfaces with increasing wearing times. In a study conducted by Jones *et al.*[3] a high water content SCL demonstrated to significantly reduce the level of deposit formation with a monthly replacement compared to a three-month replacement, having benefits in subjective satisfaction, lens front surface wettability, visible deposits, and analytically evaluated deposits. Another study by the same team concluded that FDA group IV ionic materials rapidly accumulated protein deposits reaching a plateau within the first week of lens wear, while group II non-ionic materials containing NVP progressively accumulate more lipid deposits, without plateau. Okada *et al.*[90] investigated the penetration of lysozyme in SCL materials. They found significant penetration into group IV ionic polymer without significant effect of contamination time on the level of protein. Conversely, lipid deposition did not show significant increase with time of wear in group IV lens, and little increase in proteins was present in group II lenses.[92] The exponential increase in protein deposition on group IV lenses is also supported by the results of Michaud and Giasson.[18] Subbaraman et al found for this type of material a progressive increase in protein deposition with a plateau at the end of the first week.[99] Conversely, omafilcon A, a high water content non-ionic material containing phosphorylcholine showed non significant increase in protein deposit formation over time during a month of lens wear. Conversely, the material against which it was compared (surfilcon A) demonstrated a progressive increase in lipid deposits over the same period of time, particularly in those patients that worn the lenses for more than 5 weeks.[95]

Wear of group IV SCL beyond the recommended period of replacement (overwear) was associated with an increased level of protein deposits. This increase could be somewhat responsible for the exacerbation of several clinical signs and decrease in visual acuity found by the authors.[18] The results of these studies highlight the objective impact of overwear of SCLs on lens deterioration, which has potential negative impact on clinical performance.

Clinical evaluation of surface wettability and front surface deposits was not significantly different between Si-Hi lenses worn continuously for 6 nights or 30 nights.[100] Maziarz *et al.*[96] found that the amount of cholesterol recovered from Purevision lenses worn overnight or under a daily wear schedule were similar. However, while lenses worn overnight presented values of cholesterol between 10 to 30 μg/lens, lenses worn on a daily wear schedule presented values that in the majority of patients were between 10 to 20 μg/lens. This study concluded that cholesterol was the lipid most frequently adhered to CLs of different types including Si-Hi and conventional hydrogel materials, while other authors obtained opposite results.[86]

The association between level of deposits and wearing time, is the more convincing reason to recommend more frequent replacement of SCLs. Jones *et al.*[3] have demonstrated that monthly replacement could reduce by 60% and 44% the level of protein and lipid deposits, respectively, on non-ionic high water content SCL when compared with three-month replacement. Bontempo and Rapp[83] concluded that in the short-term, variability in deposit formation is material and subject-dependent, while for longer periods of lens wear, the formation of deposits on CLs is more related to material properties and less to subject variability.

4.6.1.4. Microbial colonization

CL wear is the main risk factor for bacterial keratitis according to some authors.[101] The adhesion of microbial agents to CLs is a major concern in CL wear as the most serious complication for these patients is microbial keratitis where the CL could act as a vector of infection, increasing the possibilities of microorganisms to reach the eye as well as prolonging the amount of contact time with the corneal surface. Tripathi *et al.*[4] used the work from Gristina *et al.*[102] on the binding of bacterial to bone tissue to explain the adhesion of bacteria to CL surfaces. In that model, the CL surface will initially repel bacteria, but hydrophobic interactions, divalent cations present in tears and deposit formation will enhance the chance of bacterial binding to the CL surface (*figure 4.4*).

With the advent of overnight continuous wear of Si-Hi materials, new concerns have arised because of their hypothetic higher potential to bind bacteria as demonstrated by several studies. Recently, Henriques *et al.*[103] observed that *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* exhibited greater adhesion to Purevision and Air Optix Night & Day CLs than to Acuvue Advance and Acuvue 2 lenses. The authors argued that the relatively hydrophobic surface of these materials could justify such a behavior. Similar results had been previously reported by Beatie *et al.*[104,105] for trophozoites of *Acanthamoeba*, demonstrating a higher attachment to the Si-Hi lenses than to the conventional hydrogel lenses. Investigations conducted by the same group revealed that risk for bacterial adhesion seem to be related to material properties rather than the presence of surface treatment, that demonstrated not to be a risk factor.[106] It is of marked clinical relevance that all these microorganisms are responsible for rare but serious ocular infections in CL wearers.[107-110]

Surface roughness is considered as a potential factor for bacterial adhesion. Probably, the more extensive bacterial adhesion to rougher surfaces is associated with the fact that organisms on rough surfaces are better protected against shear forces and cleaning procedures.[111] Vermeltfoort *et al.* did not find significant changes in the surface roughness of Si-Hi materials after 1 and 4 weeks of wear, while a reduction in the wetting angle was observed. These facts were accompanied by a general decrease in the adhesion of bacteria to worn lenses.[77] These results agree with the findings of Boles *et al.*[112] who concluded that worn disposable CLs restricted the attachment of *Pseudomonas aeruginosa* compared to new lenses. Early studies from Duran *et al.*[113] also support the affinity of new CL materials for bacterial adhesion.

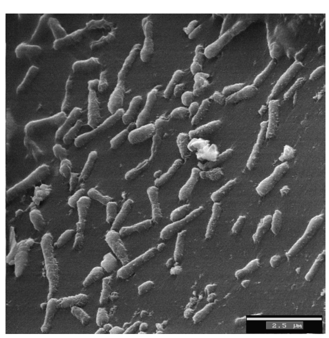


Figure 4.4. Bacterial colonization on the surface of a SCL observed with scanning electron microscopy (SEM).

For these reasons several recent studies have addressed the question of bacterial adhesion, evaluating the potential of different CL materials to allow binding of different types of microorganisms including gram positive and gram negative bacteria, fungi and amoeboid entities.

Among other parameters of the CL surface as hydrophobicity and atomic composition, Bruinsma *et al.*[12] demonstrated that surface roughness was one of the mayor determinants of *Pseudomonas aeruginosa* adhesion to SCLs made of etafilcon A. Baguet *et al.*[114] used AFM to monitor deposition of biofilms on SCL surfaces and showed that the surface roughness increased with deposit formation, supporting the common thought that a substrate of deposits adhered to the CL surface acts as an important precursor for bacterial colonization.

Increasing roughness was evident particularly during over-wear of CLs,[12] what is a real problem within CL wearers that frequently prolong wearing schedules against the practitioner recommendations. Even in new lenses the increasing roughness could be in part responsible for the higher level of bacterial attachment in Purevision compared to conventional hydrogel Acuvue lenses[104] and other Si-Hi material without surface treatment.[103]

Wearing SCL while swimming in chlorinated pools has been associated with higher contamination of CL by microbial organisms, regardless of lens material. No significant differences in types of bacteria isolated were observed between first generation Si-Hi and conventional FDA group IV conventional hydrogel.[115]

In summary, despite the great advances in CL materials and care solutions, microbial contamination continues to be present in CL and lens care accessories of CL wearers being present in almost half of the patients evaluated.[116] Importantly, the risk for contamination increased as the number of days per week of CL wear decreased. This has been attributed to a lower training of occasional users in lens handling procedures and to keeping the lenses for longer periods of time inside the cases, without cleaning or solution renewal, thus increasing the chance of deposit formation. Conversely, the number of hours per day of lens wear did not affect the risk of contamination.[116]

4.6.1.5. Changes in mechanical properties

Little is known about the changes in mechanical properties of SCL with wear. Kim *et al.*[117] have demonstrated that the surface friction and adhesive force of the hydrated CL surface were significantly reduced compared to those measured for the surface-dehydrated lenses. An increase in rigidity of SCLs as a result of on-eye dehydration during wear could be expected, however the impact of surface deposits, polymer bulk deterioration as a result of wear and care regimes along with dehydration are not yet known. If other mechanisms different from dehydration can affect the mechanical properties of SCL materials must be investigated.

4.6.1.6. Changes in dimensional parameters

The expected changes in CL parameters and their clinical impact are different for RGP and SCL. Again, dehydration is the main factor that affects the parameter stability of SCL. The natural consequence of material dehydration will be the shrinking of the material, which depends on the linear expansion coefficient of each material[118] directly related to the EWC of the material and its polymeric composition (main constituents and cross-linking agents). For example, the level of dehydration was found to be significantly higher in a 58% EWC SCL than in a 74% EWC SCL despite of its lower EWC. This dehydration was accompanied by a reduction in overall diameter, and movement.[57] These changes are more significant during the first hour of wear until a new EWC is achieved when the lens is immersed on the tear fluid at the particular biochemical and environmental conditions of the ocular surface. This happens when lens hydration reaches a new equilibrium in the new physiological environment at the ocular surface with a significantly different biochemical composition, temperature and probably pH level compared to that in the lens container. Movement of high water content hydrogel lenses decreased 0.60 ± 0.57 mm over 7 hours and the in vivo diameter of a medium water content hydrogel lenses decreased by 0.12 ± 0.16 mm. These facts were associated with an increase in dryness ratings during the same period of time.[57] These changes are likely to induce CL intolerance and reduce the number of hours of comfortable wear.

Regarding RGP materials, parameter changes as a result of use affect the curvature of the surfaces, with a trend for lenses to become toric as a result of bending with prolonged wear. This effect is more likely to be present in thinner CL designs and high Dk materials.[119-121] The clinical significance of this effect is the induced astigmatism.

Other aspects of interest in lens deterioration are for example oxygen permeability. Previous findings that demonstrate a decrease in hydration of SCLs after wear,[11] or the penetration of proteins within the bulk of the material[89-91] would lead to a decrease in oxygen permeability, at least for conventional hydrogel materials, as Dk is closely related to EWC. However, previous studies did not find a significant effect of lens deterioration with lipid and protein deposits or cosmetics under continuous wear of high EWC, on oxygen performance of hydrogel lenses.[122] Same results were achieved by Refojo *et al.*[123] that measured the oxygen permeability of hydrophilic lenses with different degrees of surface deposit coating; surprisingly, they found a non-significant trend towards increase in oxygen permeability as the coating increased.

4.6.2. Deterioration of rigid gas permeable contact lenses

Similarly to SCL, deterioration processes of rigid gas permeable (RGP) CL are dominated by deposit formation, and their potential effects on corneal physiology, vision and comfort, and parameter changes because of bending, particularly in thinner designs and high Dk materials. RGP, however, do not have bulk hydration changes and are less subjected to bacterial binding to lens surfaces and epithelial cells.[124] Furthermore, deposits on RGP CL are not as severe as in SCL because the hard surfaces resist matrix infiltration. Conversely, RGP and rigid PMMA lenses are particularly subjected to surface scratching and abrasions in their surfaces because of their rigid or semi-rigid character.

Deposit-related deterioration of RGP CLs is primarily driven by lipid deposits which are associated with the partially hydrophobic nature of these polymers.[80] However, protein deposits are also important, with a level of recovery of about 100 μg/lens,[125] which is well below the level of deposits in a hydrophilic ionic material and above the amount of proteins recovered from hydrophilic non-ionic materials according to data from Jones *et al.*.[50] Regarding lipid deposits, Bontempo and Rapp[80] have observed similar levels of lipid deposits in FSA RGP materials compared to Group I to IV hydrophilic lenses, while higher levels of lipid deposits were found in SA RGP materials, being about twice as high than hydrophilic lenses and FSA RGP materials.

4.7. Potential impact of contact lens deterioration on ocular physiology

The ocular surface under a CL suffers physiologic changes motivated by the decrease of oxygen availability under the lens, the mechanical effect of the CL and the increased evaporation rate induced by tear film disruption due to the presence of a foreign body such as the CL. However, deterioration of the CL polymer can exacerbate the manifestation of such changes and increase the risk of suffering other pathological conditions directly related to CL wear. Dryness, hypoxia and microtrauma caused by CL wear are frequently discussed as the main etiological factors for signs of intolerance or reaction to CL wear. Thus, any worsening effect in the CL properties able to affect theses issues can potentially exacerbate CL intolerance. *Table 4.2* summarizes some common problems with CL (particularly with modern Si-Hi materials).

Immediately after lens insertion, the potential effects of deterioration of CL properties and deficiencies in their physiological performance and biocompatibility are evident in the ocular surface, (i.e. corneal and conjunctival epithelium, because of the mechanical interaction with the soiled CL surface). Later, the difficulties of the CL to maintain proper wettability and the disruption of the tear film, along with potential effects of reduction in oxygen and hydraulic/ionic permeability, can induce symptoms of dryness, affect vision, exacerbate the hypoxic stimulus thus inducing limbal redness, and decrease the lens movement.

Table 4.2. Potential problems associated with Si-Hi CL wear (but not exclusive of those), clinical significance for eye health and possible strategies for appropriate management

Problem	Etiology	Clinical Significance	Solution
Inicial discomfort	High elastic modulus Flat fitting	Low	Adaptative, self-solving, change to lower modulus, steep base curve
Mucin balls	Roll-up of tear debris trapped behind CLs	Low	Artificial tear, steep base curve radius, lower modulus
SEAL	Lid pressure on high modulus CL	Moderate	Lower modulus
Poor wettability	More hydrophobic surfaces + lipid deposit build-up	Low	Daily cleaner and/or hydrogen peroxide
Topographic changes	Corneal flattening by mechanical effect	Low	Check for lens inversion, fit steeper or change to lower modulus
Orthokeratology-like effect	CL worn reversed	Moderate	Check for lens inversion
Microcysts	Transient metabolic response to higher oxygen availability	Low	Adaptative, self-solving
Focal staining (< grade II)	Indentation by tear debris trapped behind CL	Low	*(see mucin balls)*
Localized epithelial defect (> grade II)	SEAL, CL binding, foreign body, flat fitting	Moderate	Stop lens wear and act according to aetiology
Diffuse staining	Allergic reaction to care solution's preservatives	Moderate	Change MPS or use hydrogen peroxide
Papillary reaction	Mechanical friction with the upper lid, denaturized proteins	Moderate	Lower modulus, change care regime
Lipid deposit build-up	Partially hydrophobic	Moderate-Low	Rub lenses after removal, use daily cleaner and/or hydrogen peroxide
CL adherence	Poor overnight tear turnover	Moderate	Artificial tear drops before sleep and on awakening, reduce number of nights with lenses

(*) Some moderate complications can require stopping CL wear and do not resume until resolution. Low significant complications do not require CL wear interruption, although clinical action must be required sometimes according to the etiology

Finally, long term changes can affect structures at a deeper level in the ocular surface as a result of combination of mechanical, hypoxic and inflammatory stress to produce transient or permanent histological changes in the inner corneal layers, corneal neovascularization, decrease tear secretion and/or decrease in corneal sensitivity. In rare cases, the corneal and conjunctival tissue is seriously compromised resulting in adverse reactions such as corneal ulcers, infiltration, conjunctivitis and acute red eye. These effects are frequently associated with pathogenic microbial colonization of CLs, lens care products and devices, and/or the ocular surface.[20] Because of deterioration of CL material properties can affect the ability of the lens to maintain its characteristic surface properties (wettability, resistance to bacterial adhesion, deposit build-up, topography) and bulk properties (gaseous and hydraulic permeability, hydration and mechanical properties), CL deterioration can potentially induce or exacerbate the presentation of ocular complications. This is further covered in the following section 4.7.1.

There is a lot of literature dealing with physiological and pathological changes related to CL wear. It is not the goal of this review to cover all of these issues; therefore this section will only review some of those studies paying particular attention to those focused on the evaluation of corneal tissue changes as well as limbal and conjunctival reactions.

4.7.1. Cornea

At the corneal level, all the three cellular layers can suffer changes as a result of long term CL wear.[126,127] Most of these changes do not reach pathologic status and are frequently considered as "physiologic changes".[128] Their etiology is of different nature but the properties of the materials and their relatively limited compatibility motivate that deterioration can modulate their incidence and/or presentation pattern. Some complications related to CL wear and their prevalence are shown in *table 4.3*.

4.7.1.1. Epithelium

Long term wear of CLs of low oxygen transmissibility (Dk/t) induces changes in all layers of the cornea.[128-130] Liu and Pflugfelder[131] reported that long-term CL wearers had significantly thinner corneas over the central 6 mm compared to age-matched control subjects who had never worn CLs. The epithelium is particularly sensitive to this exposure. These effects include epithelial microcysts,[129,132,133] decreased cell adhesion,[134] increased permeability,[135] increased cell size[136,137] decreased cell shedding[137] and thinning of the central epithelium.[129,137] These effects could be linked to the lower epithelial turnover seen in RGP lens wearers under extender wear conditions.[138]

A recent study demonstrated that long term wear of hydrogel lenses is associated with overall epithelial thinning of the central, mid-peripheral and peripheral cornea.[139] Whilst the effect is more pronounced in eyes wearing the CL with the lower oxygen transmissibility, we could not demonstrate a cumulative effect of the duration of wear. The latter finding may be a reflection of the adaptive process described by other investigators during the first year of extended wear.[137]

Although no significant alterations of corneal curvature were observed during 1 month of overnight wear of high Dk/t RGP lenses,[140] Vreungdenhil and co-workers[141] suggested that the loss of one or two layers of superficial epithelial cells as result of a mechanical effect of rigid CL wear could account for a thinning of 10 to 15 microns in the absence of hypoxia. In the study by Perez *et al.*, the average change in central CT was 11 microns. Stapleton *et al.*[142] did not find alterations in corneal epithelial cell size of viability after 3 months wear of high-Dk SCLs when compared with those obtained from non-CL wearers. Such a finding would not support the assumption of epithelial cell loss to explain corneal thinning. Short term evidences of increased epithelial permeability were not detected with the same lenses.[143] Instead of the theory supporting that cell loss would increase epithelial fragility and permeability with subsequent superficial fluorescein staining, not present in this sample, we hypothesized that a slight compression of the central cornea under higher modulus SCLs,[144] in addition with overnight lid compression, could account for central corneal flattening and thinning. In fact, physical reduction or compression of the superficial epithelial cells have been demonstrated with conventional SCL wear under closed eye conditions.[145] Similar effects were demonstrated with reverse geometry RGP CL for orthokeratology therapy, inducing a slight redistribution of tissue volume resulting in flattening and thinning of the central cornea.[146]

Simultaneous changes in anterior corneal curvature and thickness towards central cornea thinning as curvature flattens, have been previously reported in high-Dk RGP lens wearers,[147] suggesting that changes in corneal radii may be related to the mechanical effects of lid pressure through the CL without a clear explanation for thickness changes as hypoxia seemed to be absent with those lenses. A similar behavior of parallelism between thickness and curvature changes was not observed in edematous corneas as result of induced hypoxic stimulus, not displaying changes in anterior corneal curvature as cornea becomes thicker.[148]

Although previously reported,[149] this fact was fully investigated recently by Erickson *et al.*[150] concluding that morphological changes in corneal structure under edematous stimuli are more evident in the posterior direction with unappreciable modifications in anterior corneal curvature. This has important implications in the appearance of some clinical findings of edema such as striae and folds in the posterior cornea. Additional interesting explanations about swelling dynamics have been also discussed in a previous study.[147]

Signs of hypoxia were absent with first high-Dk Si-His worn on a 30-night CW basis either in corneal epithelium, stroma, endothelium, or vascular response,[151] all considered as hypoxic stress indices during CL wear.[129,152,153] Nevertheless, this hyper-permeable lenses were found to induce mechanical changes in both cornea and conjunctiva, resulting in: Conjunctival indentation,[154] trace central corneal flattening,[38] and superior epithelial arcuate lesions (SEAL).[35] Epithelial indentation is observed after removal of these high Dk/t materials, and is presumably related with the increased incidence of spherical post-lens debris, which has been termed "mucin balls" or "lipid plugs".[39,155,156] Both, evidence of local mechanical effect and increased incidence of spherical debris behind the lens, are probably linked with a higher elasticity modulus of this hyper-permeable materials.[144] The increase in concentration of Langerhans cells in the corneal epithelium of guinea pigs wearing CLs has also been attributed in part to a mechanical effect caused by the CL.[40]

From the clinical point of view, superficial corneal epithelial staining is the most commonly observable effect of CLs. In fact, corneal staining continues to be one of the main problems related with CL wear, both RGP, hydrogel or Si-Hi. The clinical significance of the majority of these episodes is limited and staining occurs up to a certain degree in many CL wearers.[69] The presentation is very heterogeneous but specific patterns are frequently associated with different CLs. Inferior staining is typically associated with SCL dehydration, 3 & 9 o'clock is typically associated with RGP CL wear,[157] while a typical pattern of diffuse keratitis with preferred localization near the limbus in the whole circumference of the cornea has been associated with care solutions toxicity for the disinfection of Si-Hi materials (www.stainingrading.com). Despite limited clinical relevance, superficial epithelial defects should be kept as far as possible because epithelial defects increase the chance of bacterial adhesion and infection. There are not differences in the form of presentation between daily wear and extended wear modalities of SCLs. According to the same study, the most common locations that should be investigated are superior and inferior corneal areas.[158]

4.7.1.2. Stroma

Numerous studies on corneal response to hypoxia under CLs used corneal thickness as a physiological objective indicator of physiological stress. The results obtained by González-Meijome and Perez (*unpublished data*) for long term low-Dk/t SCL wearers reflected no significant differences between lens wearers and control subjects. Apparent edema was 2.1%, 1.2% and 0.7% for central, mid-peripheral and peripheral cornea, respectively. These values are not significantly different from those reported previously for the central cornea under similar conditions.[129] Long term stromal thinning is responsible for this finding, partially masking true stromal edema as previously reported in the central cornea.[129] To the best of our knowledge, there is not data of stromal apparent edema in the peripheral cornea.

Higher levels of edema have been reported with the acute response to CL wear. Holden *et al.*,[129] using optical pachometry, found lower levels of edema in the periphery (10-12%) than in the central cornea (13-16%) along the horizontal meridian. Erickson *et al.*,[159] also confirm this finding in the vertical meridian, with 14.2%, 11.5% and 8.3% of central, mid-peripheral and peripheral acute edema under a uniform hypoxic stimulus.

The effect of physical presence and mechanical effect of the CL in the ocular surface has been postulated as an aetiological factor in the loss of keratocyte in the corneal stroma during lens wear.[41,42] This fact could be related with the stromal thinning[129] and overall corneal thinning observed in long-term CL wearers.[131] Long-term thinning of the stroma has been evidenced in low-Dk SCL wearers by modified optical pachometry (*umpublished data* from González-Méijome and Perez). The mechanical effect of CLs has also been pointed as a causative effect of CL-related corneal infiltrates.[160]

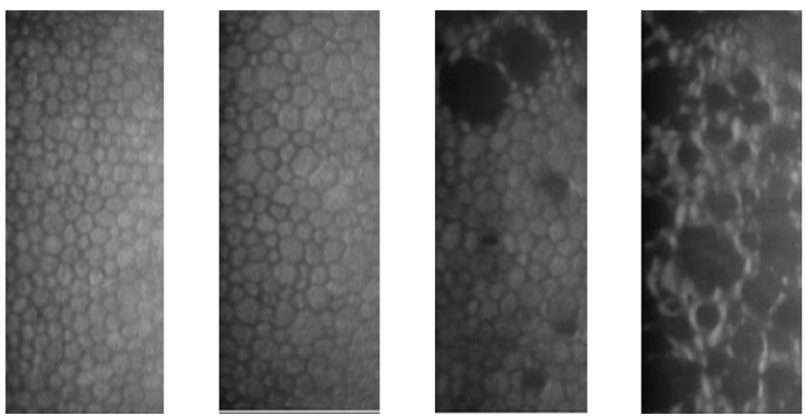
Table 4.3. Prevalence of different CL related changes in the ocular surface as quoted in different studies

Clinical Entity	Definition	Most Likely Etiologic Links	Incidence & Bibliographic Source
CLPC	CL related papillary conjuntivitis	Mechanical Deposits	1.7 [161] to 47,5[162] 4.6 to 7.2% (Si-Hi CW)
SEAL	Superior Epithelial Arquate Lesion	Mechanical	4.5% (Si-Hi CW)[87]
CLPU	CL peripheral ulcer	Bacteria	15-25%(Si-Hi CW)[87] 5.4% (CW)[87]
CLARE	CL acute red eye	Bacteria	1-13%[20]
AIK	Asymptomatic Infiltrative Keratitis	Bacteria	1-3.8% (Si-Hi CW)[87]
IK	Infiltrative Keratitis	Bacteria	5% (Si-Hi CW)[87]
SK	Superficial/punctuate keratitis	Dessication/ Mechanical/Toxicity	(see table 4.1 and corresponding reference for further details)[33]
MK	Microbial Keratitis	Bacteria/Fungus	0.01% (Si-Hi CW) [87] (see table 4.1 and corresponding reference for further details)[33]
LR	Limbal Redness	Hypoxia	
Dryness	CL-related dry eye	Evaporation/ Hyposecretion	

Si-Hi: silicone hydrogel; CW: continuous wear

4.7.1.3. Endothelium

The response of the corneal endothelium to CL wear is in some way enigmatic because almost none of the potential effects of lens wear or lens deterioration or oxygen deprivation would have a direct impact in this corneal layer. In fact, the endothelial layer is not under hypoxia during lens wear because oxygen requirements are satisfied by the aqueous humor, does not suffer dehydration and is less likely to be affected by mechanical impact, compared to the epithelium and stroma. However, the corneal endothelium of CL wearers displays significant changes in the number, shape and size of cells,[163] particularly for patients wearing their lenses on an extended or continuous modality.[126,129] These effects are less evident with high Dk materials,[154,163,164] so despite the absence of a direct decrease of oxygen availability, endothelial changes under CL wear seem to be paradoxically driven by hypoxic stimulus. It has been postulated that metabolic debris resulting from hypoxic metabolism of the epithelium and anterior stroma will induce an acidic stress in the endothelial cells, causing cell death.[128,165,166] Different stages of deterioration of the human corneal endothelial layer are shown in *figure 4.5*.



(A) (B) (C) (D)

Figure 4.5. Different degrees of endothelial damage. Normal to slight distorted endothelial mosaic (A), moderate polymegatism and pleomorphism (B), moderate polymegatism and endothelial guttata (C) and totally distorted endothelial mosaic with severe guttata (D).[167]

4.7.2. Limbal region

Redness or hyperemia of the limbal region is the most common sign of physiological interaction with hydrophilic CLs. Staining in the peripheral cornea near limbus are also a common finding with modern Si-Hi materials, particularly when combined with certain care solutions. The etiology of this effect seems to be multi-factorial, including sensitivity to CL care solutions, deposits in the mid-peripheral region of the CL, stagnation of the tear film in this area, mechanical pressure or thicker peripheral designs in negative lenses. Furthermore, 3 & 9 o'clock staining are also common with RGP CLs and this effect is attributed to desiccation of the corneo-conjunctival surface near the edge of the lens.[157]

4.7.3. Conjunctiva

Conjunctival reaction to CL wear and material deterioration can be summarized into hyperemic, hypertrophic and staining responses. Hyperemic conjunctival reaction seems to be associated with hypoxia, sensitization by care solutions, microbial entities or mechanical effects and affects both bulbar and tarsal conjunctivas. Hypertrophic changes are typical of the palpebral conjunctiva and are frequently associated with allergic responses to denaturized proteins in the CL surface and recently with the higher mechanical impact of first generation Si-Hi materials. Staining can occur because of dryness of the ocular surface, which can be related to tear dysfunction exacerbated by the presence of the CL, or by mechanical indentation. Stapleton *et al.*[168] observed that after an episode of CL-related corneal inflammation in the form of CL-related acute red eye (CLARE), CL wearers increase the chance of experiencing recurrent episodes. Risk of recurrence after previous episodes of inflammatory events have also been observed for other CL related adverse events as CL peripheral ulcer (CLPU).

A contaminated surface which tends to dehydrate more would potentially increase the friction forces with the ocular surface and such process has been proposed as a major determinant of giant papillary conjunctivitis. High Dk Si-Hi lenses do not appear to accumulate greater levels of deposits when worn on 30-night replacement extended wear schedules.[169] However, even in the absence of greater levels of deposits, physical interaction of these CL made of slightly stiffer materials and the superior palpebral conjunctiva has been proposed as the main cause of local CLPC in patients with high Dk SCL during extended wear.[16] However, Jones *et al.*[86] demonstrated that a higher level of lisozyme denaturizing was present in Si-Hi balafilcon A and lotrafilcon A materials compared to conventional hydrogel etafilcon A. Recently, the same research group evaluated the activity of hen egg lysozyme using an in vitro model and concluded that etafilcon A presented the highest level of protein deposition and denaturizing, while Si-Hi materials presented lower levels of protein deposits and lower denaturizing. Proteins and denaturizing levels in Si-Hi varied with material composition (poster by Jones *et al.* available at www.siliconehydrogel.com).

To confirm this, a recent study[100] suggests that a greater proportion of patients wearing high Dk Si-Hi lenses during extended wear develop CLPC, being one of the main reasons for CL discontinuation. A new Si-Hi CL, Acuvue Advance® (galyfilcon A) has demonstrated in a study that induces less CLPC than Focus Night & Day® (lotrafilcon A).[170] This could be in part justified by the lower modulus of galyfilcon A material and perhaps the smoother surface due to the absence of surface treatment.[171] Conjunctival staining is also a sign of dryness of the ocular surface both in non-CL wearers and CL wearers.[172]

4.8. Conclusions

Several advances have been recently made in terms of CL material. These improvements have been focused on the increase of oxygen flux to the corneal surface and they have proved to be effective in the relief of ocular redness,[170,173] hypoxic stress,[133] and refractive changes[37,38] associated with extended wear of low Dk SCLs. All these facts have certainly contributed to confirm a lower incidence of serious complications under extended and continuous wear, when compared with extended wear of conventional hydrogels for fewer consecutive nights.[153,174,175] However, other questions remain unsolved, as highly permeable materials have demonstrated to be associated with a higher incidence of other inflammatory events, such as papillary conjunctivitis,[176] and probably some infiltrative conditions of the cornea and conjunctival inflammation.[87,177] Other clinically significant events such as muco-lipid balls behind the lens,[178] surface deposits,[170,179] or superior epithelial arcuate lesions[35] are still present with first Si-Hi materials. New large scale studies will give an insight on whether such conditions are improved or not with the new lower Young modulus Si-Hi materials.

The pattern of deposit formation in modern SCLs depends strongly on material composition. Protein deposits are more predominant in ionic materials, while lipids are more prevalent in non-ionic high water content materials containing NVP and Si-Hi materials. Overwear of CLs beyond recommended indicated wearing period, should be avoided because this is correlated with increasing levels of deposits and ocular symptoms.

Concerning to symptoms of dryness, both biomimetic and Si-Hi materials have been promissory to overcome this common symptom. The approach in biomimetic materials was to delay water release from the bulk of the material by incorporating hydrophilic monomers that established strong bonds with water molecules. This is the case of phosphorilcholine (PC Technology™) in Proclear and glycerol methacrylate (GMA) in hioxifilcon materials. In the first generation Si-Hi, the lower water content combined with a conventional design in terms of thickness was thought to be a warranty for lower dehydration. Other new Si-Hi incorporate highly hydrophilic materials such as PVP in Acuvue with Hydraclear™. Despite some studies support the lower dehydration of biocompatible materials and a significant relief of dryness symptoms,[54] significant differences have not been found with Si-Hi materials regarding to their dehydration process or relief of dryness symptoms in recent studies.[15,180]

Serious complications still occur with modern lenses, although at a very low rate if adequate hygiene, care with CLs, CL replacement and adequate patient follow-up are warranted.

Frequent replacement has several advantages in terms of avoiding lens material deterioration, with positive outcomes in terms of comfort, which is one of the main points to avoid drop-outs.[181] Considering the positive experiences with daily disposable CLs as the most problem-free option when considering the deterioration of polymers,[182-185] we think about the new frontier towards lenses that can be daily disposable using the most recent advances in physiologic biocompatibility provided by Si-Hi. By now, this is not an option, but maybe in the following years, this can be a reality.

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Chapter 5

Microscopic Observation of Unworn Silicone Hydrogel Soft Contact Lenses by Atomic Force Microscopy†

5.1. Abstract

Purpose: To characterize the surface topography of silicone hydrogel (Si-Hi) contact lenses (lotrafilcon A, balafilcon A and galyfilcon A) different samples were observed with Atomic Force Microscopy (AFM).
Methods: Contact lenses (CLs) were observed by AFM in Tapping Mode at areas ranging from 0.25 to 400 μm^2. Mean roughness (*Ra*), root-mean-square roughness (*Rms*) and maximum roughness (*Rmax*) in nanometers were obtained for the three lens materials at different magnifications.
Results: The three CLs showed significantly different surface topography. However, roughness values were dependent of the surface area to be analyzed. For a 1 μm^2 area, statistics revealed a significantly more irregular surface of balafilcon A (*Ra* = 6.44 nm; *Rms* = 8.30 nm; *Rmax* = 96.82 nm) compared with lotrafilcon A (*Ra* = 2.40 nm; *Rms* = 3.19 nm; *Rmax* = 40.89 nm) and galyfilcon A (*Ra* = 1.40 nm; *Rms* = 1.79 nm; *Rmax* = 15.33 nm). *Ra* and *Rms* were the most consistent parameters, with *Rmax* presenting more variability for larger surface areas. The higher roughness of balafilcon A is attributed to the plasma oxidation treatment used to improve wettability. Conversely, galyfilcon A displays a smoother surface.
Conclusion: Present observations could have implications in clinical aspects of Si-Hi CL wear such as lens spoliation, resistance to bacterial adhesion or mechanical interaction with the ocular surface.

5.2. Introduction

A smooth surface is essential for the optical quality and the biocompatibility of CLs and the ocular surface. Conventional hydrogel CLs provide good mechanical interaction with ocular surface and lids due to softness and surface moisture. However, the limited oxygen transport through these materials is a handicap for continuous wear (day/night) of the traditional hydrogel CLs. Oxygen and carbon dioxide exchange is necessary for the maintenance of normal ocular surface homeostasis and particularly for the maintenance of cornea's physiology.[1]

† Gonzalez-Meijome JM, Lopez-Alemany A, Almeida JB, Parafita MA, Refojo MF. Microscopic observation of unworn siloxane-hydrogel soft contact lenses by atomic force microscopy. *J Biomed Mater Res B Appl Biomater* 2006;76:412-418.

The advent of Si-Hi materials in the late 1990s was a revolutionary breakthrough in the contact lens field. Such materials combine the comfort of the traditional hydrogel lenses with the high oxygen and carbon dioxide permeability of silicone used in the elastomeric CL and the siloxane materials used in rigid gas permeable (RGP) CLs.

The surfaces of original Si-Hi materials, because of the hydrophobic siloxane moieties migrating to the surface, were non-wettable by tears and poorly tolerated. Therefore, the two currently available Si-Hi lenses are finished with treatments to obtain wettable surfaces, Purevision™ (balafilcon A) by plasma oxidation[2] and Focus Night & Day™ (lotrafilcon A) by plasma polymerization of a mixture of trimethylsilane, oxygen and methane[3]. Acuvue Advance™ (galyfilcon A) does not need surface treatment to induce wettability according to the manufacturer. A fourth lens, O_2OPTIX™ (lotrafilcon B), not included in this study, was delivered to the marketplace recently with no data available about the superficial structure or treatments to increase wettability. However, this material (lotrafilcon B) is second generation to lotrafilcon A (Focus Night & Day) and could be surmised to have the same surface treatment.

Several techniques have been recently applied to contact lens microscopic examination with different purposes, including X-ray photoelectron spectroscopy (XPS),[4] atomic force microscopy (AFM),[5] scanning electron microscopy (SEM),[6] and time-of-flight secondary ion mass spectrometry.[7]

In AFM, a sharp tip stylus, attached to a small cantilever scans the sample surface within a subnanometer range or resolution. Several studies have revealed that AFM is a proper technique to study hydrogel contact lens surface because it can explore the contact lens surface in aqueous environments and can provide microscopic information with a spatial resolution relevant to the size of polymeric functional groups proteins and cells. Because the sample for AFM does not need to be electrically conductive, no metallic coating is required as it is in SEM. Therefore, some of the surface irregularities such as ondulations or wrinkles observed under conventional SEM that are artifacts of the critical point dehydration and subsequent metallic coating process,[6] are not seen in the AFM samples.

AFM was previously used to characterize superficial structure of conventional hydrogels.[8] Some applications of AFM to contact lens field include the comparison of surface roughness of hydrogel contact lenses (HCL) produced via a cast-mold process, or a double-side lathe cut process,[9] to monitor biofilm deposition on the CLs,[10] to determine the adhesion and friction properties of HCL,[5] and to evaluate the surface mechanical properties of hydrogel lenses under different environment humidities.[11] One limitation of AFM is that does not give chemical information of the surface examined, as could be obtained with XPS or time-of-flight secondary ion mass spectrometry, for example.

In the present study, we used AFM to characterize the surface topography of unworn Si-Hi CLs in physiological solution as commercially obtained. To the best of our knowledge this is the first time that the surface structure of Si-Hi soft contact lenses (SCLs) are studied with AFM and reported in a peer-reviewed journal.

Table 5.1. Identification and nominal parameters of contact lenses used in the study in alphabetical order

	Acuvue Advance™	Night & Day™	Purevision™
Manufacturer	Vistakon J&J	Ciba Vision	Bausch & Lomb
Material (USAN)	Galyfilcon A	Lotrafilcon A	Balafilcon A
FDA Group	I	I	III
Manufacturing	Cast molding	Cast molding	Cast molding
Surface Treatment	None	Plasma coating	Plasma oxidation
Hydration	47%	24%	36%
Dk (barrer)	60	140	99
Center thickness (in mm@ -3.00)	0.070	0.080	0.090
Dk/t @ (-3.00)	87	175	110
Base curve (mm)	8.30	8.40	8.60
Diameter (mm)	14	13.80	14.20
Refractive Power (D)	-3.00	-3.00	-3.00
Wearing schedule	DW	EW / CW	EW / CW
Replacement	Bi-weekly	Monthly	Monthly
Special features	UV Blocking		Handling tint

USAN: United States Adopted Names Council; FDA: Food& Drug Administration; Dk: oxygen permeability; Dk/t: oxygen transmissibility; Rx: refractive power in diopters (D); DW: daily wear; EW: extended wear; CW: continuous wear.

5.3. Material and Methods

5.3.1. Samples

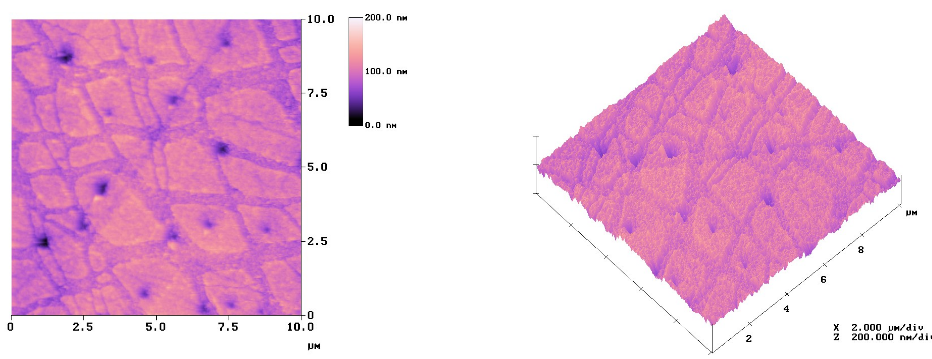
Three of four Si-Hi CLs currently available were examined under AFM. They were Focus Night & Day™ (lotrafilcon A, CIBA Vision, Duluth, GA), Purevision™ (balafilcon A, Bausch & Lomb, Rochester, NY) and Acuvue Advance™ (galyfilcon A, Vistakon, Jacksonville, FL). A newer Si-Hi lens O_2OPTIX™ (lotrafilcon B, CIBA Vision, Duluth, GA) is not included in this study. Technical details of the lenses examined are summarized in *table 5.1*. The lenses were obtained in the original containers filled with a physiological saline solution.

5.3.2. Sample preparation

After lens removal from the original containers using sterile silicone protected tweezers, a small piece of the contact lens was obtained and fixed with a double-face adhesive to a flat support without inducing material bending. The same saline solution used to store the soft contact lens was added to the sample to maintain its hydration during microscopic observation. All these procedures as well as microscopic examinations were carried out in the same room kept at 20ºC and approximately 50% relative humidity during sample preparation and examination procedures.

5.3.3. AFM observations

All observations were conducted in an aqueous environment using the liquid cell of the AFM (Nanoscope III, Digital Instruments, Santa Barbara, CA). Cantilevers with a nominal force constants of k=0.58 N/m and oxide-sharpened Si_3N_4 tips (Olympus Ltd., Tokyo, Japan) were used for imaging. The samples were observed at different scanning ranges in order to obtain different magnifications in Tapping Mode™. In the Tapping Mode™ the sample can be used again after imaging. The sample may be tested again as is or further processed, and then re-imaged to provide images of a time-series of repetitive exposures.



(A) (B)

Figure 5.1. AFM surface analysis of balafilcon A contact lens. The scale represents local roughness in nanometers (nm). The three-dimensional image (B) is rotated 45º clockwise.

The three samples were scanned over lengths of 20, 10, 5 and 1 µm to give a surface area scanned of approximately 400, 100, 25 and 1 µm^2. *Figure 5.1* is an example of surface imaging using two-dimensional and three-dimensional representation facilities of Nanoscope III. Additionally, samples of the galyfilcon A and lotrafilcon A lenses were analyzed at higher magnification over a 0.25 µm^2 surface area.

5.3.4. Surface roughness analysis

Mean surface roughness (*Ra*), mean-square-roughness (*Rms*), and maximum roughness (*Rmax*) were obtained from the roughness analysis facility of the Nanoscope III software (*figure 5.2*). *Ra* indicates the average distance of the roughness profile to the center plane of the profile. *Rms* represents the standard deviation from the mean surface plane. *Rmax* represents the maximum high identified within the observed area. All the roughness parameters are expressed in nanometers (nm).

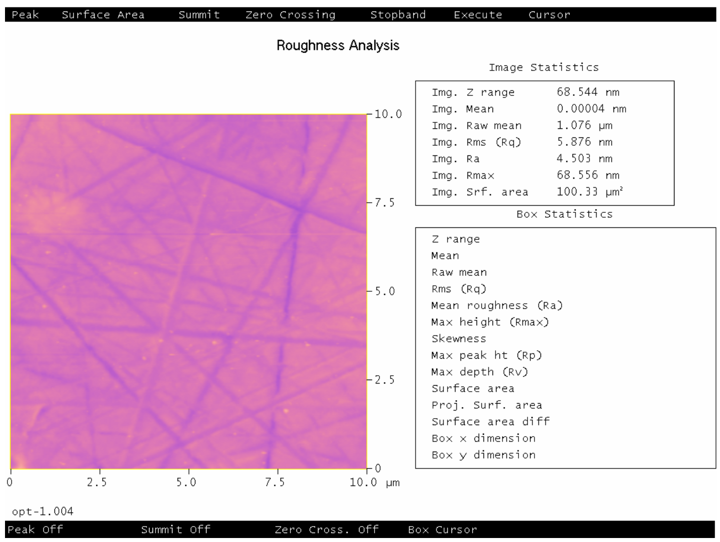


Figure 5.2. AFM display for roughness analysis of lotrafilcon A contact lens for a 100 μm^2 area. Parameters are specified in nanometers (nm).

5.4. Results

Substantial differences were seen in the three Si-Hi lenses examined (*figure 5.3*). This difference is obviously due in part to the plasma treatment which is particularly relevant for Purevision™ (balafilcon A) lens as seen in the lower magnification microphotographs in *figure 5.3*. The silicate island structure is not seen when the area of observations is below 5 microns. Macropores are seen with excellent resolution and their diameter reached up to 0.5 microns (*figure 5.3B*).

The Acuvue Advance™ (galyfilcon A) shows a particular surface structure that consists of a homogeneously distributed pattern of globular formations which are evident at all magnification range (*figures 5.3 and 5.4A*). Similar structures were also observed under high magnification in Focus Night & Day™ (lotrafilcon A) as seen in *figure 5.4B*. Lotrafilcon A material exhibits also a pattern of linear marks on the material that are seen under lower levels of magnification and almost disappear under higher magnification (*figure 5.4B*).

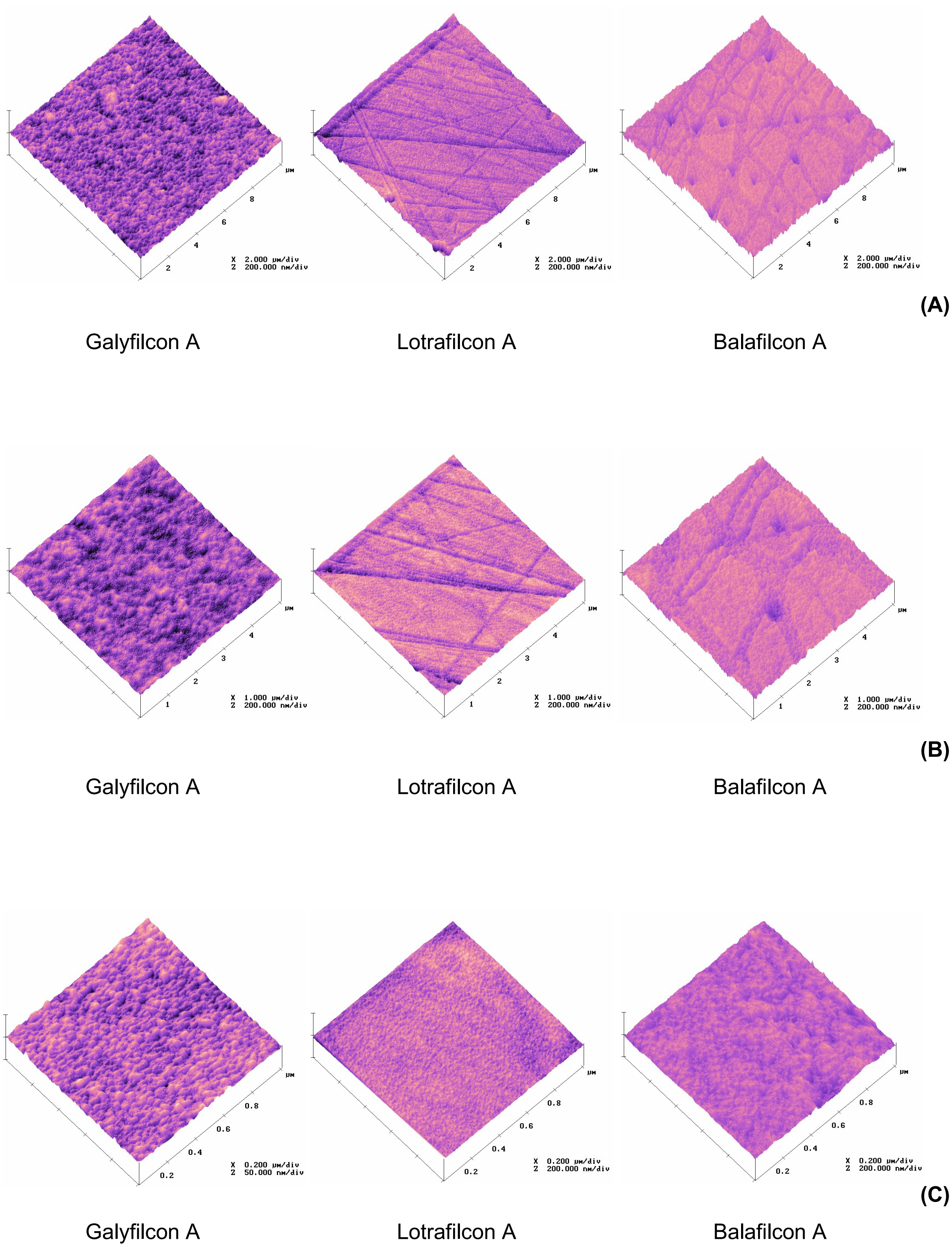
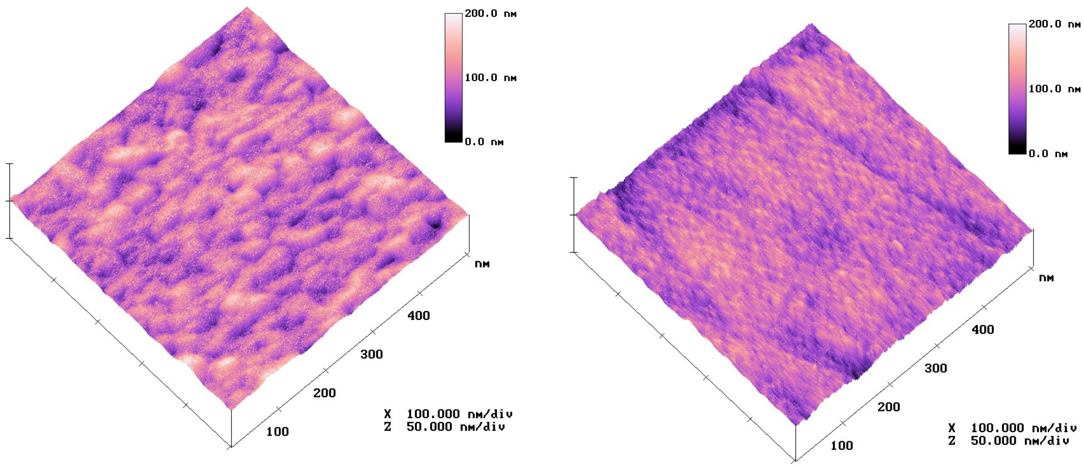


Figure 5.3. Surface appearance of silicone hydrogel contact lens at different magnification. Surface areas: (A) 100 µm^2, (B) 25 µm^2, (C) 1 µm^2. Quantitative roughness parameters are presented in *table 5.2*.



(A) **(B)**

Figure 5.4. High magnification view of galyfilcon A (A) and lotrafilcon A (B) contact lenses over a 0.25 μm^2 area.

Figure 5.5 represents quantitative roughness parameters of the three materials for 1μm^2 area. *Tables 5.2, 5.3* and *5.4* display the roughness parameters for all lenses and different analyzed areas. Despite qualitative globular appearance, galyfilcon A was significantly smoother than lotrafilcon A, and balafilcon A had the highest roughness scores. This order was maintained irrespective of the analyzed area as seen in *figure 5.6* for *Rms* (*figure 5.6A*), *Ra* (*figure 5.6B*) and *Rmax* (*figure 5.6C*). Close observation of the data showed that the estimates of surface roughness for the three materials follow almost parallel behavior as a function of the observed area, except *Rmax*, which seems to increase higher than expected when the area of 400 μm^2 was evaluated.

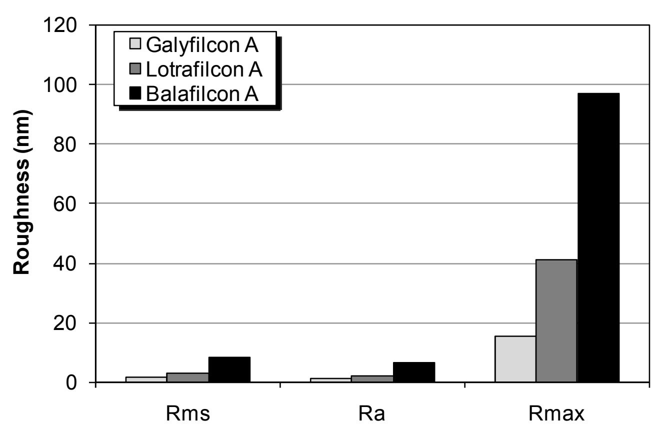


Figure 5.5. Diagrammatic comparison of roughness parameters for the three silicone-hydrogel lens surfaces. Values expressed in nanometers (nm).

Table 5.2. Root-mean-square roughness (*Rms*) of the three contact lens surfaces at various magnifications for different areas of 1, 25, 100 and 400 μm^2

	1μm^2	25μm^2	100μm^2	400μm^2
Lotrafilcon A	3.19 ± 0.97	4.67 ± 0.76	7.40 ± 1.14	10.37 ± 1.19
Galyfilcon A	1.79 ± 0.6	6.75 ± 2.23	6.68 ± 2,35	7.05 ± 2.17
Balafilcon A	8.30 ± 1.02	12.26 ± 3.27	13.38 ± 3.9	19.11 ± 3.34

Roughness is expressed in nanometers (nm)

Table 5.3. Average roughness (*Ra*) of the three contact lens surfaces at various magnifications for different areas of 1, 25, 100 and 400 μm^2

	1μm^2	25μm^2	100μm^2	400μm^2
Lotrafilcon A	2.40 ± 0.56	3.60 ± 0.98	5.58 ± 0.78	7.65 ± 1.27
Galyfilcon A	1.40 ± 1.09	5.39 ± 1.96	5.25 ± 2.12	5.52 ± 2.34
Balafilcon A	6.44 ± 0.50	9.55 ± 4.14	10.42 ± 4.12	11.84 ± 4.14

Roughness is expressed in nanometers (nm)

Table 5.4. Maximum roughness (*Rmax*) of the three contact lens surfaces at various magnifications for different areas of 1, 25, 100 and 400 μm^2

	1μm^2	25μm^2	100μm^2	400μm^2
Lotrafilcon A	40.89 ± 25.45	42.05 ± 32.58	88.87 ± 45.26	157.09 ± 50.12
Galyfilcon A	15.33 ± 36.45	61.56 ± 49.25	57.65 ± 52.36	115.02 ± 65.41
Balafilcon A	96.82 ± 27.50	116.92 ± 30.81	140.32 ± 40.79	389.90 ± 73.21

Roughness is expressed in nanometers (nm)

Galyfilcon A displayed higher values of roughness than lotrafilcon A only for the 25 μm^2 area. Conversely, the most significant differences between materials surface is observed at 400 μm^2. At higher magnification, both galyfilcon A and lotrafilcon A display similar roughness scores, while balafilcon A doubles those values. Nevertheless, qualitatively differences are evident for all the magnification ranges.

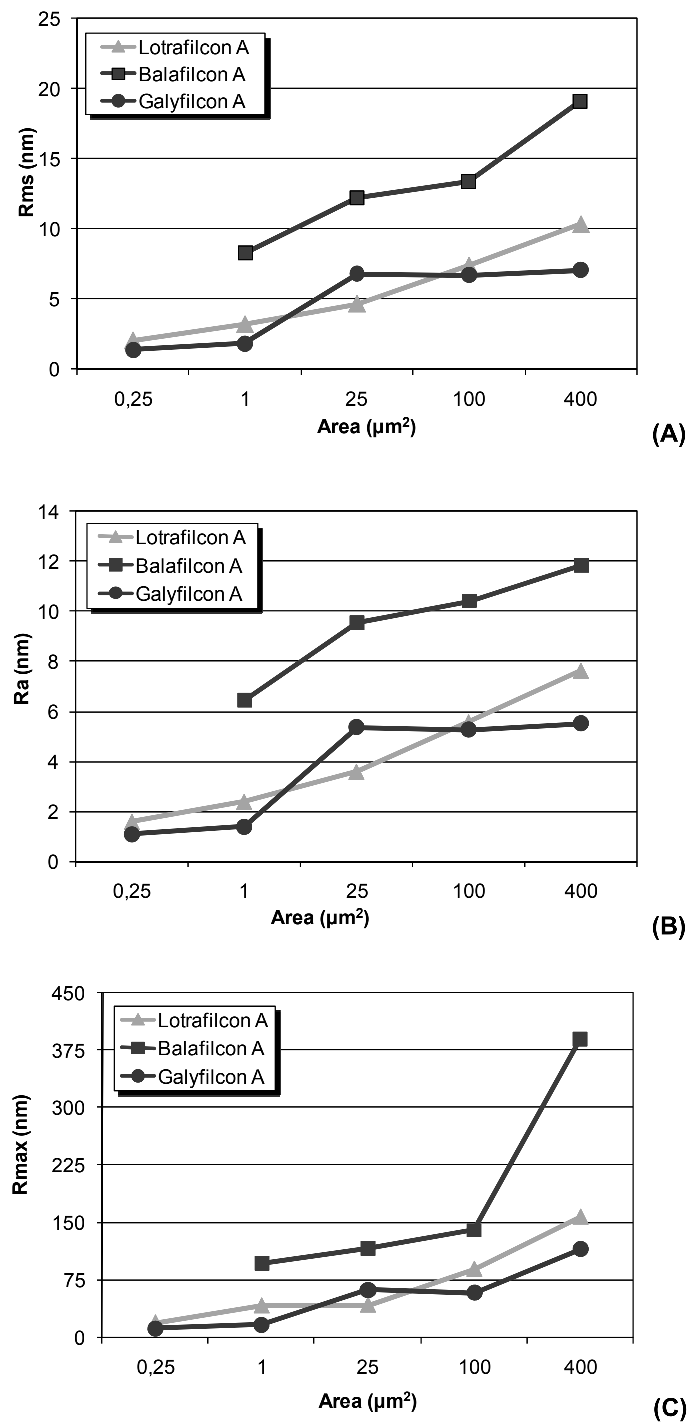


Figure 5.6. Variation of *Rms* (A) *Ra* (B) and *Rmax* (C) parameters for different scanning surface areas. Values are in nanometers (nm).

5.5. Discussion

Among other factors, surface roughness of devices in indirect contact with living systems will influence their biological reactivity. The relationship between surfaces is particularly important in contact lens practice as the polymer should interfere as little as possible with the epithelial surface of the cornea and the conjunctiva. This is necessary to maintain corneal transparency, epithelial cell integrity, and patient tolerance of the contact lens. However, after the contact lens is exposed to the tears, the adsorption of the tears components could contribute to an increase in surface roughness. These interactions are of primary interest to understand biocompatibility and deterioration of CLs. To make the lenses wettable by tears, the balafilcon A lenses are treated by plasma oxidation, resulting in deposits of a thin silicate (SiOx) surface on the lens.[2] On the other hand, the lotrafilcon A lenses are treated by a plasma polymerization process with a mixture of trimethylsilane, oxygen or dry air, and methane that deposits a thin film of cross-linked hydrocarbon containing hydrophilic radicals on the surface.[3]

The silicate islands clearly seen on the dehydrated balafilcon A lenses by scanning electron microscopy[6] are also evident by AFM in the hydrated state. The estimated diameter of 0.5 μm in this study is consistent with the observations of Lopez-Alemany *et al.*[6] suggesting that the macroporous structure of balafilcon A does not vary significantly between the fully hydrated state and the critical-point dehydration needed to perform SEM observations.

The hydrophilic nature of the surface of galyfilcon A lenses is due apparently to the presence of polyvinyl pyrrolidone (PVP) moving from the bulk to the lens surface. The surface pattern observed by us for galyfilcon A is different from the uniformly smooth, nontreated surfaces shown before for conventional hydrogel CLs.[6] We hypothesize that these features could be polymer moieties observed at the sample surface under AFM as uniformly distributed globular formations. The more uniform surface and the lower modulus of galyfilcon A could be reflected in a lower incidence of papillary conjunctivitis.[12] The potential involvement of a lower incidence of deposits or the lower modulus of the material is still to be investigated.

One fact that deserves discussion is the surface topography of linear marks observed on lotrafilcon A. Similar appearance was observed before by Merindano *et al.*[13] in RGP contact lens surfaces using interferential shifting phase microscopy, particularly in those made of higher permeable materials. As all RGP CLs are made by lathe-cut technology, the observations of Merindano *et al.*[13] are justified due to the manufacturing technique. Grobe[9] reported that SCLs produced by cast-molding presented smoother surfaces that those produced by lathe cut. However, all lenses in this study were produced by cast-molding, so one possible explanation of the linear marks on lotrafilcon A could be attributable to defects on the mold surfaces that would be transferred to the lens material during polymerization.

In new lenses surface roughness has two possible origins: material properties and manufacturing method. Baguet *et al.*[8] calculated mean roughness (*Ra*) using homemade software to be within a range of 4.9 to 16.98nm for a 78% water content cast-molded P(MMA/NVP) hydrogel lens and a 55% water content, lathe-cut P(HEMA/MA) hydrogel lens, respectively, in a scanning range of 19μm.

Our results demonstrate that the roughness analysis varies significantly with magnification. Thus, for a 20 μm scan range (400 μm^2 surface area) our results are of the same order of magnitude, 5.52 nm for galyfilcon A and 11.84 nm for balafilcon A. Bagget and co-workers attributed some responsibility for the higher roughness to the presence of methacrylic acid (MA) in the 55% water content lathe-cut lens. Conversely, they found a smoother surface on the 78% water content lens with NVP made by cast-molding.[8] This agrees with the smooth structure of galyfilcon A that has a significant content of PVP.

The systematic application of AFM to worn CLs is also of interest. Kim *et al.*[14] have demonstrated that the surface friction and adhesive force of hydrated contact lens surfaces were significantly reduced compared to that of the surface of dehydrated lenses. This would be an interesting study using Si-Hi because their mechanical interaction with the ocular surface has been one of the main concerns.

The clinical implications of contact lens roughness have been previously discussed. Among other properties of the contact lens surface, such as hydrophobicity and atomic composition, Bruinsma *et al.*[15] demonstrated that surface roughness was one of the most important factors determining adhesion of *Pseudomonas aeruginosa* to etafilcon A [P(HEMA/MA)] SCLs. Similar findings were also reported by the same authors for RGP CLs.[16] Also, Baguet *et al.*[10] used AFM to monitor deposition of biofilms on hydrogel contact lens surfaces and showed that as the surface roughness increased the biofilms deposited on the lens also increased.

In summary, the ability of AFM to study hydrated samples is very important with hydrogels used in CLs and its application is of enormous interest in the development and evaluation of new materials.

Roughness parameters *Rms* and *Ra* seem to be the most useful and reliable to characterize surface topography of Si-Hi CLs. On the other hand, *Rmax* can be easily affected by local imperfections or sample contamination leading to higher values than expected and so material characterization based on this parameter could be unreliable and poorly repeatable.

With this study we present original data on the qualitative and quantitative characterization of the surface topography of modern Si-Hi CLs. The present results suggest that existing differences among the three lenses studied could have implications on their clinical behavior regarding deposit formation and bacterial colonization which could result in subsequent eye infection and eye inflammation in the form of papillary conjunctivitis.

***Acknowledgments*:**

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Chapter 6

Surface Topography and Mechanical Properties of Silicone Hydrogel Contact Lens Materials With AFM

6.1. Abstract

Purpose: Accurate measurement of CL surface topography and mechanical properties is important to understand the interaction of contact lens (CL) materials with the ocular surface, particularly with the cornea and the conjunctiva. The purpose of this study is to perform a review of the literature on the measurement of mechanical properties with atomic force microscopy (AFM) and to evaluate the topography and mechanical parameters of the CL surface using this device.
Methods: Four commercial silicone hydrogel soft contact lenses (CLs) had been evaluated in the hydrated state using atomic force microscope. Tapping mode was used to obtain surface topography and quantitative roughness parameters (*Rms* and *Ra*) over a 25 μm^2 area. Contact Mode was used to obtain indentation curves that will be used to compute mechanical parameters of the materials including Young modulus and hardness.
Results: The process of calculation of surface parameters from indentation curves is explained in detail. The values obtained for the Young modulus has good repeatability which could be expected from the highly repeatable indentation process.
Conclusions: The values of Young modulus we obtained with AFM are not interchangeable with the values given by manufacturers using other methods of mechanical testing. These parameters were computed for all CLs and the values obtained although different were in the same order of magnitude to those reported previously in the literature for the same materials. A high level of repeatability has been found what make this method suitable for evaluate and compare the mechanical properties of the material before and after wearing the lenses.

6.2. Introduction

The mechanical impact of CL materials on the corneal surface has become a matter of concern for several years. However, it has been with the advent of silicone-hydrogel (Si-Hi) materials that this question has attracted more attention of clinicians and material engineers. Different clinical entities such as mucin balls,[1] corneal flattening[2] or superior epithelial accurate lesions (SEAL)[3] have been found more frequently with modern Si-Hi soft contact lenses (SCLs) that include in their formulas a significant amount of siloxane moieties, as in the first generation of Si-Hi materials.

The most commonly accepted theory to explain those findings is the higher elastic modulus of the materials.[4] Despite the importance of the mechanical properties on modern

SCL tolerance, only a few publications have addressed this question, and most of them did not considered Si-Hi materials.[5] Regarding the information available about mechanical properties of CL materials, its comparability among studies is limited because of the different approaches used to characterize these properties. The methodology of engineering stress-strain curves is usually used to evaluate the tensile properties SCL materials including Young modulus.[6] This method evaluates the properties of the CL as a whole, however, most of the CL changes associated to wear are related to the surface of the CL, so there is interest in studying the mechanical properties of the CLs at their surface to understand how they change with wear and the degradation effects experienced by the material including surface dehydration and deposit formation.

In the last years, atomic force microscopy (AFM) has become a useful tool for high resolution imaging of SCL materials in the natural hydrated state being applied in material characterization at a nanometric scale[5,7-10] with different purposes as evaluation of deposit formation[11-13] or determination of bacterial adhesion.[14,15] Despite some reports on the measurement of elastic properties of SCL with this technique,[5,10] we believe that the potential demonstrated in other fields to analyze soft samples in the hydrated state and other materials,[16-18] has not yet been fully explored in the field of CL research concerning the characterization and comparison between materials. This analysis could help to understand the interactions of CL materials with the outer layers of the ocular surface, particularly epithelial surface of cornea, bulbar conjunctiva and palpebral conjunctiva which suffers directly the impact of CL interactions as described in chapter 4.

The goals of the present study were twofold. First one was to review some parameters with the potential to be used in the quantitative characterization of SCL surfaces by nanoindentation with AFM. The second one was to apply this methodology to different CL polymers in order to obtain some of those mechanical properties, as elastic modulus, hardness and other related parameters.

6.3. Material and Methods

6.3.1. Sample materials and sample preparation

Four Si-Hi CLs were tested. The lenses were obtained in the original containers filled with a physiological saline solution. Prior each analysis, lenses where allowed to be fully hydrated in buffered saline at least for 24 hours. Technical details of the samples are listed in *table 6.1*.

Table 6.1. Technical details of Si-Hi contact lenses used in the study

	Air Optix Night & Day	Acuvue Advance	Air Optix	Purevision
USAN[†]	Lotrafilcon A	Galyfilcon A	Lotrafilcon B	Balafilcon A
Material[‡] **(main monomers)**	TRIS+DMA+silo-xane monomer	HEMA+PDMS+ DMA+PVP	TRIS+DMA+silo-xane monomer	TRIS+NVP+TPVC +NCVE+PBVC
Surface Treatment	Plasma Coating	No	Plasma Coating	Plasma Oxidation
Dk	140	60	110	99
t_c (mm @-3.00)	0.08	0.07	0.08	0.09
Dk/t (barrer/cm)	175	87	138	110
H_20 (%)	24%	47%	33%	36%
FDA	I	I	I	III
Power (D)	-3.00	3.00	-3.00	3.00
Diameter (mm)	13.8	14.6	14.2	14
Base Curve (mm)	8.6	8.7	8.6	8.6
Schedule/ Replacement	CW/DW Monthly	DW Bi-weekly	DW Bi-weekly	CW/DW Monthly

†USAN: United States Adopted Name Council
‡DMA: *N,N*-dimethl acrylamide; HEMA: 2-hydroxyethyl methacrylate; NCVE (*N*-carboxyvinyl ester); PC: phosphorylcholine; TRIS: 3-methacryloxy-2-hydroxypropyloxy propylbis (trimethylsiloxy)methylsilane; TPVC (tris-(trimethylsiloxysilyl) propylvinyl carbamate); PBVC (poly[dimethysiloxy] di [silylbutanol] bis[vinyl carbamate])

For AFM analysis three different samples of each material where placed in the holder shown in *figure 6.1* resting on its concave face keeping the lens fully hydrated during the measuring process. The convex face of this holder has been designed to mimic the curvature of the CLs used (approximately 8.6 mm). All these procedures as well as microscopic examinations were carried out in the same room kept at 24ºC and approximately 50% relative humidity. All observations were conducted in an aqueous environment using the liquid cell of the AFM (Nanoscope III, Digital Instruments, Santa Barbara, CA). Cantilevers with a nominal force constants of k=0.58 N/m and oxide sharpened Si_3N_4 tips (Olympus Ltd., Tokyo, Japan) were used for Tapping Mode imaging and Contact Mode nanoindentation.

6.3.2. Surface topographic analysis

Average surface roughness (*Ra*) and mean-square-roughness (*Rms*) were obtained from the roughness analysis facility of the Nanoscope III software as we did in previous studies.[9,19] *Ra* represents the average distance of the roughness profile to the center plane of the surface profile. *Rms* represents the standard deviation from the mean surface plane. Both roughness parameters are expressed in nanometers (nm). In the present study, we did not include maximum roughness (*Rmax*) as this parameter represents the maximum high identified within the observed area and does not reflect the actual topography of the lens with large variability being expected depending on the target area.[9] Samples were scanned over lengths of 5 μm to give a surface area of 25 μm^2. Although this is a very small area considering the full CL surface, it has been shown that provides a good resolution for the identification of the particularities of each material surface with good repeatability.[9]

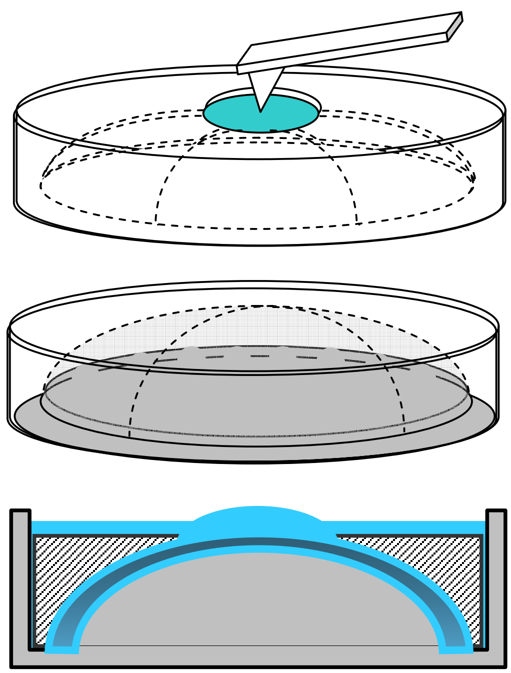


Figure 6.1. Holder to maintain the sample hydrated and to conform lens shape during topography an indentation analysis with the AFM.

6.3.3. Indentation and quantitative mechanical properties

6.3.3.1. Experimental conditions for indentation curves in Contact Mode and determination of Force vs Penetration curves

Characteristics of the cantilever and tip probe are listed in *tables 6.2* and *6.3* Because of the known influence of temperature in bending of silica nitride cantilevers, all experiments were carried out at the same room temperature of 24ºC.

Different procedures to compute mechanical properties from these curves are described in further detail in the following sections as this review of methods and formulations is one of the goals of the present chapter. For these determinations, we follow the recommendations of Hues and Draper.[20]

Table 6.2. Nominal characteristics of the AFM tip

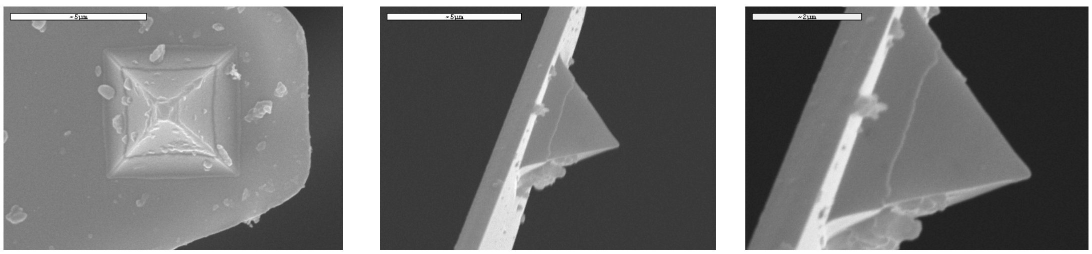
Parameter	Value
Designation	NP-S
Nominal tip radius	5-40 nm
Spring Constant	0.58 N/m
Cantilever lengths	100 micron
Cantilever shape	V-shaped
Reflective coating	Gold
Tip's shape	Square pyramidal
Tip half angle	35º

Table 6.3. Experimental set up of the AFM microscope for indentation experiments

Parameter	Value
Scan rate	0.996 Hz
Advance rate	0.797 nm/s
Reverse rate	0.797 nm/s
Ramp Size	400 nm
Tip velocity	2 μm/s
Sample lines	256
Deflection constant*	5.101 ± 0.14 nm/V
Spring Constant	0.58 N/m
Sample Indentation Setup	5x2 @100 nm separation

* average of 10 measurements on calibration sample (silica)

Indentation was performed in Contact Mode, at a scan rate of 1 Hz using a ramp size of 400 nm which gives an approaching speed of 2 μm/s. This value was used by other authors to evaluate CL materials.[5] The approaching speed of the tip during the indentation process determines the reaction of the material and so the results obtained. The spring constant as measured by calibration with a reference material (silica) was 0.58 N/m. The deflection sensitivity of the cantilever was measured ten times against the same reference material and the value was 5.10 ± 0.14 nm/V. This measurement is a part of the calibration process and is repeated before each measurement session. For each sample, indentation was made in 10 different locations over the surface area arranged in a 5 x 2 rectangular matrix with a 100 nm separation (0.05 μm^2) centered within the area of 25 μm^2 previously analyzed in Tapping Mode. These and other relevant experimental specifications are listed in *table 6.3*.

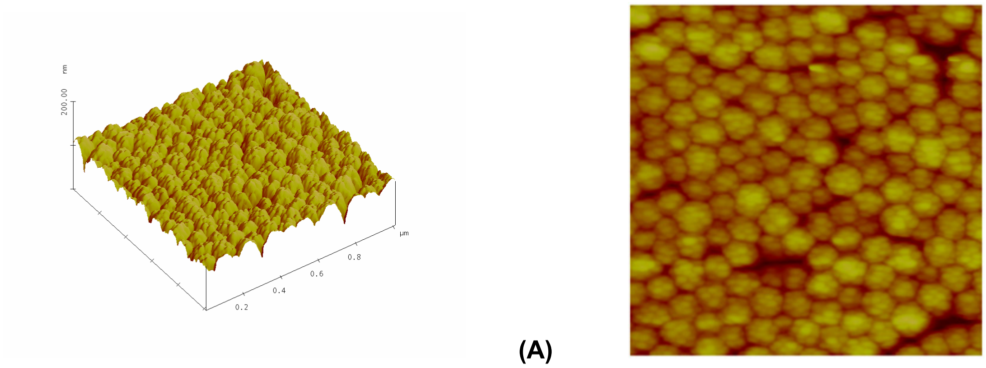


(A) (B) (C)

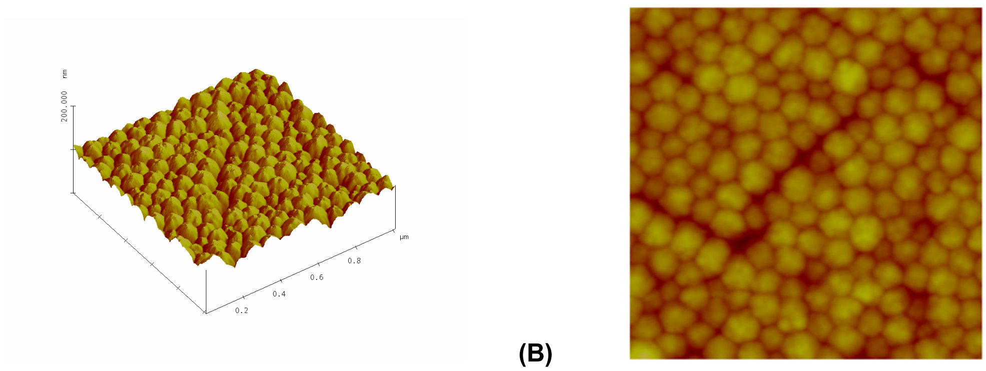
Figure 6.2. Microphotographs of the tip geometry observed with a scanning electron microscope (SEM). Scaled bar represents 5μm (A,B) and 2μm (C).

In this study all measurements were done with the same tip. The state of the tip was checked at the beginning of each session as another part of the calibration process. Damage to the tip will result in loss of resolution on topographic evaluation and errors in tip geometry and contact area during indentation leading to errors in the calculation of the mechanical properties. This evaluation can be made in two ways. One is observing the tip at the electron microscope (*figure 6.2*). This is time consuming and less convenient for frequent and systematic procedures. The other one consists on the topographic analysis of a known surface geometry as a sample of silica as shown in *figure 6.3*. Poor resolution due to soiled or damaged tip will result in underestimation of surface roughness, because of lack of sensibility to detect minor changes in height. Roughness analysis of these images revealed that root mean square (*Rms*) and average roughness (*Ra*) decrease as the resolution of the tip decreases with values of *Rms* = 9.40 nm/ *Ra* = 6.851 nm for the new tip (*figure 6.3A*), *Rms* = 6.68 nm / *Ra* = 5.23 nm for the soiled tip (*figure 6.3B*) and *Rms* = 3.25 nm / *Ra* = 2.62 nm for the damaged tip (*figure 6.3C*). The qualitative inspection of the images allows to evaluate the state of the tip prior to proceed with a new experimental session.

An example of the output of sample displacement vs cantilever deflection is shown in *figure 6.4*. Sets of repeated indentation curves for three different materials are displayed in *figure 6.5*. Given the good repeatability of the indentation process, only three of the ten indentation curves will be used for further calculations.



(A)



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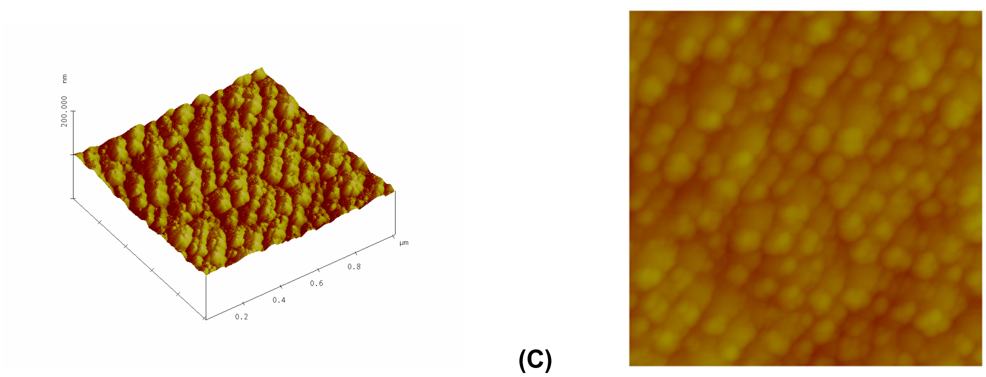
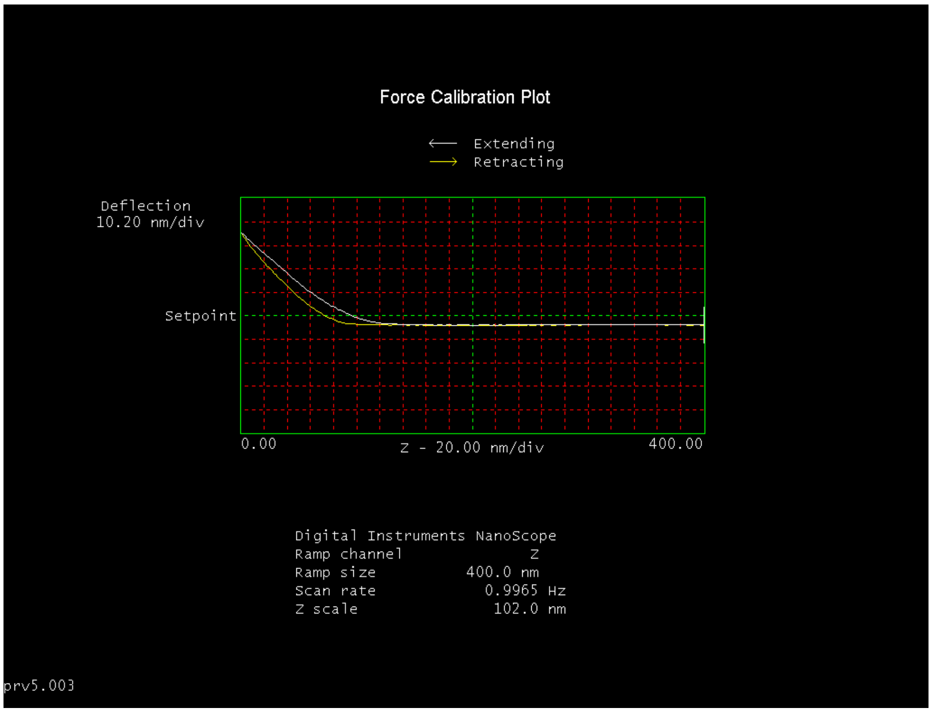


(C)

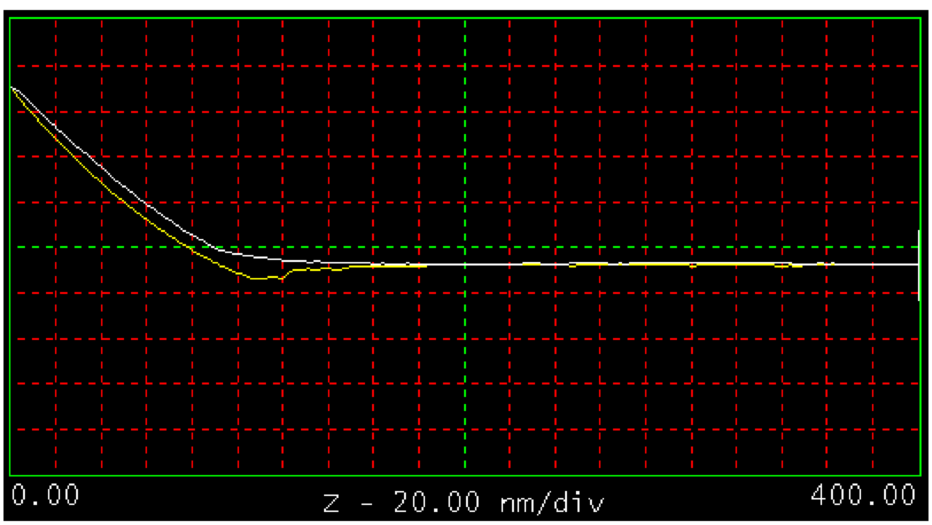
Figure 6.3. Surface topography of a silica sample with a new tip (A), with a used tip with no defects but soiled by pieces of the specimen (B) and with a damaged tip (C). Images represent 1µm^2 area- Vertical scale is ±100 nm.

Each one of this three indentation curves were exported as ASCII files and opened using Microsoft Excel Spreadsheet. Decimal places must be separated by commas to work properly on Excel File; then continuous data imported as text from ASCII were separated into columns for data of Time (in seconds), Calculated Z Displacement of the sample (in nanometers), cantilever Deflection (in volts), cantilever Deflection (in nanometers) and Deflection as Load (in nN) for extend and retract portions of the indentation process. Only

Calculated Z Displacement which represents the displacement of the sample in nm, Deflection in nm and nN are used. Deflection in Volt and nm are related to each other by the deflection sensitivity (mm/V). Deflection in nm and nN are mutually related by the spring constant (nN/nm).



(A)



(B)

Figure 6.4. Output of indentation trace (advancing) and retrace (retract) curves from the Nanoscope III (A) and detailed view (B).

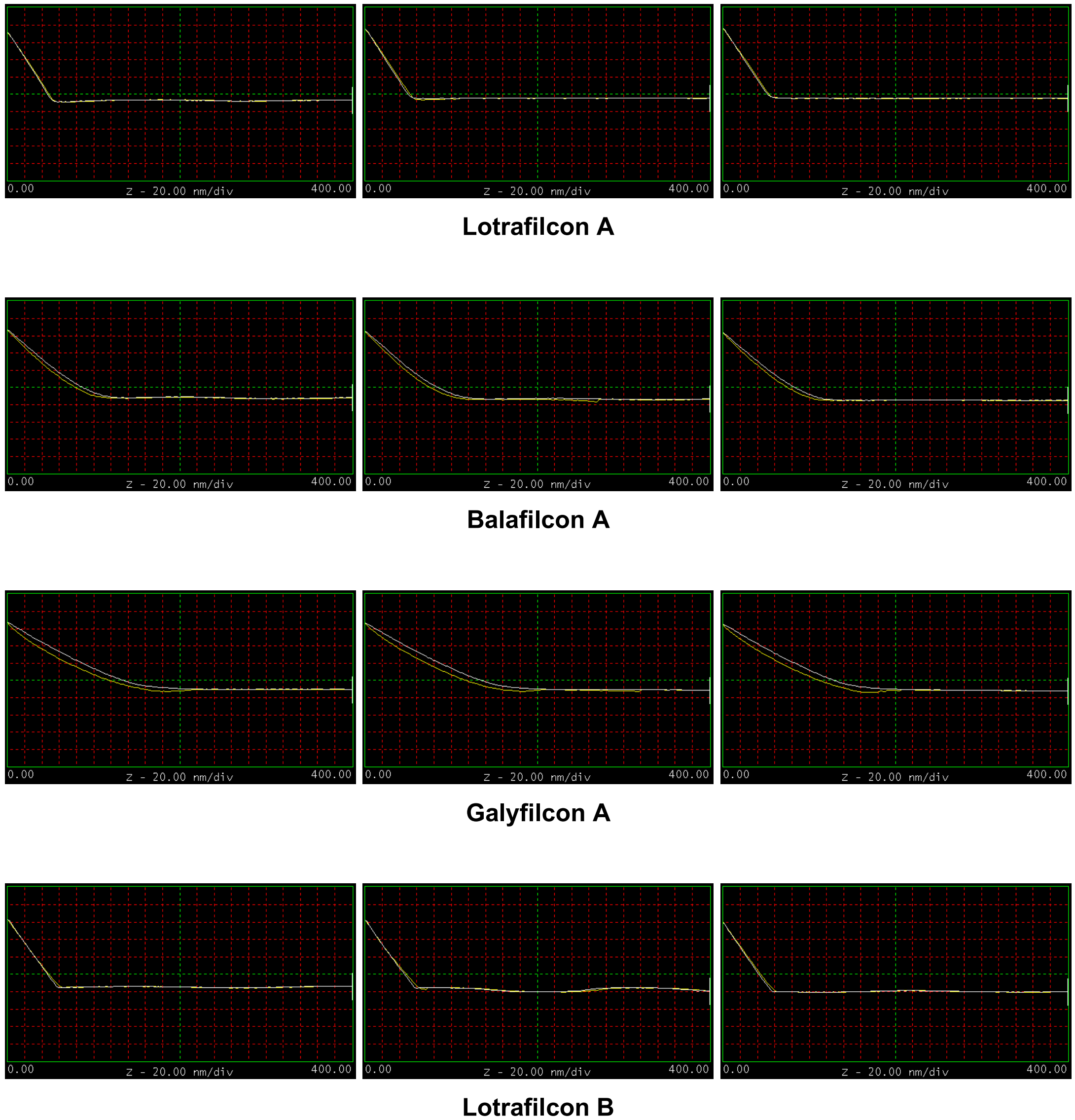


Figure 6.5. Examples of indentation curves obtained directly with the AFM on contact mode for the four materials under investigation. Three of the ten indentations made in a 5 x 2 array separated 100 nm of each other are presented for each material.

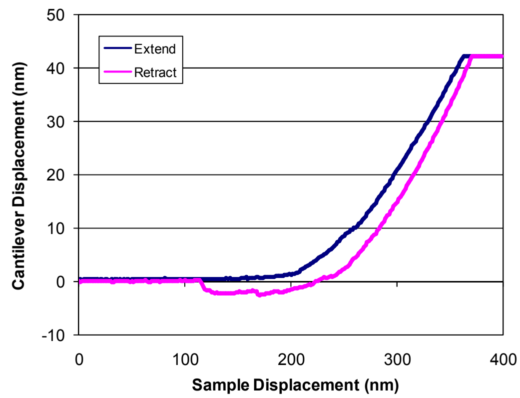
The following step is to obtain force vs penetration curves that are necessary to obtain quantitative mechanical properties of materials with AFM. This process is explained in detail for further clarification. We followed the procedure described by Hues *et al.*:[20]

- 1) In order to obtain a curve of cantilever Displacement against sample Displacement such as that presented in *figure 6.6A*, retract data of cantilever Displacement should be pasted in reverse order so that retract curve data will start at the end of the extend curve.
- 2) Load (nN) versus sample displacement can be represented in the same way using the Deflection of the cantilever in nN instead of nm. This curve is usually referred in

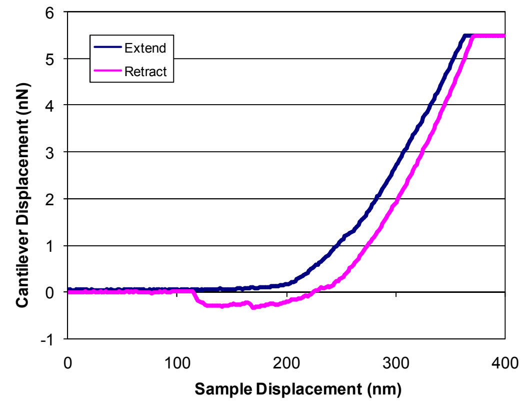
the literature as the Force vs Sample Displacement curve and is displayed in *figure 6.6B*.

- 3) In the following step, the contact point of the cantilever with the sample during the approaching of the tip to the sample surface should be determined as this will be the starting point of the indentation process. Different approaches have been used to obtain an accurate determination of this position. Kim *et al.* determined this point as the intercept of the average slope line and the zero force line in the force versus displacement curves.[5] Hues *et al.* discussed the subjectivity of this parameter, otherwise, critical for the accurate final result. Sometimes a sharp contact point is not appreciable, as it is the case of irregular and/or softer surfaces. For this reason they recommended to define the contact point as the point on the loading curve at which the cantilever position increases, above the rest position, by more than two standard deviation times (2xSD) of the rest position noise.[20] For indentation measurements, each curve consists of 256 data points for advancing (trace) and retracting (retrace) phases. To exclude any possible contribution from plastic deformation (permanent) which can occur during the loading phase (advancing), only data from the initial parts of the unloading curves were used to compute mechanical properties.[21-23]
- 4) Once the contact point is determined, the value of sample Displacement at this point is subtracted to all sample displacement positions obtained from the original data as Calculated Z Displacement of the sample in nm. This allows us to rescaling the graph to place the beginning of the indentation process as the Zero Displacement as seen in *figure 6.6C*.
- 5) The next step consists on deleting all negative values of sample Displacement to isolate the positive part of the curve that represents the part of the entire curve where the tip is "within" the sample during the advancing or extending (indentation) and retract (extracting or pull-off) process. This is displayed in *figure 6.6D* and this curve, also called force vs penetration curve contains the information needed to evaluate the response of the material to the load applied.
- 6) Finally the initial straight part at the beginning of the retraction curve is isolated to obtain the slope from which the mechanical quantitative parameters will be computed (*figure 6.6C*).

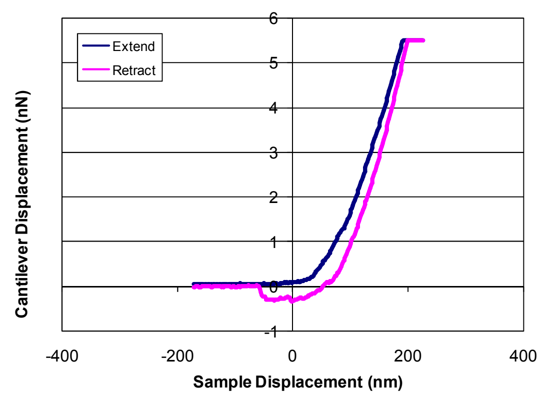
The formulation to obtain quantitative parameters differs slightly in different studies depending on the type of materials to be analyzed and the geometry of the indentation tips. For this reason, the following parts of the methods section are devoted to make a review of these different approaches found in the visited literature, with particular emphasis on elastic modulus.



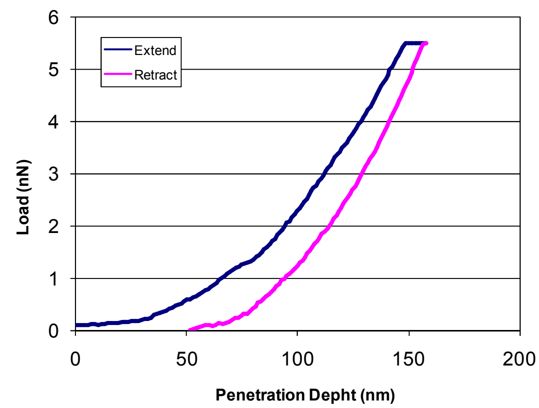
(A)



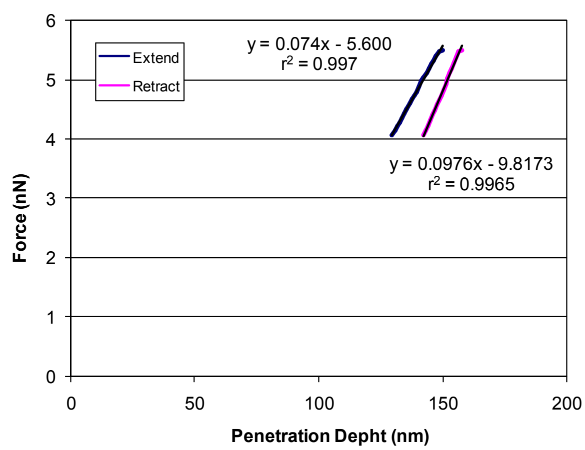
(B)



(C)



(D)



(E)

Figure 6.6. Examples of indentation curves. Sample displacement vs cantilever deflection in nm (A) and applied load in nN (B); sample displacement vs applied load adjusted at the contact point (C); penetration depth vs applied load (C); slope at the initial phase of the retracting (retracting) curve (E).

6.3.3.2. Elastic modulus

The indentation formulation of the pyramidal Si_3N_4 cantilever tip used in this study was done using a cone shaped model as described earlier for similar pyramidal tips. In the work of Radmacher *et al.*, this model showed higher correspondence with experimental data than the indentation of a spherical tip[16] the model followed in other studies. The authors justified this fact because the indentations are large compared with the radius of curvature at the very end of the tip (usually 20 nm, 5 to 40 nm as quoted by some manufacturers). This is the case for our experiments where penetration depths in the order of hundred nm are found. An opening angle of 35º for our tip is quoted by the manufacturer which is in agreement with the values reported by Radmacher *et al.*[16] for different tips from the same wafer. Spring constant was obtained by calibrating the deflection of the cantilever against an infinitely stiff sample (i.e. silica). The spring constant of the tip links the stiffness of the cantilever with the cantilever displacement to obtain the force on the tip via the Hook's law.

Another parameter commonly used in nanoindentation experiments is the Poisson's ratio. Poisson's ratio represents the ratio of transverse contraction strain to longitudinal extension strain in the direction of stretching force. For SCL materials, a Poisson ratio (ν) of 0.5 is commonly accepted as in the previous work of Radmacher *et al.*[16] This value has been assumed for silicone rubbers since Rinde's work in 1970.[24] This value is very close to the 0.48 used by Kaul *et al.*[17] for silicone elastomers, while they referred 0.33 for other materials.

Different equations linking loading force (F) and indentation depth (h) have been used to calculate the Young modulus (E) from the indentation curves obtained with AFM. Some of them compute elastic modulus using the slope of the unload curve in the force vs penetration depth curves. Slope is obtained from the upper part of the unloading curve.[20,21] In the formula used by Stoltz *et al.*,[21] slope was replaced by the product of $(1-\nu^2)$ and $S = dP/dh$, where ν is the Poisson's ratio of the material, S is the contact stiffness at the first portion of the unloading curve when a pressure P results in an indentation or penetration depth h.

$$E = \frac{\sqrt{\pi}}{2} \cdot \frac{slope}{\sqrt{A}} \qquad \text{(Equation 6.1)}$$

A represents the contact area between the sample and the indenter. For a spherical indenter of radius R the contact area A and the radius of this area r can be calculated by equations 6.2 and 6.3; h_{max} is the maximum penetration depth at maximum load. Values are substituted in equation 6.1 to obtain elastic modulus E.

$$A = \pi \cdot r^2 \qquad \text{(Equation 6.2)}$$

$$r = \sqrt{R \cdot h_{\max}} \qquad \text{(Equation 6.3)}$$

For a nominally pointed indenter, as in our study, the contact area of the tip as a function of depth must be determined from electron micrographs of the tip apex. In our case, we assumed the values given by the manufacturer regarding the geometry of the tip in order to calculate contact area. These calculations will be presented later in this chapter. Now, the formulations for other indenters used in the literature are presented. Sneddon derived the following expression for a cylindrical flat ended indenter[25] as quoted in Kaul's experiences to measure the elastic modulus of silicone elastomers.[17]

$$F = \frac{2 \cdot E \cdot r \cdot h}{\left(1 - \nu^{2)}\right)} \qquad \text{(Equation 6.4)}$$

For forces applied by a spherical indenter (F_{sphere}) of radius (r) or a conical indenter (F_{cone}) of half-opening angle (α), the expressions derived by Radmacher *et al.* can be applied.[16]

$$F_{sphere} = \frac{4}{3} \cdot \frac{E}{(1-\nu)} \cdot \sqrt{r \cdot h^{3/2}} \qquad \text{(Equation 6.5)}$$

$$F_{cone} = \frac{\pi}{2} \cdot \frac{E}{(1-\nu)} \cdot \tan(\alpha) \cdot h^2 \qquad \text{(Equation 6.6)}$$

In a more recent study, Domke and Radmacher[18] used a variant of the second formula.

$$F_{cone} = \frac{2}{\pi} \cdot \frac{E}{\left(1-\nu^2\right)} \cdot \tan(\alpha) \cdot h^2 \qquad \text{(Equation 6.7)}$$

There is still another expression to describe what is called in the literature the "reduced modulus" (E_r) which is a combination for the surface and indenter compliance with elastic modulus E_s and E_i and the corresponding Poisson's constants ν_s and ν_i, respectively.[20]

$$\frac{1}{E_r} = \frac{1-\nu_s^{\ 2}}{E_s} + \frac{1-\nu_i^{\ 2}}{E_i} \qquad \text{(Equation 6.8)}$$

Finally, for the purposes of the present study, the Young modulus will be calculated as a function of the contact area (A) for indentation h, and the slope at the beginning of the unloading curve (slope or S = dF/dh) in the indentation curve using equation 6.9.[20,26] Semi-angle of 35º will be considered according to the manufacturer specifications listed in *table 6.2*. Contact area will be computed as described in section 6.3.3.5. The steps for the determination of indentation depth are graphically presented in *figure 6.6*.

$$E = \frac{\sqrt{\pi} \cdot \left(\frac{dF}{dh}\right)}{2 \cdot \sqrt{A}} \qquad \text{(Equation 6.9)}$$

Oliver *et al.*[23] further discussed the use of a correction factor β related to the actual calculation of the contact area. However, this factor won't be considered in the present work because it takes a value very close to 1 for the majority of indenters, particularly for a square pyramid based indenter as it is the case in our experiments.

$$E = \frac{\sqrt{\pi} \cdot \left(\frac{dF}{dh}\right)}{2 \cdot \sqrt{A} \cdot \beta} \qquad \text{(Equation 6.10)}$$

Units of modulus are obtained in nN/nm^2 or 1 10^9 N/m^2 = Pascal. In order to convert the results to the most commonly used units MPa (Megapascal or 10^6 N/m^2) each result will be multiplied by 10^{-3}.

6.3.3.3. Hardness

According to Oliver and Pharr,[23] hardness (*H*) of a material can be measured with AFM as a function of maximum load (F_{max}) and the contact area at maximum load (A_{max}).[27] This parameter is also known as Meyer hardness.[20] A more extensive discussion about this parameter can be found in the literature.[20,22,28] Units are MPa.

$$H = \frac{F_{\max}}{A_{\max}} \qquad \text{(Equation 6.11)}$$

6.3.3.4. Hardness/Elastic Modulus² Ratio (H/E^2)[29]

This parameter has been proposed by Joslin and Oliver[29] to measure the relative properties of surfaces under conditions when precise quantitative values of the individual material properties may be difficult or impossible to obtain. According to the authors, this parameter is a good indicator of the material's resistance to indentation and reduces the scatter of results when surface roughness is of the same order of magnitude than the indentation depth. As it does not require the area of indentation to be known, it is ideal to obtain a relative measure of mechanical properties of materials with highly rough surfaces. It is applicable to any shape indenter described by rotation of a smooth function.[20] The equation to obtain this parameter results from the combination of equation 6.9 and 6.11 previously described:

$$\frac{H}{E_r^{\,2}} = \frac{4}{\pi} \cdot \frac{F_{\max}}{slope^2}$$ (Equation 6.12)

Units of H/E^2 ratio are nm^2/nN or we can divide by 10^3 to obtain 1/MPa.

This equation assumes a correction factor $\beta = 1$ so $(2\beta)^2 = 4$. Oliver and Pharr[23] further discussed the usefulness of another parameter related to this equation, the load divided by stiffness squared (F_{max}/S^2).

$$\frac{F_{\max}}{S^2} = \frac{H}{E_r^{\,2}} \cdot \frac{\pi}{4}$$ (Equation 6.13)

According to other authors the effect of surface roughness on the hardness value is expected to be very small when the roughness parameter is small (i.e. 1/10th of the maximum penetration depth). In this case, average roughness of materials is at maximum 14 nm on average, while maximum penetration depth exceeded 150 nm.

6.3.3.5. Determining indentation contact area

This is a key point for our calculations as modulus and hardness calculations depend on this parameter. Considering the specifications provided in *table 6.2* for the tip used in this work whose picture is shown in *figure 6.5* we can assume that the tip indents the surface normally. Under these circumstances, we can calculate the area of the tip in contact with the surface as a function of the indentation depth h, changing as a function of the load force F according to the relationship observed in the load vs penetration curves (*figure 6.4*).

$$A_1 = \frac{1}{2} \cdot b \cdot h$$ (Equation 6.14)

$$A = 4 \cdot \tan\alpha \cdot h^2$$ (Equation 6.15)

In fact for a square pyramidal tip with same back, front and lateral half-angles, the contact point of the tip can be approached to a cube-corner indenter. According to the previous details, area of the shaded triangle can be defined as A_1 and its value can be calculated with the following equation. Considering b=h tan(α) the total area in contact with the sample surface for a square pyramidal NS-P tip of half-angle α is given by the following equation for a an indentation depth *h*. *Figure 6.8* illustrates the theoretical contact area for the given tip as a function of indentation depth.

This is the total contact area between the tip and the indented material surface. The projected area (A_p) over the plane of the original surface will be defined by a square area of side = 2b as observed in *figure 6.4* and is defined by the following equation:

$$A_p = (2b)^2 = [2 \cdot (\tan\alpha \cdot h)]^2 \qquad \text{(Equation 6.16)}$$

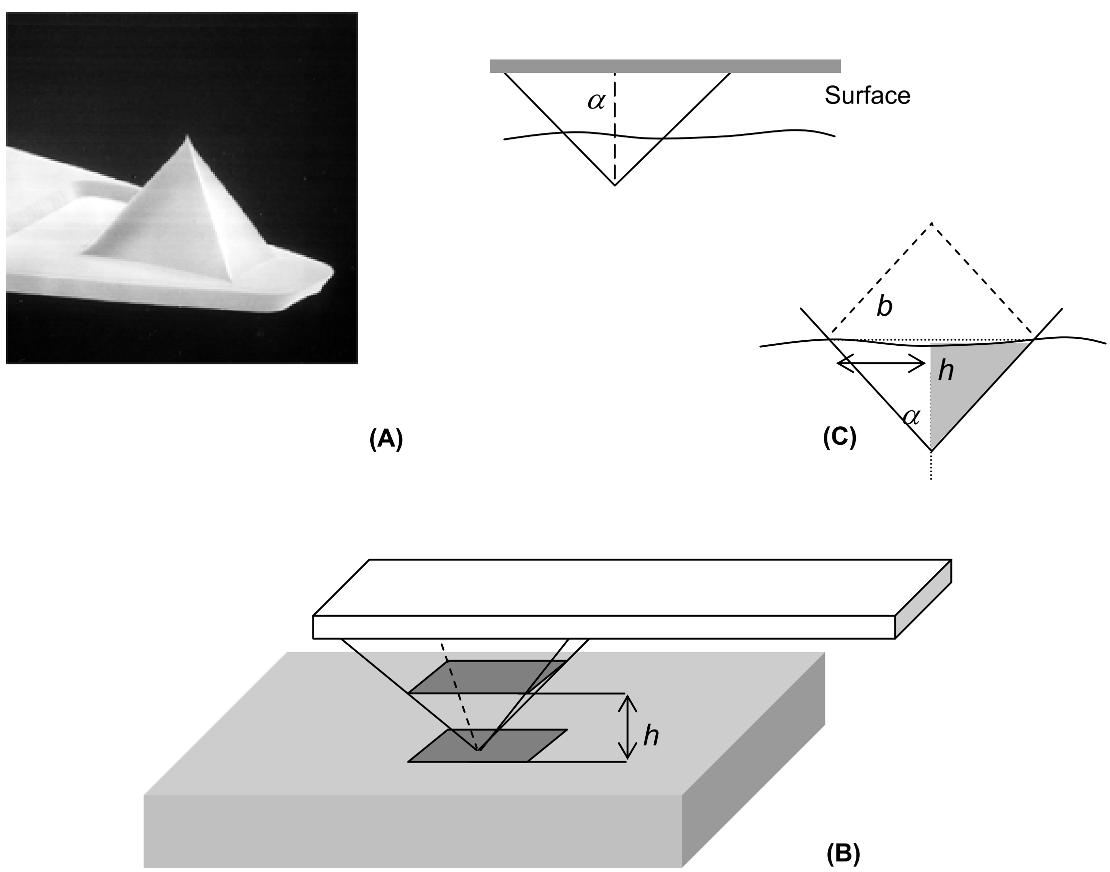


Figure 6.7. Scanning electron microphotograph of the NP-S tip used in our study (A). Diagram of specifications for contact area calculations as a function of the indentation depth (h) at a load force F (B). A magnified diagram of the indentation area of depth h is presented (C). Projected area onto the original flat surface will be defined by a square of side = 2b for a given penetration depth h and is graphically represented in (B).

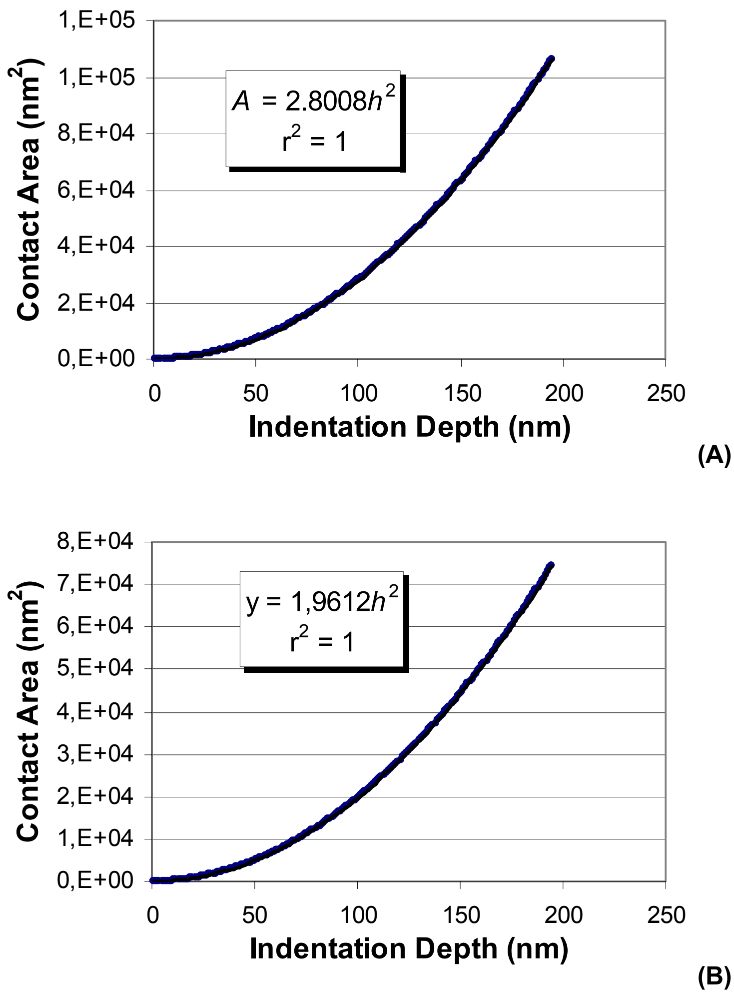


Figure 6.8. Theoretical contact area for square pyramidal NS-P tip of half-angle α as a function of indentation depth, for the total area of contact between the tip sides and the surface of the indented sample (A) and for the projected area over the originally plane of the unreformed surface (B).

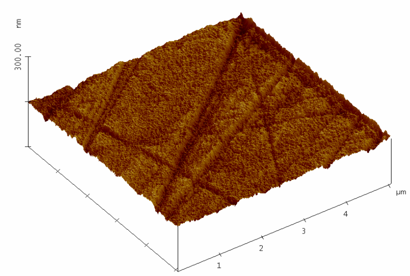
These area calculations assume that the sample is perfectly flat and that the tip approaches the surface normally. This is not totally true, as we cannot warrant that a certain tilt does not exist in the sample preparation. Surface roughness also accounts for some uncertainties in this regard. Also, in some commercially available AFM instruments, the cantilever approaches the sample surface with a fixed angle of approximately 10º. Despite these ambiguities in the determination of the contact area, we consider that the measures are valid and that reliable and comparable estimates of mechanical properties can be obtained from SCL materials at the nanometric level using AFM. Only total contact area will be used to calculate modulus.

6.4. Results

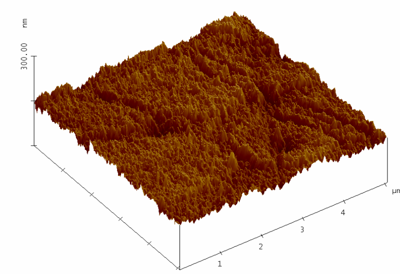
6.4.1. Surface topography

Microphotographs of the surface of the polymers for scans of 25 μm^2 are shown in *figure 6.9*. It is apparent from this view that galyfilcon A has the smoother surface while balafilcon A shows the more irregular surface, with evidences of porous structure and typical silicate islands. Lotrafilcon A and B materials display similar features in their surfaces.

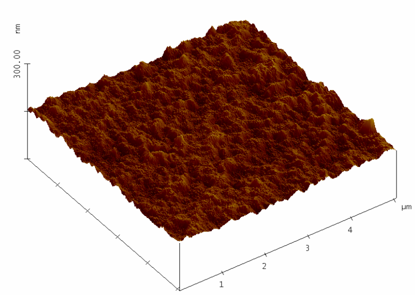
Figure 6.10 illustrates the quantitative topographic analysis with the average values of *Ra* and *Rms* being illustrated along with their SD of 4 different samples of the same material. It is quite obvious how different is the topography of balafilcon A compared with the remaining materials. However, such obvious difference is not as evident in the qualitative evaluation of the maps in *figure 6.9*. This could be in part due to the contribution of holes seen in the superficial structure of this lens to the average roughness, thus increasing the quantitative values



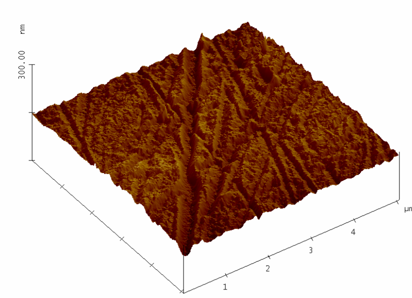
Lotrafilcon A
Rms: 4.5 nm / Ra: 3.4 nm



Balafilcon A
Rms: 13.82 nm / Ra: 9.98 nm



Galyfilcon A
Rms: 6.68 nm / Ra: 5.25 nm



Lotrafilcon B
Rms: 6.04 nm / Ra: 4.73 nm

Figure 6.9. Topographic appearance of contact lens surfaces over a 25 μm2 area. For uniformization, all pictures are presented with a vertical scaling of ±150 nm and frontal tilt (pitch) of 35º.

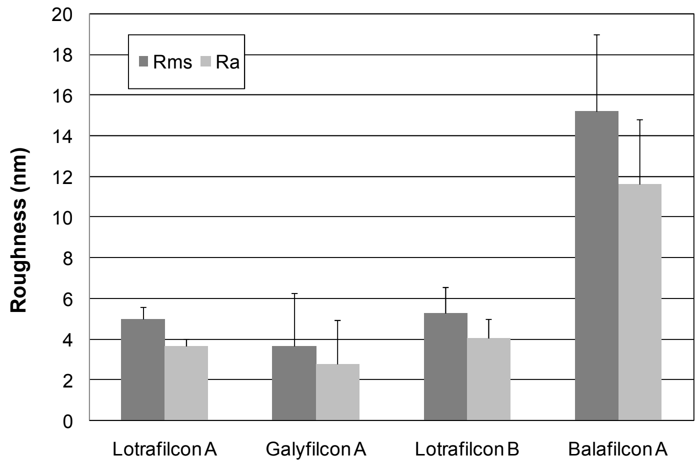


Figure 6.10. Quantitative roughness parameters (*Rms* and *Ra*) for a 25 μm^2 scanning area. Bars represent SD of three repeated measurements.

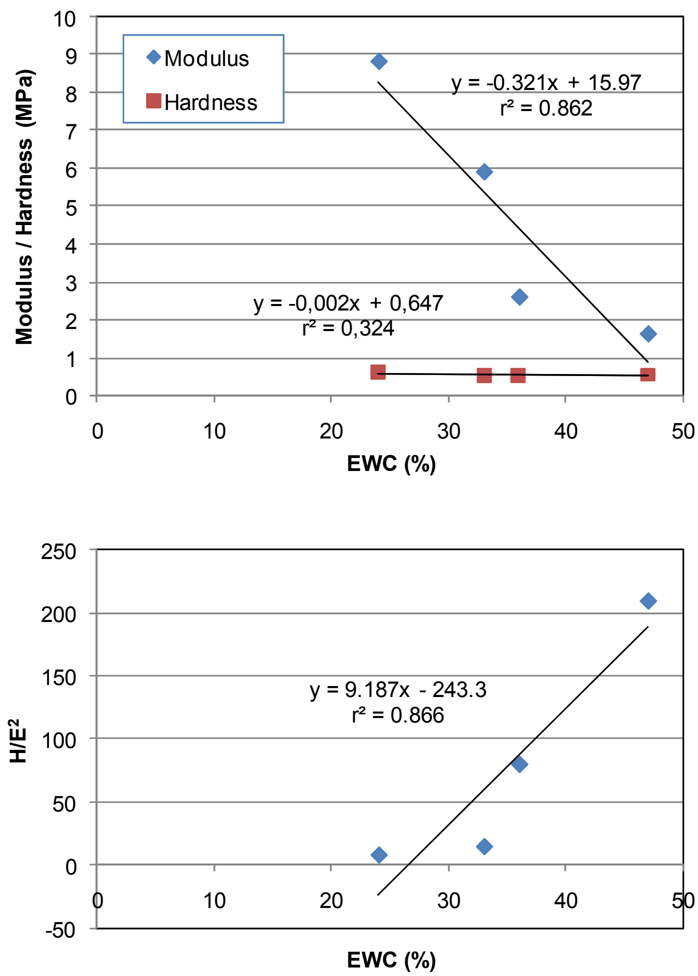
6.4.2. Mechanical analysis

Quantitative mechanical analysis is presented in *table 6.4*. Values of Young modulus obtained in the present study are presented along with other values previously obtained by other investigators for CL polymers and similar materials in *table 6.5*. The values obtained in this study, although different, are of the same order of magnitude than those given by previous works regarding to elastic modulus (E) for similar materials. *Figure 6.11A* shows the correlation of modulus and hardness parameters with the EWC of the materials. While a good correlation is observed for modulus and EWC ($r^2 = 0.862$), the relationship of EWC with hardness is much weaker ($r^2 = 0.324$), although is still well described by a linear regression equation.

The parameter H/E^2 in *figure 6.11B* shows the relationship of this parameter with EWC of the material. The relationship of this parameter with EWC had a coefficient of determination $r^2 = 0.866$.

Table 6.4. Descriptive statistics for quantitative parameters derived from indentation analysis

	Modulus -*E*- (MPa)	Hardness -*H*- (MPa)	*H/E*^{2} Ratio (1/MPa)
Balafilcon A	2.32 ± 0.23	0.52 ± 0.01	80.13 ± 14.58
Lotrafilcon A	8.81 ± 0.78	0.62 ± 0.03	8.14 ± 1.37
Galyfilcon A	1.62 ± 0.06	0.54 ± 0.05	209.97 ± 16.21
Lotrafilcon B	5.90 ± 0.14	0.51 ± 0.02	14.76 ± 0.19



(A)

(B)

Figure 6.11. Relationship between values of modulus, hardness (A) and H/E^2 Ratio (B) with EWC.

6.5. Discussion

For devices contacting living systems, surface roughness as well as other quantitative mechanical properties will influence their biological reactivity. The relationship between surfaces is especially important in CL practice as the polymer should interfere as less as possible with the epithelial surface of the cornea and the conjunctiva. This is important to maintain corneal transparency, epithelial cell integrity and patient tolerance of the CL. However, after the CL is exposed to the tears, the adsorption of the tear components could contribute to increase surface roughness. These interactions are of fundamental interest to understand biocompatibility and deterioration of CLs.

The theoretical model used to study the elastic deformation of surfaces under a certain load was first described by Hertz in 1881.[30] That model was valid for two spherical surfaces touching under load. More recently, Sneddon[25] expanded the calculations to other geometries, like a cone indenting a flat sample as used in this work. Whatever the model used, different formulations had been used to characterize the elastic properties of different materials under AFM and other experimental settings and the name "Hertz model" is commonly accepted and widely used by the scientific community in this branch of science.[5,16,18]

In the present work we have obtained repeated images of different Si-Hi materials in Tapping Mode of AFM and repeated indentation curves using Contact Mode of AFM in order to evaluate the elastic properties of the SCL polymers at a nanometric scale.

Present results of modulus are different from those given by the manufacturers. These are the reference values we have because these parameters are not usually obtained for contact lenses in recent studies, at least not using AFM. However, they are slightly different from those quoted by other authors. For example, Court *et al.*[31] obtained significantly lower values of modulus using AFM for balafilcon A and lotrafilcon A materials than those reported by the manufacturers. Tranoudis and Efron evaluated the tensile properties of soft CL materials not containing silicone moieties with a different methodology.[6] These instruments called tensiometers use higher loads to measure the response of the entire material rather than the superficial portion evaluated with the nanoindentation method of AFM.[6,31] This fact could be relevant as some materials revealed differences between the properties of the surface and the bulk of the material. Given our experimental conditions and the low forces used (about 5 nN) and the small indentation depth (about 150 nm), we can conclude that we are in fact measuring only surface properties rather than bulk properties. However, our results, although different in numerical terms, are in the same order or magnitude of those previously reported using AFM. Kim *et al.* reported values of 1.34 and 0.47 MPa for p-HEMA (38% EWC) and p-HEMA+MA (55% EWC) soft polymers, respectively.[5] Court *et al.*[31] using a different approach to that of the AFM obtained values of Young modulus of 0.3, 0.5 and 0.85 for experimental copolymer containing silicone moieties and phosphatidilcholine (46% EWC), balafilcon A (36% EWC) and lotrafilcon A (24% EWC), respectively. Furthermore, those authors found a perfectly linear correlation between EWC and Young modulus. Our results, although quantitatively different also support these relationship. Regarding the remaining parameters involving hardness, we do not have terms of comparison for our values although the linear correlation of hardness with EWC (although weaker) seems to be reasonable. The role of harness on the clinical behavior of SCL is still to be evaluated because there is no data about the potential usefulness of this parameter to characterize SCL materials. Although H/E^2 parameter also has a good correlation with modulus and EWC of the material, we cannot ensure that can be more representative of the material's properties than the modulus alone. As with hardness, we still do not know its actual relevance for SCL research.

Table 6.5. Elastic modulus of some hydrophilic polymers for drug delivery and contact lens manufacture

Author (Year)	Method	Material (EWC)	Modulus (MPa)
Huang et al (2005)[32]		timolol-loaded poly(D,L-lactide-co-glycolide) films	1.13 – 2.49
Tighe (2000)[4]	Unknown	Balafilcon A Lotrafilcon A	1.1 1.2
Court *et al* (2001)[31]	Tensiometer	PC-coated silicon-hydrogel (47%) Balafilcon A Lotrafilcon A	0.3 0.55 0.8
Kim *et al* (2002)[5]	AFM	HEMA (38%) HEMA + MA (55%)	1.34 ± 0.13 0.47 ± 0.04
Perez *et al* (2003)[33]	Tensiometer	Polymacon (38%) Etafilcon A (58%)	0.6 0.3
Tranoudis and Efron (2004)[6]	Compression tester	HEMA/VP 40% HEMA/VP 55% HEMA/VP 70% VP/MMA 55% VP/MMA 70% HEMA 40% HEMA/MAA 55% HEMA/MAA 70%	0.701 ± 0.44 0.372 ± 0.68 0.587 ± 1.52 1.625 ± 1.18 0.504 ± 0.95 0.880 ± 0.49 0.592 ± 1.51 0.783 ± 1.10
Maldonado-Codina and Efron (2004)[34]	Modified tensiometer	Lathed HEMA (38%) Spun-cast pHEMA (39%) Cast-mould pHEMA (38 %) Cast-mould HEMA/MAA (53%) Cast-mould HEMA/GMA (60%)	≅ 0.7 ≅ 0.4 ≅ 1.0 ≅ 0.6 ≅ 0.5
Papas 2005[‡]	Unknown	Lotrafilcon A (24%) Lotrafilcon B (33%) Balafilcon A (36%) Senofilcon A (38%) Galyfilcon A (47%)	1.4 1.2 1.1 0.7 0.4
Present study	AFM	Lotrafilcon A Balafilcon A Galyfilcon A Lotrafilcon B	8.81 ± 0.78 2.32 ± 0.23 1.62 ± 0.06 5.90 ± 0.14

[‡] Papas E. Elastic Modulus and Silicone Hydrogel Contact Lens Fitting at http://www.siliconehydrogels.org/editorials/aug_05.asp

Perez *et al.*,[33] performed measurements of Young's modulus using a parallel strip cut through the center of sample CLs at a strain rate of 100% per minute at 35°C. They obtained valus of 0.3 and 0.6 MPa for etafilcon A (58% EWC) and polymacon (38 EWC), respectively. Variability represented as the standard deviation of 3 repeated measurements of Young modulus determination are of the same order or magnitude of those reported by Court *et al.*

for Focus Night & Day, Purevision and an experimental polymer containing silicone moieties and phosphatidilcholine.[31] The measurements of Kim *et al.*[5] with AFM also reported similar SD values than those obtained by us. In fact, the variability of repeated measurements of modulus in the studies using AFM are much lower than other studies using tensiometers as show the results from Kim *et al.*, Tranoudis and Efron and the results of the present study summarized in *table 6.5*.

Softer samples showed less consistency for topographic imaging as well as for indentation analysis. This is a reflection of the less stability of softer samples as observed in gelatin samples by Radmacher *et al.*[16] Other conclusions from this work include the higher repeatability of measurements compared with previous determinations made by compression testers.[6] Also, the more irregular surfaces of certain lenses (i.e. balafilcon A) induce higher errors in the calculation of the contact area between the indenter (tip) and the surface.

Further work must be done to evaluate how temperature, room humidity or pH of the solution where the polymer is immersed affects these properties and what could be the clinical relevance of such environmental changes in on the ocular surface under CL wear.

The load used in our study was lower than that used by Kim *et al.*[5] in their AFM indentation analysis. However, we have obtained very similar indentation profiles for our most hydrated Si-Hi polymers compared to their pHEMA lenses. This could be explained because in thick samples, the modulus do not depends on the load applied during indentation.[18]

We were able to obtain surface mechanical properties of CL materials using an AFM. Values obtained correlated well with EWC of the materials but differ significantly from those obtained in other studies for similar materials using different methods. These facts could mean that we are actually measuring properties that are more representative of the surface of the material instead of mechanical properties of the bulk, as measured with other instruments. As a result, the mechanical behavior of the material can be reflected in a different way in nanoindentation at the surface of the contact lens with AFM, as in the present study. The differences between our results and those obtained by others with AFM could be due to different procedures in the determination of the mechanical properties from the data provided by the microscope. The shape and mechanical properties of the indenters could also have significant effect on the final results.

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Chapter 7

Refractive Index and Equilibrium Water Content of Conventional and Silicone Hydrogel Contact Lenses†

7.1. Abstract

Purpose: The purpose of the present study was to measure equilibrium water content (EWC) and refractive index of conventional and silicone hydrogel (Si-Hi) soft contact lenses (SCLs) using a hand refractometer and an automated refractometer.
Methods: Sixteen SCLs were used in this study including twelve conventional SCLs not containing siloxane moieties (EWC range: 38.6–74%) and the four Si-Hi CLs currently available (EWC water content range: 24-47%). Two experienced observers performed the measurements in a randomized order being masked by a third party during the three sessions at which the measurements were collected. The Atago N-2E hand refractometer and the CLR 12-70 digital refractometer were used. Data were analyzed separately for conventional and Si-Hi materials.
Results: Measured EWC and refractive index correlate better when measured with the instruments used in this study ($r^2 = 0.979$, $p < 0.001$) than the nominal parameters ($r^2 = 0.666$, $p < 0.001$). The linear relationship that correlates nominal and measured EWC shows higher spread of data when all lenses are analysed together ($r^2 = 0.840$) than when conventional hydrogel ($r^2 = 0.953$) and Si-Hi CLs ($r^2 = 0.967$) are analyzed separately. Regarding refractive index, the relationship between nominal and measured values when all the lenses are considered together ($r^2 = 0.794$) becomes weaker when conventional hydrogel are considered separately ($r^2 = 0.688$), while a stronger relationship is observed for Si-Hi lenses ($r^2 = 0.939$). Hence, hand refractometry overestimates the EWC of Si-Hi, while automated refractive index measurements are more accurate in Si-Hi than in conventional hydrogels.
Conclusions: New relationships are presented that correlate nominal and measured values of EWC and refractive index for the silicone containing hydrogels. The linear relationships derived fit well to the data. Hand refractometry overestimates the EWC of Si-Hi materials and this bias is related to the proportion of siloxane moieties in the material. Conversely, refractive index can be obtained more accurately with automated refractometry for Si-Hi than for conventional hydrogels. Present results are of interest in planning future clinical studies involving the measurement of EWC of current hydrogels.

7.2. Introduction

Refractive index (RI) of SCLs is an important parameter not only from the optical, but also from the physiological perspective, since it is a measurable parameter that reflects

† Gonzalez-Meijome JM, Lira M, Lopez-Alemany A, Almeida JB, Parafita MA, Refojo MF. Refractive index and equilibrium water content of conventional and silicone hydrogel contact lenses. *Ophthalmic Physiol Opt* 2006;26:57-64.

changes in the equilibrium water content (EWC) of the polymer. EWC of SCL is affected by many different factors while on the eye, thus compromising the physiological performance of the polymer, ocular integrity and tolerance. Patient-related factors that affect *in vivo* hydrogel lens EWC include tear secretion and stability, ocular surface temperature and blinking. Lens-related factors are also important which include nominal material EWC, lens thickness, ionicity and monomer composition.[1-5] Other external factors which seriously affect water content (WC) and hence RI are wearing schedule, lens cleaning regime or the application of artificial humectants.[6,7]

Clinical consequences of *in vivo* dehydration of SCL include changes in lens parameters and fitting characteristics,[8] oxygen transmissibility of conventional hydrogels[9] and Si-Hi,[10] comfort and wearing time,[4] deposit build up and denaturation of proteins.

Estimates of the RI of hydrogel materials can be achieved by refractometry.[11] Nowadays, instruments are available which offer direct measurements[12] or these can be derived indirectly from the relationship which exists between this parameter and the EWC measured by different methods.[13] However, with new siloxane-based hydrogels, this relationship seems not to hold true as refractometers have been demonstrated to provide lower RI values than expected for their EWC, and consequently overestimate the EWC of such materials.[12]

During refractometry, the EWC is determined by measuring the RI of the contact lens relative to the RI of the prism used in the refractometer. This method is based on the property that refractivity of a simple solution, such as sucrose solution, is closely related to its concentration. As the swelling process of hydrogel materials is similar to that experienced by sucrose in water, it has been long known that the refractivity of a hydrogel follows the same rules as for homogeneous solutions.[14] Refractometers can measure either percent water or solid content in a solution or hydrogel material.

The Atago N-2E (Atago Ltd, Tokyo, Japan), is a hand-held refractometer that measures the percentage of sucrose in a solution (the Brix scale represents the number of sucrose grams in 100 g of sucrose solution) within a range of 28 to 62%. This means that EWC ranging from 72% to 38% can be measured with this instrument. It has also been used to measure the EWC of hydrogel lenses[15] providing indirect values as the scale reads a percentage value that represents the solid part of the polymer, which can then be converted to EWC percentage values.

Other refractometers typically used in experimental research included the Abbe-type refractometers,[16-18] and the Atago CL-1.[8,19,20] Other instruments measure only RI, either manually as the Atago N3000[21] or automatically which is the case of the CLR 12-70 automated refractometer (Index Instruments, Cambridge, UK).[12] The CLR 12-70 provides direct RI readings with minimal operator influence, and has demonstrated excellent within- and between-operator reliability.[12]

Table 7.1. Nominal EWC and nominal refractive index for different conventional hydrogel soft contact lens materials as reported by the manufacturer or by previous investigations. The values chosen for statistical analysis are shown in bold type

Manufacturer	Brand	USAN	Water Content (%)	Refractive Index
CooperVision	Actifresh 400	Lidofilcon A	73	-[¥]
Johnson & Johnson	Acuvue 2	Etafilcon A	58	1.4055[a] // 1.405[b] // 1.3999[c] // **1.40**[d]
CooperVision	Aspheric	Methafilcon A	55	**1.41**[a,d] // 1.415[b]
CIBA Vision	Focus Dailies	Nelfilcon A	69	**1.38**[a,b,d]
CIBA Vision	Focus Monthly	Vifilcon A	55	**1.415**[b,d] // 1.4119[c]
CIBA Vision	Freshlook	Phemfilcon A	55	**1.44**[a,d]
CIBA Vision	Precision UV	Vasurfilcon A	74	**1.379**[b] // 1.38[d]
CooperVision	Proclear	Omafilcon A	62	1.38[a] // **1.387**[b,d]
Bausch & Lomb	Soflens 1-day	Hilafilcon A	70	**1.38**[b]
Bausch & Lomb	Soflens 38	Polymacon	38.6	**1.43**[a,b] // 1.44[b] // 1.4452[c]
Bausch & Lomb	Soflens 66	Alphafilcon A	66	**1.39**[b]
Johnson & Johnson	Surevue	Etafilcon A	58	1.4055[a] // 1.4051[b] // 1.3999[c] // **1.40**[d]

FDA: Food & Drug Administration; USAN: United States Adopted Names

[a]obtained from FDA pre-market approval forms
[b]reported by Nichols and Berntsen (2003) as nominal refractive index for the same material
[c]reported by Fatt (1997) as nominal refractive index for the same material
[d]reported by Young and Benjamin (2003) as nominal refractive index for the same material
[¥]nominal refractive index for this material could not be obtained

To date, no studies have elucidated the actual relationship between EWC and RI of Si-Hi materials, either nominal or measured. These materials could follow a different behavior than conventional hydrogels.[16] Now with two new Si-Hi materials (galyfilcon A and lotrafilcon B) joining the first generation Si-Hi (lotrafilcon A and balafilcon A), investigation of this relationship is necessary.

In the present study, the relationships between nominal and measured values of RI taken with the CLR 12-70 automated refractometer as well as the relationships between nominal and measured EWC as measured with the hand refractometer Atago N-2E, will be analyzed with the aim of differentiating between conventional SCL and Si-Hi materials. To clarify relationships between measurable and nominal RI and EWC in Si-Hi SCL is of interest in investigations regarding changes in these parameters, and for the evaluation of the suitability of current techniques to determine them. To the best of our knowledge, the two instruments have never been used together to estimate RI and EWC of a sample of various conventional and Si-Hi CLs.

7.3. Material and Methods

Sixteen lenses of different materials were included in the study. Twelve lenses were made of conventional hydrogel material and four were Si-Hi SCL. Nominal parameters are presented in *tables 7.1 and 7.2*, respectively, for each type of lens.

Table 7.2. Nominal EWC and nominal refractive index for different silicone hydrogel soft contact lens materials as reported by the manufacturer or previous investigations

Manufacturer	Contact lens	USAN	EWC (%)	Refractive Index
Johnson & Johnson	Acuvue Advance	Galyfilcon A	47	1.4055[a]
CIBA Vision	Focus Night & Day	Lotrafilcon A	24	1.43[a,b]
CIBA Vision	O_2Optix	Lotrafilcon B	33	1.42[a]
Bausch & Lomb	Purevision	Balafilcon A	36	1.426[a]

FDA: Food & Drug Administration; USAN: United States Adopted Names

[a]obtained from FDA pre-market forms
[b]reported by Nichols and Berntsen (2003) as nominal refractive index for the same material

Lenses were allowed to equilibrate for at least 24 hours before testing in preservative-free saline solution meeting the criteria of BS EN ISO 10344:1998 (BSI, 1998).[22] EWC readings were performed with the Atago N-2E hand-held refractometer. This instrument was designed to measure sucrose concentration in a solution and can also be applied to the estimation of EWC in hydrophilic SCL with a reasonable degree of accuracy. Three measurements were taken by a trained observer (JMG-M) on different days under the same room conditions (T^{a} = 20 ± 1ºC, RH = 50 ± 3%). Once the measures were obtained as %Brix, the EWC of the lens was obtained by the following equation:

$$EWC = 100 - \%Brix \qquad \text{(Equation 7.1)}$$

In our protocol, some preliminary tests with samples of the same lenses were made, using the Atago N-2E and two other manual refractometers (Atago N-1E and Zuzi 58-92 Brix (Auxilab SL, Beriain, Navarra, Spain)) which extended the measurement range from 8%

to 100% EWC. Lenses with EWC above 72% could fall beyond the Atago N-2E's upper range; conversely, balafilcon A as well as other Si-Hi CLs could have the same problem falling below the lower refractometer limit. However, all these lenses that will theoretically fall outside the range of measurement of the Atago N-2E, were satisfactorily measured with this instrument. Hence, only values obtained with the Atago N-2E were considered in the study. As a preliminary part of this study, different samples of the materials assayed here were measured. As positively powered (+3.00D) and negatively powered (-3.00D) lenses taken from different batches did not show significantly different results, only -3.00D samples were considered in the current study.[23]

Before each measurement session, the refractometer was calibrated using a saturated NaCl solution adjusting the scale-adjustment screw to 29.6% as recommended by the manufacturer for a room temperature of 20ºC. A second calibration was randomly ordered by a third investigator within each session. Refractometer manipulation was performed as described by previous authors regarding instrument focusing and reading.[15] However, instead of daylight, readings were taken against a bright source of white light in order to increase contrast and obtain more precise readings.

The CLR 12-70 automated refractometer was used to directly measure the RI of the CLs. Three measurements were taken by an experienced observer (ML) on different days under the same room conditions as described above for the hand refractometry. Measurement procedures followed the guidelines given by the manufacturer and previous authors.[12] The instrument was set in the continuous scan mode and the reading was taken when stability was reached. As quoted by Nichols and Berntsen (2003) the CLR 12-70 measures RI by back reflection at 589nm. Calibration was performed before each measurement sequence using water at room temperature and the instrument was adjusted if values were outside tolerance.

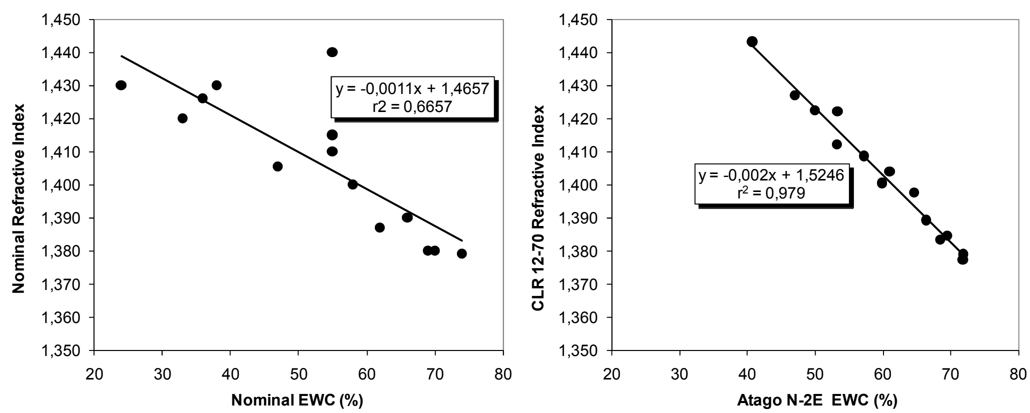
The Actifresh 400 lens made of copolymer MMA/VP (lidofilcon A - 73% EWC) was not considered in any statistical analysis where nominal RI was necessary, as this parameter could not be obtained.

A third investigator took all the lenses from the commercial blister packs and placed them on identical glass vials filled with buffered preservative-free sterile saline solution meeting the criteria of EN ISO 10344:1998 (BSI, 1998). A number under each vial identified each lens. This operator presented the lenses in a randomized order to each investigator at each session. Readings were registered by this operator while the investigator was masked to the number of the lens being measured. After each session, all lenses were kept by the third operator without manipulation by either of the two investigators.

7.4. Results

Surprisingly, lenses whose EWC falls below the lower limit of the Atago N-2E (WC<38% which equates with the upper limit of the Brix% scale) or lenses whose EWC surpassed the lower limit of the Brix% (28% Brix which equates to 72% EWC) were satisfactorily measured with this instrument giving exactly the same values as those measured with the "appropriate refractometers".

Figures 7.1A and 7.1B represent the relationships between nominal EWC and RI and the measured values, respectively. While nominal EWC and RI did not correlate well (*figure 7.1A*), an excellent correlation is observed for the values obtained in the present study (*figure 7.1B*).



(A) **(B)**

Figure 7.1. Relationships between nominal refractive index and EWC as quoted by the manufacturer (A) and between the same parameters as measured in this study (B).

Figure 7.2 displays the relationship between nominal EWC and values obtained with the Atago N-2E. It seems that a linear model fits reasonably well to these data with the exception of two outliers. However, this relationship tends to deviate from the ideal 1:1 relationship as the EWC decreases. A closer view of the data showed us that the four Si-Hi are in fact the outliers that shift the linear relationship inducing the bias previously quoted. This is clearly seen in *figure 7.3* where separate models were fitted to conventional and Si-Hi CLs. The four Si-Hi CLs fit very well to a linear relationship different from that of conventional hydrogel lenses as a result of a systematic bias as the Atago N-2E measures higher values than those nominally reported by the manufacturers.

True EWC as defined by the manufacturer (nominal value) can be obtained for Si-Hi by the following equation:

$$Nominal\ EWC_{SI\text{-}HI} = (Atago\ N\text{-}2E_{SI\text{-}HI}EWC\ /\ 0.4575) - 35.886 \qquad \text{(Equation 7.2)}$$

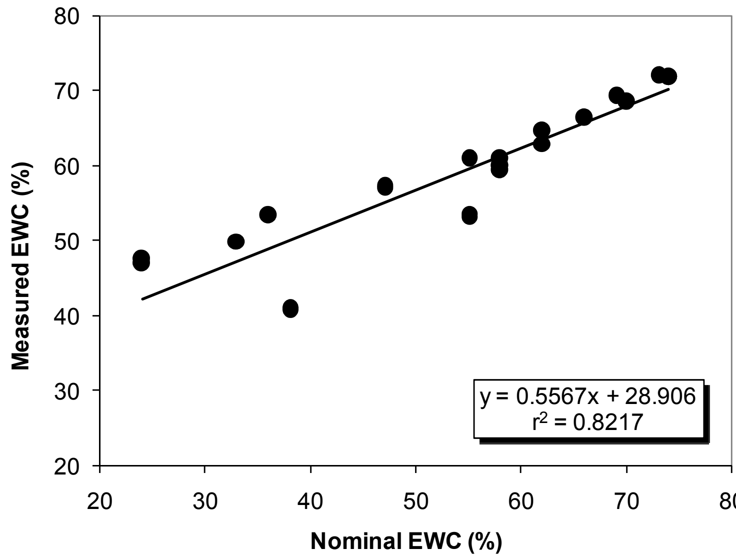


Figure 7.2. Relationship between nominal equilibrium water content and equilibrium water content measured with the Atago N-2E hand refractometer.

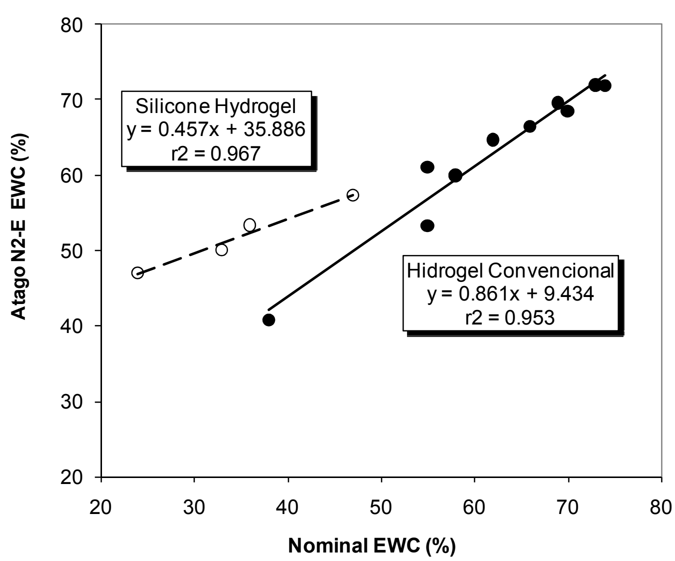


Figure 7.3. Relationship between measured and nominal equilibrium water content for conventional hydrogel SCL (filled circles, continuous line) and silicone hydrogel CLs (open circles, broken line).

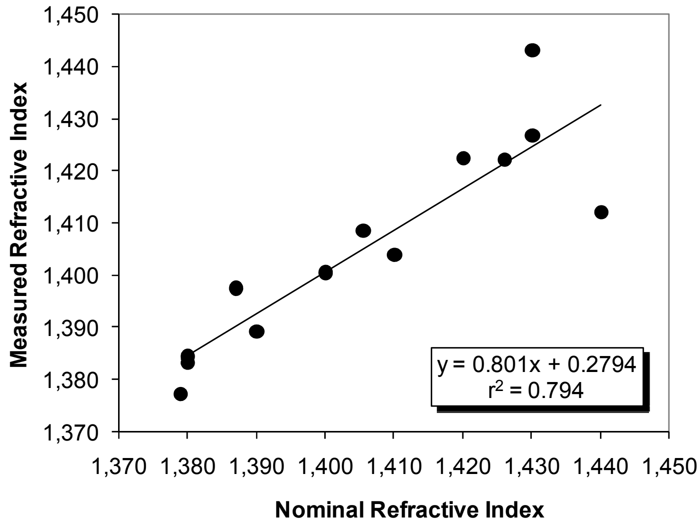


Figure 7.4. Relationship between nominal refractive index given by the manufacturer and the refractive index measured with the CLR 12-70 automated refractometer. The two outliers correspond to Soflens 38 (polymacon) and FreshLook (phemfilcon A).

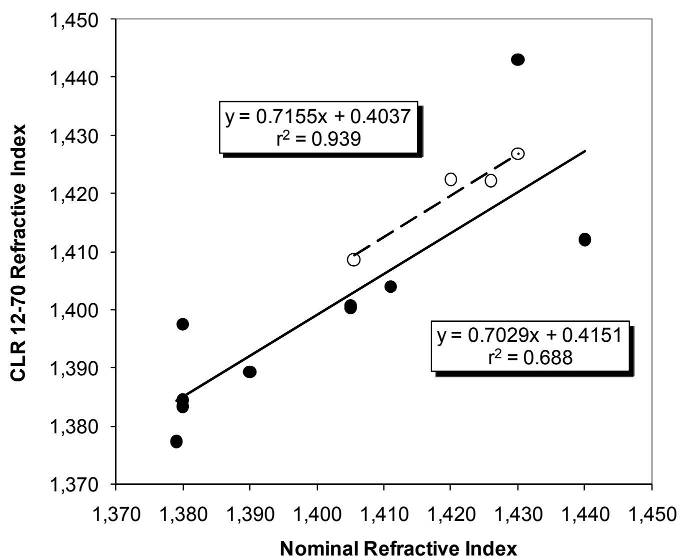


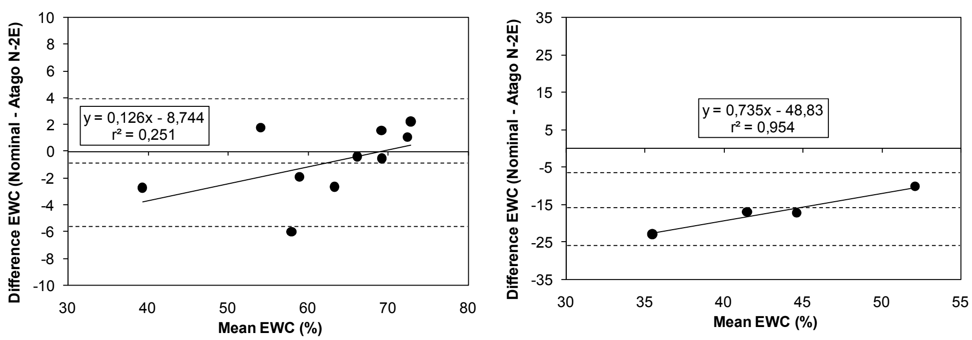
Figure 7.5. Relationship between measured and nominal refractive index for conventional hydrogel SCL (filled circles, continuous line) and silicone hydrogel CLs (open circles, broken line).

Figure 7.4 displays the relationship between nominal and measured RI with the CLR 12-70 for all the lenses measured in this study. A higher spread of the data is observed for the higher values, corresponding to polymacon and phemfilcon A. Although conventional hydrogels did not fit better to their specific model, Si-Hi fit better to a specific relationship

($r^2 = 0.939$) as seen in *figure 7.5*. Hence, true RI as given by the manufacturer (nominal value) can be obtained for Si-Hi by the following equation:

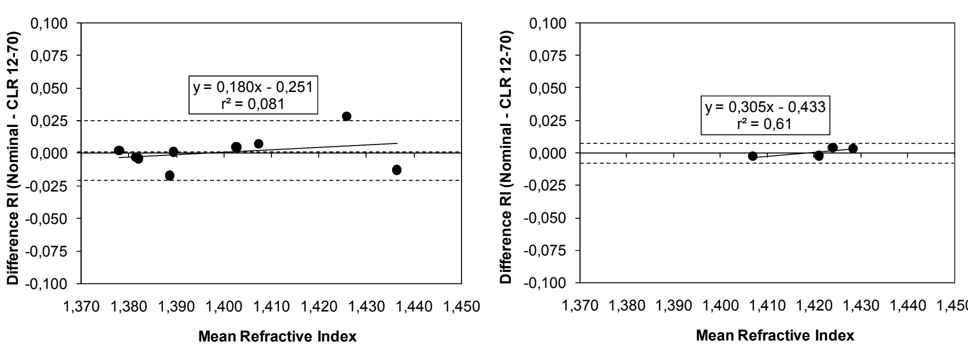
$$\textit{Nominal } RI_{SI\text{-}HI} = (CLR\ 12\text{-}70_{SI\text{-}HI} / 0.7155) - 0.4037 \qquad \text{(Equation 7.3)}$$

Figure 7.6 shows the plots of measured values of EWC and RI against those reported by the manufacturer for conventional hydrogel (*figure 7.6A*) and Si-Hi CLs (*figure 7.6B*). From this data we can conclude that EWC can be measured for conventional hydrogels with the Atago N-2E with a mean bias of –0.88 ± 2.48 for a 95% confidence interval between 3.98 and –5.73%. The outlier that displays the maximum bias corresponds to the methafilcon A which was associated with measuring difficulties during data acquisition. Si-Hi measurements of EWC display poor agreement with reported nominal values as expected from *figure 7.3*.



(A) **(B)**

Figure 7.6. Plots of difference against mean for the values of water content obtained with the Atago N-2E hand refractometer for conventional hydrogel CLs (A) and silicone hydrogel CLs (B).



(A) **(B)**

Figure 7.7. Plots of difference against mean for the values of refractive index obtained with the CLR 12-70 hand refractometer for conventional hydrogel CLs (A) and silicone hydrogel CLs (B).

Statistically significant differences were found between measured and nominal RI values for conventional hydrogel SCL. Conversely, RI measurements with the CLR 12-70 displayed a very good agreement with nominal data for Si-Hi materials. These analyses are graphically illustrated in *figures 7.7A and 7.7B* for conventional and Si-Hi CLs, respectively.

7.5. Discussion

The hand refractometer Atago N-2E has been recently used to measure the EWC of CLs in clinical practice with good results in terms of accuracy and precision.[15] Recently, a digital refractometer (the CLR 12-70) which provides rapid and accurate values of RI with minimal observer intervention has been marketed.[12] However to the best of our knowledge, there has been no previous investigation using both instruments on the same samples. As both instruments use the same principle of measuring RI to estimate the EWC of solutions and hydrogel materials, such a study is of interest for researchers and clinicians in the contact lens field. A highly significant linear relationship between EWC as measured with the Atago N-2E manual refractometer and the RI measured with the new automated refractometer CLR 12-70 was obtained. Such results are not surprising since the manual refractometer, although simpler and less sophisticated, uses the same optical principle as the more advanced digital refractometer.

The relationship between conventional hydrogel EWC and RI is well established and has been recently studied.[16] However, due to the lower RI of dry Si-Hi compared with dry conventional hydrogels, RI methods to estimate water content based on the "sucrose scale" or Brix scale relationships are not valid with these modern materials.[12] In that study, only the material lotrafilcon A was used, however the other silicone-containing material available at the time (balafilcon A) was not evaluated. Now that four Si-Hi CLs are on the market, it is possible to determine if some linear or other type of relationship could correlate the values of EWC and RI obtained with the current methods to those nominally reported and considered as "true" values. On the basis of our results, this seems to be possible with a good level of confidence, both for EWC and RI. For the former parameter, although the coefficient of correlation defining the linear relationship is lower than that for the model predicting the measured value of EWC from nominally reported parameter, the maximum difference for these four Si-Hi lenses was <0.03%.

Some difficulties found during the measuring process have to be highlighted. Vifilcon A in the Focus Monthly conventional hydrogel soft contact lens could not be measured at any of the sessions with either of the two procedures. Other investigators have noted difficulty in measuring lenses made of vifilcon A. It has been suggested that the cast molding process used to produce these lenses results in a continuously variable EWC (and thus continuously variable RI) through the lens.[15] The same authors, measuring RI with the CLR 12-70 automated refractometer found difficulties with the material vifilcon A in the Focus Progressives, but could measure Focus Monthly, which proved impossible in our study. They also found difficulties in measuring the RI of a lens made of polymacon. Curiously, the polymacon lens displayed a higher variability in RI measurements in our study.

The present study has characterized the relationships between EWC and RI of the four Si-Hi SCL, being different from that which is valid for conventional hydrogels. This is the first time that such lenses have been measured simultaneously in the same study with automated and hand refractometry. It has been shown that current methods to obtain EWC and RI of SCL can be also used with the new Si-Hi CLs.

Acknowledgments:

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Chapter 8

Relationship Between Refractive Index and Equilibrium Water Content of Conventional and Silicone Hydrogel SCL from Automated and Manual Refractometry†

8.1. Abstract

Purpose: The purpose of the present study was to develop mathematical relationships that allow obtaining equilibrium water content and refractive index of conventional and silicone hydrogel soft contact lenses (SCLs) from refractive index measures obtained with automated refractometry or equilibrium water content measures derived from manual refractometry, respectively.
Methods: Twelve HEMA-based hydrogels of different hydration and four siloxane based polymers were assayed. A manual refractometer and a digital refractometer were used. Polynomial models obtained from the sucrose curves of equilibrium water content against refractive index and vice versa where used either considering the whole range of sucrose concentrations (16-100% equilibrium water content) or a range confined to the equilibrium water content of current SCL (approximately 20-80% equilibrium water content).
Results: Values of equilibrium water content measured with the Atago N-2E and those derived from the refractive index measurement with CLR 12-70 by the applications of sucrose-based models displayed a strong linear correlation ($r^2 = 0.978$). The same correlations were obtained when the models are applied to obtain refractive index values from the Atago N-2E and compared with those (values) given by the CLR 12-70 ($r^2 = 0.978$). No significantly different results are obtained between models derived from the whole range of the sucrose solution or the model limited to the normal range of soft CL hydration.
Conclusions: Present results will have implications for future experimental and clinical research regarding normal hydration and dehydration experiments with hydrogel polymers, and particularly in the field of CLs.

8.2. Introduction

Refractive index (RI) and equilibrium water content (EWC) are closely linked in conventional soft hydrophilic materials.[1,2] In fact because of the inverse relationship between EWC and RI, this parameter has been widely used to estimate the degree of water lost of SCL while on the eye or after several hours of use.[3-5]

† Gonzalez-Meijome JM, Lopez-Alemany A, Lira M, Almeida JB, Oliveira ME, Parafita MA. Equivalences between refractive index and equilibrium water content of conventional and silicone hydrogel soft contact lenses from automated and manual refractometry. *J Biomed Mater Res B Appl Biomater* 2007;80:184-91.

The interest in studying EWC is supported by the many factors that affect on eye hydrogel lens EWC, including ocular surface characteristics as well as lens material and environmental circumstances.[6-12] All these factors have the potential to adversely affect CL fitting characteristics, deterioration and tolerance.[9,13] Many studies link CL wear discontinuation to dehydration of the ocular surface driven by the CL[14-16] being one of the main limiting factors for CL market growth.

Methods currently available to obtain EWC of SCL include gravimetric techniques[17-19] and refractometry.[3,13] Although the gravimetric technique is accurate, relative to nominal EWC values given by the manufacturer, it is difficult and time-consuming.[17] Refractometry is more feasible in the clinical setting, although there could be issues with its accuracy depending on the instrument used.

Refractometry is based in the property that refractivity of a simple solution, such as sucrose solution, is closely related to its solid content. As the swelling process of hydrogel materials is similar to that experienced by sucrose in water, it has been known for long that the refractivity of a hydrogel follows the same rules as for homogeneous solutions.[20] Refractometers can either measure percent water or solid content in a solution or hydrogel material.

The instruments that have been used with SCL include the Abbe-type refractometers,[17,21,22] the Atago CL-1,[3,5,13] or Atago N-2E.[23] Other instruments measure only RI, either manually as the Atago N3000[24] or automatically, which is the case of the new CLR 12-70 automated refractometer.[25]

The Atago N-2E (Atago, Tokyo, Japan), is a hand-held refractometer that measures the percentage of sucrose in a solution (Brix scale[‡]) within a range of 28-62%. This means that EWCs ranging from 72% to 38% can be measured with this instrument. It has also been used to measure the EWC of hydrogel lenses,[23] providing indirect estimates of EWC as the scale reads the percentage that represents the solid part of the polymer (Brix scale), which can then be converted to percentage values of EWC.

The CLR 12-70 provides direct RI readings with minimal influence of operators subjectivity displaying excellent within- and between-operator precision.[25] The instrument also allows the evaluation of the EWC of hydrogel CL by measuring their RI in the hydrated and dehydrated states. However, this procedure is time-consuming and might be inconvenient for many clinical applications.

In clinical practice, the evaluation of hydrogel lenses EWC assumes that this parameter could be obtained from the RI. The higher the RI was in relationship with the

‡ Brix scale represents the number of sucrose grams in 100 g of sucrose solution

nominal RI reported by the manufacturer for unworn lenses of the same material under the same conditions, the greater the dehydration experienced. However, previously published results including one Si-Hi material (Lotrafilcon A) showed that such materials did not follow the same relationships between EWC and RI that have been applied to SCL given false values of hydration when measured by conventional refractometry.[25]

Moreover, against earlier believes,[26] Nichols *et al.*[23] discussed that with current soft lens materials, including a great diversity of polymeric formulas, the application of Brix scale to obtain the RI of hydrogels from EWC or vice-versa could be inaccurate. They concluded that under/overestimations of nominal EWC values given by the manufacturer will depend on each material's characteristics.[23]

With the present study, we try to evaluate the agreement of RI and EWC values obtained by the application of sucrose-based Brix models to a wide range of conventional SCL materials and Si-Hi materials. We are particularly interested in the precision of deriving RI from a hand-held refractometer such as the Atago N-2E or deriving EWC from such a precise refractometer as the CLR 12-70. Of remarkable interest is also to know how such models are valid for new Si-Hi CL materials.

8.3. Material and Methods

Sixteen CL made of different materials were included in the study. Twelve lenses were conventional HEMA-based hydrogels and four were Si-Hi SCL. Nominal EWC of lenses was within the interval 38–74%. Nominal parameters as given by the manufacturers from different lenses materials (EWC and RI) are listed in *table 8.1*.

Lenses were allowed to equilibrate in preservative-free saline solution meeting the criteria of ISO 10344:1996 (EN ISO 10344:1998)[27] establishing the requirements for saline solution in CL testing for at least 24 hours before testing. EWC estimates were done with the Atago N-2E hand refractometer (Atago, Tokyo, Japan). This instrument was designed to measure sucrose concentration in a solution and can also be applied to the measurement of EWC in hydrophilic SCL with excellent degrees of reliability and reproducibility.[23] Three measures were done by a trained observer (JMG-M) on different days under the same room conditions ($T^a = 20 \pm 1°C$, $RH = 50 \pm 3\%$). Once the measures were obtained as %Brix, the EWC of the lens was obtained by the following equation:

$$EWC = 100 - \%Brix \quad \text{(Equation 8.1)}$$

Table 8.1. Nominal EWC and nominal RI for different lens materials as reported by the manufacturers or recent publications for HEMA-based conventional hydrogel and silicone hydrogel SCL

Contact lens	**Material (USANC)**	**FDA**	**EWC (%)**	**RI**
Actifresh 400	(Lidofilcon A)	II	73	-[¥]
Acuvue 2	(Etafilcon A)	IV	58	1.40
[†]Acuvue Advance	(Galyfilcon A)	I	47	1.4055
Aspheric	(Methafilcon A)	III	55	1.41
Focus Dailies	(Nefilcon A)	II	69	1.38
Focus Monthly	(Vifilcon A)	IV	55	1.415
[†]Focus Night & Day	(Lotrafilcon A)	I	24	1.43
Freshlook	(Phemfilcon A)	III	55	1.44
[†]O_2OPTIX	(Lotrafilcon B)	I	33	1.42
Precision UV	(Varsufilcon A)	II	74	1.379
Proclear	(Omafilcon A)	II	62	1.387
[†]Purevision	(Balafilcon A)	III	36	1.426
Soflens 1-day	(Hilafilcon A)	II	70	1.38
Soflens 38	(Polymacon)	I	38,6	1.43
Soflens 66	(Alphafilcon A)	II	66	1.39
Surevue	(Etafilcon A)	IV	58	1.40

USAN: United States Adopted Names Council
[¥] RI not found
[†]Silicone hydrogel CL

Before each measurement session, the refractometer was calibrated using a saturated NaCl solution adjusting the scale-adjustment screw to 29.6% as recommended by the manufacturer for a room temperature of 20ºC. Refractometer manipulation was performed as described by previous authors regarding focusing and reading.[23]

Because of limitations in the refractometer scale, Nichols *et al.*[23] only included lenses on the range 42.5% to 69.0% to allow bias in the measures at each end of the instrument's scale. In our protocol, we made some tests of samples of the lenses used, using the Atago N-2E and two other manual refractometers, which extended the measurement range from 8% to 100% EWC covering the wider hydration range in our sample (24-74% nominal EWC). The two instruments were Atago N-1E (Atago, Tokio, Japan); Atago N-2 E (Atago, Tokio, Japan) y Zuzi 58-92 Brix (Auxilab S.L, Beriain, Navarra, Spain). Those instruments revealed very good agreement with Atago N-2E when measuring isolated samples within the regions where they overlap what could be expected having in mind that the three instruments use the same optical principle.

Surprisingly, lenses whose EWC values were expected to fall below the inferior limit of the Atago N-2E (WC<38% which equates the upper limit of the Brix% scale) or lenses whose EWCs surpassed the lower limit of the Brix% (28% Brix which equates 72% EWC) were measurable with the Atago N-2E, giving exactly the same values as those measured with the "appropriate scale refractometers". Differences were less than 0.5% in all cases.[28]

The CLR 12-70 automated refractometer (Index Instruments, Cambridge, UK) was used to directly measure the RI of the CL. Three measures were done by the same trained observer (ML) on different days under the same room conditions as for the hand refractometry measures previously described. The instrument was set in the continuous scan mode, and each reading was taken only when stabilization was reached. As for manual refractometry, the average value was used for subsequent statistical analysis.

As quoted by Nichols and Bernsten,[25] the CLR 12-70 measures RI by back reflection at 589nm wavelength. Calibration was performed before each measurement sequence, using water at room temperature, while the instrument was adjusted if out of tolerance values were obtained. No temperature correction was introduced, as the measures with Atago N-2E were taken in the same conditions.

A third investigator extracted all the lenses from commercial blisters and placed them in identical glass vials filled with buffered sterile saline solution. A number under each vial identified each lens with purposes of randomization and identification. This investigator presented the lenses in the randomized order to each observer at each session. Readings were registered by this investigator while the operator was blind to the number under the lens storage.

With the purpose of EWC and RI conversion from CLR 12-70 and Atago N-2E, respectively, mathematical equations were derived by correlating EWC or sucrose concentration and its RI. With this purpose a normalized table correlating Brix% and refractive index of sucrose ($C_{12}H_{22}O_{11,}$ relative specific refractivity = 1.032; molecular weight = 342.30 at 20ºC in sodium yellow light of 589 nm wavelength) was used.[§] Data were plotted using a Microsoft Excel Worksheet and the plotted points were fitted to linear, logarithmic or exponential, and polynomial models. The model displaying the higher correlation coefficient (r^2 closer to 1) was set as eligible for subsequent calculations. Equations and corresponding coefficient of determination are displayed in *tables 8.2* and *8.3* for the relationships derived from the whole Brix model (16.07-100%) and for the relationships derived from the reduced Brix model (Brix 20-80%).

[§] AFAB Enterprises (2000). Refractive index tables *at* http://www.refractometer.com/refindextab.html

8.4. Results

Tables 8.2 to 8.5 display all the models tested to obtain the higher coefficient of determination (r^2), from the simpler linear models to the complex polynominal models. While the derivation of RI from EWC follows an exponential relationship, the equivalent for the reverse operation, this is, the derivation of EWC from RI is better described by a logarithmic equation. The model that best fits the relationship between sucrose concentration or water portion and RI is given by a polynomial equation.

Table 8.2. Equations derived by regression analysis to obtain the RI of a sucrose solution by using the Brix (%) or EWC (100-Brix%) values measured with the manual refractometer Atago N-2E. Whole model was used (Brix 16.07-100%)

Conversion	Linear	Exponential	Polynomial
From Brix (%) *to* RI	$RI=0.002\cdot Brix+1.3271$ $r^2 = 0.994$	$RI=1.3283\cdot e^{0.0014\cdot Brix}$ $r^2 = 0.996$	$RI=8\cdot 10^{-06}\cdot Brix^2+0.0014\cdot Brix+1.3333$ $r^2 = 1$
From EWC = 100-Brix *to* RI	$RI= -0.002\cdot WC+1.5229$ $r^2 = 0.994$	$RI=1,5267\cdot e^{-0,0014\cdot EWC}$ $r^2 = 0.996$	$RI=8\cdot 10^{-06}\cdot EWC^2-0,0029\cdot EWC+1.5447$ $r^2 = 1$

Data source: AFAB Enterprises (2000). Refractive Index Tables. http://www.refractometer.com/refindextab.html

Table 8.3. Equations derived by regression analysis to obtain the Brix (%) or EWC (100-Brix%) of a sucrose solution by using the RI values measured with the automatic refractometer CLR 12-70. Whole model was used (Brix 16.07-100%)

Conversion	Linear	Logarithmic	Polynomial
From RI *to* Brix (%)	$Brix=507.45\cdot RI-673.2$ $r^2 = 0.994$	$Brix=715.49\cdot Ln(RI)-202.99$ $r^2 = 0.996$	$Brix = -952.85\cdot RI^2 +3193.9\cdot RI-2564$ $r^2 = 0.999$
From RI to EWC = 100-Brix	$EWC=-507.45\cdot RI+773.2$ $r^2 = 0.9936$	$EWC=-715.49\cdot Ln(RI) + 302.99$ $r^2 = 0.996$	$EWC=952.85\cdot RI^2 -3193.9\cdot RI+2664$ $r^2 = 0.999$

Data source: AFAB Enterprises (2000). Refractive Index Tables. http://www.refractometer.com/refindextab.html

Table 8.4. Equations derived by regression analysis to obtain the RI of a sucrose solution by using the Brix (%) or EWC (100-Brix%) values measured with the manual refractometer Atago N-2E. Reduced model was used (Brix 20-80%)

Conversion	Linear	Exponential	Polynomial
From Brix (%) *to* RI	$RI=0.0021 \cdot Brix+1.3166$ $r^2 = 0.996$	$RI=1.3202 \cdot e^{0.0015 \cdot Brix}$ $r^2 = 0.998$	$RI= 8 \cdot 10^{-06} \cdot \%Brix^2 +0.0013 \cdot Brix+1.3346$ $r^2 = 1$
From EWC = 100-Brix <u>*to* RI</u>	$RI=-0.0021 \cdot WC +1.5285$ $r^2 = 0.996$	$RI=1.5318 \cdot e^{-0.0015 \cdot EWC}$ $r^2 = 0.998$	$RI= 8 \cdot 10^{-06} \cdot EWC^2 -0.0029 \cdot EWC+1.5454$ $r^2 = 1$

Data source: AFAB Enterprises (2000). Refractive Index Tables.
http://www.refractometer.com/refindextab.html

Table 8.5. Equations derived by regression analysis to obtain the RI of a sucrose solution by using the Brix (%) or EWC (100-Brix%) values measured with the manual refractometer Atago N-2E. Reduced model was used (Brix 20-80%)

Conversion	Linear	Logarithmic	Polynomial
From RI *to* Brix (%)	$Brix=470.28 \cdot RI-619.01$ $r^2 = 0.996$	$Brix=671.19 \cdot Ln(RI)-186.34$ $r^2 = 0.998$	$Brix=-834.62 \cdot RI^2 +285.3 \cdot RI-2317.4$ $r^2 = 1$
From RI to EWC = 100-Brix	$EWC=-470.28 \cdot RI +719.01$ $r^2 = 0.996$	$EWC=-671.19 \cdot Ln(RI) +286.34$ $r^2 = 0.998$	$EWC=834.62 \cdot RI^2 -2852.3 \cdot RI+2417.4$ $r^2 = 1$

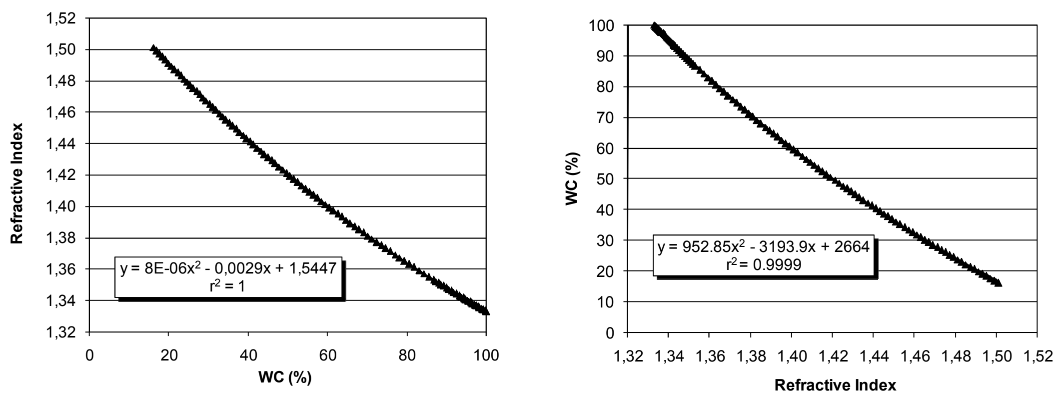
Data source: AFAB Enterprises (2000). Refractive Index Tables.
http://www.refractometer.com/refindextab.html

When we compare the model derived from the whole range of sucrose concentration (0-83.93% Brix or 16.07-100% EWC) against that derived considering only the normal EWC range for current SCL (20-80% EWC or 80-20% Brix), not statistical significant differences are observed. Minor changes between both models when RI is derived from EWC are obtained as seen in *tables 8.2* and *8.4* and graphically displayed in *figures 8.1A and 8.2A.* Conversely, some remarkable differences are observed between models that predict EWC from RI as seen in *tables 8.3* and *8.5* as well as *figures 8.1B and 8.2B.* The practical consequences of this fact will be explored later in this section.

Hence, to obtain EWC from RI measurements made with the CLR 12-70, we can use the following equation:

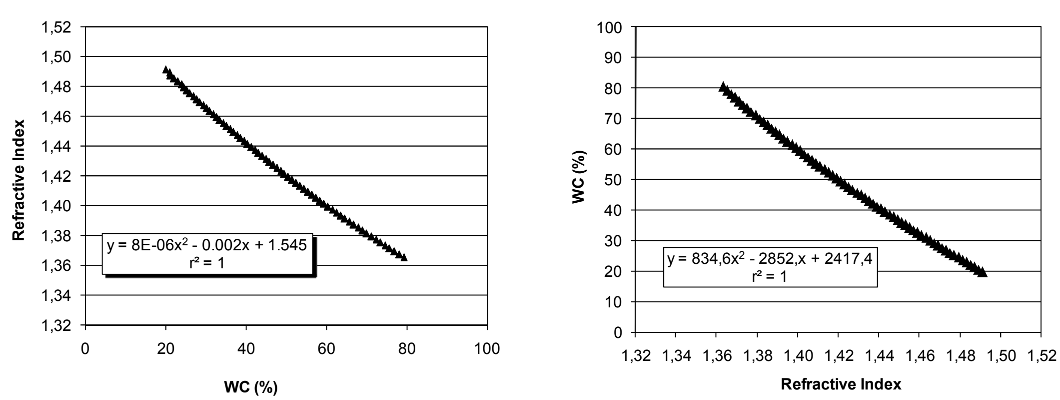
$$EWC = 952.85 \cdot RI^2 - 3193.9 \cdot RI + 2664 \qquad \text{(Equation 8.2)}$$

Figure 8.3 shows the relationship between the EWC converted from the RI measured with CLR 12-70 automated refractometer from the whole Brix range, and the nominal EWC and with the measured EWC with Atago N-2E. Both regression lines display a high coefficient of determination (r^2), although the relationship between derived EWC and measured EWC with manual refractometry displayed the stronger relationship.



(A) **(B)**

Figure 8.1. Relationship correlating the RI of a sucrose solution as a function of the Brix% (sucrose concentration) and the equations to derive RI from EWC (A) and vice versa (B) for a range of EWC from 16 to 100%.



(A) **(B)**

Figure 8.2. Relationship correlating the RI of a sucrose solution as a function of the Brix% (sucrose concentration) and the equations to derive RI from EWC (A) and vice versa (B) for a range of EWC from 24 to 80%.

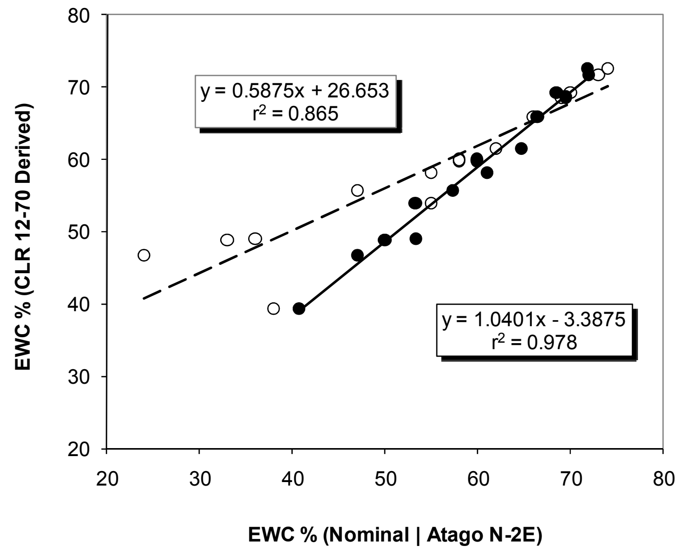


Figure 8.3. Regression analysis displaying the relationship between EWC converted from RI measurements made with the CLR 12-70 (polynomial equation in table 8.3-2nd row-whole Brix model) against nominal EWC (open circles, dotted line) and EWC measured with Atago N-2E (closed circles, solid line).

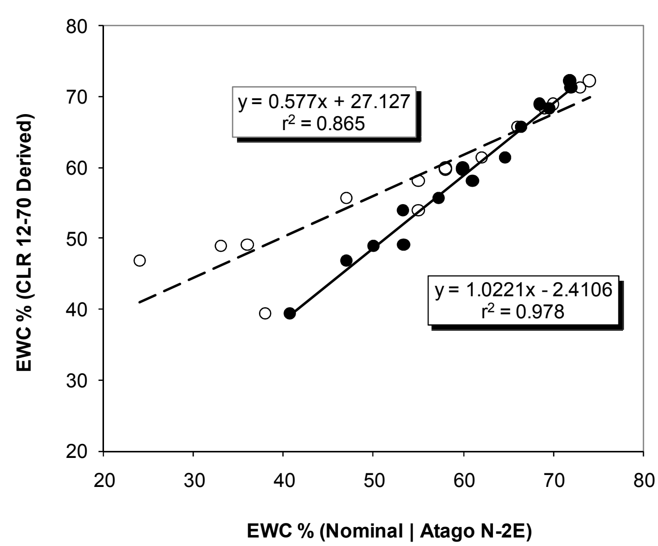


Figure 8.4. Regression analysis displaying the relationship between EWC converted from RI measurements made with the CLR 12-70 (polynomial equation in table 8.5-2nd row-reduced Brix model) against nominal EWC (open circles, dotted line) and EWC measured with Atago N-2E (closed circles, solid line).

The same is also valid when the conversion equation derived from the reduced Brix scale (SCL EWC range) are used, being only slightly different in the terms of the regression equations but, with the same level of correlation as defined by the correlation coefficients (r^2)

which is observed in *figure 8.4*. In this case, the equation used to convert RI from the CLR 12-70 to WC values is given by the following expression:

$$EWC=834.62 \cdot RI^2-2852.3 \cdot RI+2417.4 \qquad \text{(Equation 8.3)}$$

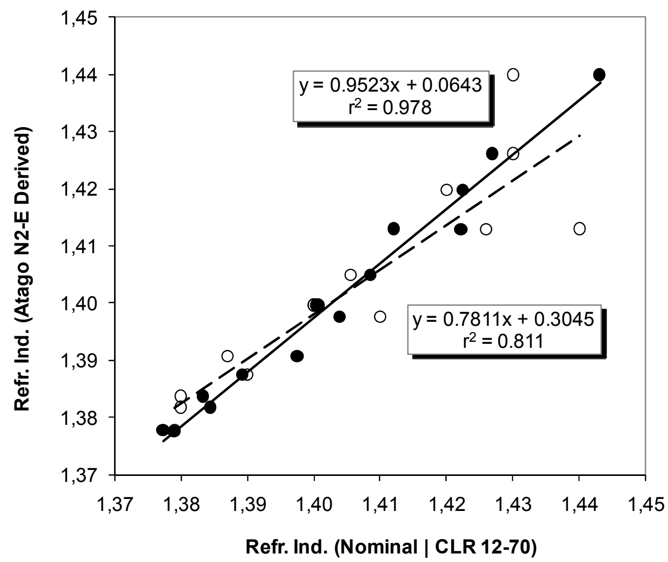


Figure 8.5. Regression analysis displaying the relationship between RI converted from EWC measurements made with the Atago N-2E (polynomial equation in table 8.2-2nd row-whole Brix model) against nominal RI (open circles, dotted line) and RI measured with CLR 12-70 (closed circles, solid line).

Figures 8.5 and *8.6* show the relationship between RI calculated from the EWC readings with the Atago N-2E by using whole Brix range relationships or reduced Brix range relationships, respectively. In this case, to obtain RI from Atago's EWC reading by using the whole Brix range, we have applied equation 8.4 and the equation 8.5 to obtain the same conversion, using a reduced Brix range confined to the normal EWC interval for current SCL (reduced Brix scale).

$$RI=8 \cdot 10^{-06} \cdot EWC^2-0.0029 \cdot EWC+1.5447 \qquad \text{(Equation 8.4)}$$

$$RI= 8 \cdot 10^{-06} \cdot EWC^2-0.0029 \cdot EWC+1.5454 \qquad \text{(Equation 8.5)}$$

Again there are minimal differences between both equations what is reflected on the almost identical representations seen in *figures 8.5* and *8.6*.

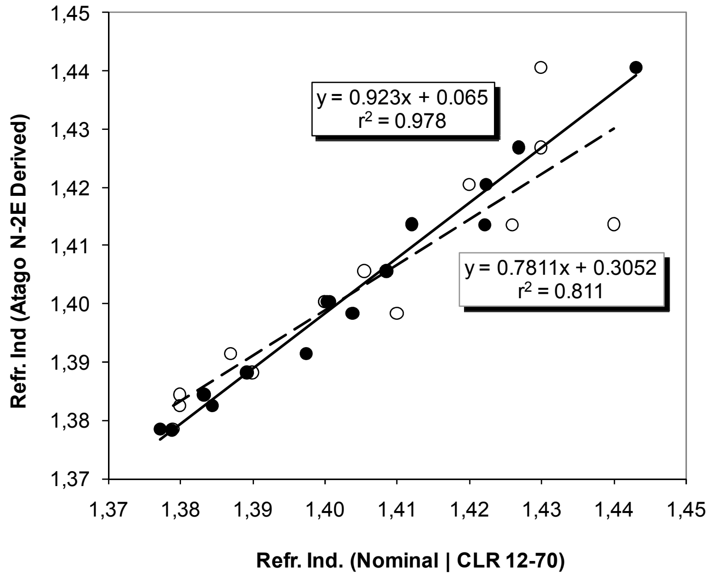


Figure 8.6. Regression analysis displaying the relationship between RI converted from EWC measurements made with the Atago N-2E (polynomial equation in table 8.4-2nd row-reduced Brix model) against nominal RI (open circles, dotted line) and RI measured with CLR 12-70 (closed circles, solid line).

8.5. Discussion

We have used two models based on the relationship between sucrose concentration in a solution and RI to derive EWC from CLR 12-70 measures of RI and to derive RI values from Atago N-2E EWC readings. Both models were based on the relationship existent between sucrose RI and EWC or Brix value measured with refractometry. The first model considers the whole range of sucrose concentrations (0-84%) which equates EWC from 16% to 100%. The second one was produced considering only values within the normal range of hydration for currently available SCL, this is, EWC ranging from 20% to 80%, which equates Brix values within the range from 80% to 20%.

When the specific relationships derived within the interval for SCL hydration to obtain RI from EWC measured with the Atago N-2E are used, small differences are noticed (only the third decimal place are affected in one unit in some cases (≤0.05% in all cases). Therefore, we conclude that the reliability of equations derived from the whole EWC interval of sucrose are as valid as those obtained by limiting the range to that of current SCL EWC to derive RI values from manual refractometry with Atago N-2E. Regarding the reverse operation, to obtain EWC from the RI obtained with the CLR 12-70 automated refractometer limiting the scale according to normal hydrogel lenses EWC, more significant differences were observed reaching 0,5% of EWC in some cases. This resulted in overestimation of EWC for medium and high EWC SCL from 0.01% for Galyfilcon A which displays a reading of EWC around 55% with refractometry (47% nominal), to 0,53% for the 72% Vasurfilcon A. Conversely, the same model tends to underestimate EWC of SCL with lower EWC readings, being -0.37% for Polymacon. However, this approach is much more simple than that recommended by the manufacturer by measuring the RI of the polymer in the hydrated and dried state. We must claim the attention for the larger spread of data for the relationship between nominal EWC and derived EWC from RI measured with CLR 12-70 seen in *figures 8.3* and *8.4* for the less hydrated materials. This is likely to be due because of the misinterpretation of the EWC of Si-Hi materials by refractometry. It is known, that because of lower RI of siloxane compared to conventional hydrogel monomers, these lenses give lower RI than expected due to its lower EWC, hence given higher EWC values when Brix-based methods are used to measure RI.[25] We have investigated this fact for the four Si-Hi CL currently in the marketplace and have found that such materials follow their own liner relationship regarding the correlation between RI and EWC.[29]

From these results, we can conclude that using a model of sucrose solution limited to the normal range of EWC of current hydrogels, we avoid negligible underestimations of RI as derived from Atago N-2E, but we can reduce more significant bias in EWC estimates from the CLR 12-70 automated refractor induced if we use the model obtained by considering the whole range in the sucrose solution model. Errors will overestimate EWC for high water CL and underestimate EWC for the less hydrated samples. Also, it seems to be a trend such as the higher the EWC, the higher the overestimation, and the lower the EWC, the more significant the underestimation.

Nevertheless, we have to remember that these models are not corrected for their direct application with Si-Hi materials. For such materials, the lower RI of siloxane compared to HEMA-based polymers is interpreted by the manual refractometers as possessing a higher EWC than they actually have. We have recently studied this topic for the four Si-Hi CL currently available in the marketplace and demonstrated that those materials follow their particular relationship between RI and EWC that must be considered when EWC is to be obtained by refractometry.[29]

Both manual and automated refractometers have their own advantages and disadvantages. Both instruments are easy to use, although hand refractometry requires training, while automated refractometry with the CLR 12-70 is more accurate and less operator dependent. Regarding affordability and portability, hand refractometry, is more convenient and has been successfully applied in clinical trials[4,5,9,9,18,22] and even in the hands of patients.[3]

Present results can be applied by clinicians and researchers to derive and maybe compare readings of EWC or RI obtained with automated and manual refractometry with a high level of confidence. Potential applications of this investigation include studies of CL dehydration, hydrogel polymer deterioration and spoilation, etc. The expensive and accurate automated refractometer CLR 12-70 could be used to evaluate hydrogel material EWC as well as the inexpensive, portable, and relatively easy to use hand refractometer Atago N-2E could be used to analyze RI of hydrogel materials. To the best of our knowledge, this is the first time that such considerations were elucidated in a peer-reviewed journal.

Nichols *et al.*[23] studied nineteen soft lenses not including Si-Hi lenses using the Atago CL-1. The range of nominal EWC was from 42.5 to 69%. In another study, the same authors reported the RI of twenty-three soft lenses including Focus Night & Day as Si-Hi lens using the CLR 12-70 (Index Instruments, Cambridge, UK).[25] Surprisingly, they found difficulties on measuring Vifilcon A with the CLR 12-70 automated refractometer in the second, but only cited difficulties on measuring it with the Atago CL-1. In the present study, we were not able to measure this material either with the CLR 12-70 automated refractometer or with the Atago N-2E hand refractometer.

With the present study, we have proved that we can obtain EWC or RI from manual and automated refractometers. This will have important implications for the development of experimental and clinical research, regarding the level of EWC of hydrogel CL and the changes experienced under different conditions.

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Chapter 9

Determination of the Oxygen Permeability and Other Relevant Physiological Parameters of Soft Contact Lenses Using a Polarographic Method

9.1. Abstract

Purpose: To measure the apparent oxygen transmissibility (Dk/t_{app}) of four silicone hydrogel (Si-Hi) contact lenses (CLs). Biological oxygen apparent transmissibility (BOAT), equivalent oxygen percentage (EOP), partial pressure of oxygen at the cornea-CL interface (p_{tc}) and oxygen flux (j_c)were also obtained in order to evaluate the physiological environment under the lens using the formulations derived from previous studies.

Methods: The oxygen performance of four Si-Hi materials was evaluated using a polarographic cell coupled to a permeometer. For each material, five samples were stacked in order to obtain the resistance $(Dk/t_{app})^{-1}$ and the corresponding value of permeability (Dk). The first measurement from each of the five repeated stacks was also considered to compute a single value of Dk/t_{app} in order to evaluate the error of this methodology compared with the recommended stack method. Room and cell temperature were maintained at 24 and 35 ºC, respectively.

Results: Values of Dk/t_{app} and Dk obtained from the two different procedures (stack method and measurement of single sample) were significantly different from nominal values given by the manufacturer, particularly for some samples. However, the impact of these differences in the values of the other physiologically relevant parameters (BOAT, EOP, p_{tc}, and j_c) was not significant. Furthermore, despite the different Dk/t_{app} values, BOAT, EOP, p_{tc}, and j_c these values were very similar for the four lenses. The relationships of Dk/t_{app} with the remaining physiological parameters were calculated and graphically represented for open and closed eye conditions.

Conclusion: Despite values of Dk/t_{app} and Dk can vary significantly depending on the method of measurement, the physiological values that are relevant to evaluate the physiological performance of CLs do not suffer significant changes. Thus, in the range of high Dk/t (110-175 barrer/cm), significant variations in the values of Dk/t will have low impact on physiological performance of the lenses and the results won't be significantly different if calculated from single sample readings or stacked samples of Dk/t_{app}. However, this assumptions are not true for low- Dk/t_{app} values (i.e. below 70 barrer/cm) and for material characterization and differentiation between materials, the stack method should be used, although some variability in the results can be expected even with this method for materials with high- Dk/t_{app}. On the view of the significant variability of current techniques to measure material properties, more accurate methods are necessary.

9.2. Introduction

To raise the oxygen permeability of CL materials has been a challenge for scientists involved in CL engineering since the first attempts to prescribe overnight CL wear during the 80's and the consequences of hypoxia were observed with low-Dk soft and rigid contact lenses. This was motivated by the known fact that oxygen transmission through CLs is the most important property governing physiological response of the ocular surface during CL wear. Corneal swelling,[1] limbal redness,[2] epithelial thinning,[3] mycrocists[4,5] are just some of the complications attributed to corneal oxygen depletion during CL wear.

Under normal open eye conditions, at sea level, the cornea requires a minimum oxygen supply of 5 to 7.5 $\mu l \cdot cm^{-2} \cdot hour^{-1}$.[6,7] Holden and Mertz[8] predicted that lenses to be worn under daily wear conditions should provide a minimum Dk/t of 34 barrer/cm, or an equivalent oxygen percentage (EOP) of 9.9%, while this value would increase up to 84 barrer/cm (EOP = 17.9%) to prevent corneal hypoxia and limit corneal edema to physiological levels (<4%). However, more recent estimates considering the metabolic requirements of the cornea under hypoxic conditions made by Harvitt and Bonanno[9] concluded that it would be necessary to provide the cornea with higher levels of oxygenation to avoid hypoxia through the whole cornea under overnight CL wear conditions. In this case a minimum Dk/t of 125 barrer/cm would be necessary.

These criteria are even more critical when we consider powered CLs with thicker areas at center or periphery depending on the attempted refractive correction. So, as Fatt *et al.*,[10] demonstrated that lateral diffusion of oxygen is almost absent under soft CLs (SCLs), these criteria should be satisfied even at the thickest parts of the CL. This was confirmed by clinical observations of topographic edema done by Holden et al using a "donut" CL with a large central aperture.[11] For this reason, Papas *et al.* proposed that to avoid limbal redness, negative CLs should display a minimum Dk/t value at lens periphery of 56 barrer/cm.

Recent studies conducted by Compan *et al.*[12] reported that CLs with oxygen transmissibility higher than 100 barrer/cm provide the lens-cornea interface with an oxygen tension that reduces the gradient of concentration decreasing the oxygen flux into the cornea. According to their results, to increase value of Dk/t over 70 barrer/cm will have minor impact on the oxygen flux onto the cornea even under overnight conditions. Brennan[13] reported that values of Dk/t of 15 and 50 barrer/cm will be enough for the cornea to satisfy 96% of its normal oxygen consumption under daily wear and overnight wear conditions.

Nowadays, new polymers incorporating highly transmissible siloxane moieties that significantly improve the oxygen performance are available. Some of these materials have been worn under continuous wear conditions for periods up to 30 days without relevant ocular complications.[14-19] As a consequence, these materials also offer the possibility to be worn under continuous wear conditions for therapeutic use.[20-23]

Four different procedures have been used to determine the oxygen transmissibility and permeability coefficients of CLs. Three of these procedures use a Clark oxygen electrode covered by the lens, directly[24] or separated by a thin Teflon membrane of known oxygen transmissibility,[25,26] to measure the oxygen flux through the lenses. The first method was developed for use with hydrogel lenses that in the hydrate state are swollen in the electrolyte required for the electrochemical reaction to take place on the electrode. The second method is similar to the first one, but is adapted for use with rigid hydrophobic contact lenses. In this case, a thin piece of cigarette paper soaked in the electrolyte solution is sandwiched between the hydrophobic lens and the electrode to establish the electrolytic contact between the lens and the electrode.[27,28] The third method, which can be used for hydrogels as well as for rigid lenses, contains the electrolyte solution between the Teflon membrane and the electrode.[25,29] The fourth method uses dual chambers separated by the membrane whose Dk/t is to be obtained. The oxygen is introduced into one of the chambers and diffuses through the lens from the chamber with the higher partial pressure of oxygen to the second chamber fitted with an oxygen consuming electrode.[30]

The electrochemicsal technique described by Aiba *et al.*[31] for polymeric membranes, has been used often for the determination of the oxygen permeability coefficient of hydrogel CLs placed directly on the electrode. This technique is also known as the polarographic method. By mean of this method the oxygen flux through the lens is determined from the measurement of the electric current in a potentiometer. When the gold cathode is maintained at 0.75V with respect to the silver anode, all the oxygen passing through the sample is reduced at the cathode. For small electric current densities, the nature of the reduction process in the cell varies with the pH of the solution.[32] However, at pH between 5 and 12 (borax, buffer), used in most experiments, the same assumption can be made.

However, this technique is adversely affected by the so called boundary layer effect that leads to underestimations of oxygen transmissibility of materials. This effect is induced by the aqueous layers over the CL (anterior boundary layer) and between this and the polarographic cell (posterior boundary layer), both needed for the oxygen to be dissolved and transferred into the lens material from the environment and to the measuring cell where the electrochemical reaction takes place. The resistance of the boundary layers induces a lower oxygen partial pressure at the anterior boundary layer and eventually an increased concentration in the posterior one, leading to a lower concentration gradient across the membrane than expected. The result will be a decrease in oxygen transport through the membrane. However, this problem can be overcome by measuring material samples of different thickness or stacking several lenses of known thickness.[33] Young and Benjamin[34] obtained a similar approach by modifying sample thickness by using different power CLs made of lotrafilcon A and balafilcon A. The other major concern with the polarographic technique is the so called "edge effect" that affects measurements when the area at both sides of the membrane (i.e. CL) is not the same as is the case for powered CLs or when we cannot ensure that all oxygen detected at the posterior lens surface has passed perpendicular to the lens surface. A small lateral diffusion could happen, thus the actual area of the membrane exposed to the atmosphere will by higher than that assumed. The result will be an overestimation of oxygen transmissibility. This effect can be avoided by adjusting for the actual surface area of the CL exposed to the cathode of the cell and by incorporating different correction factors. This correction is already available in some commercial devices.

The non-idealities, described above, are the reasons why the polymer samples should not be thicker than 0.4 mm for a cathode diameter of 4 mm and not more permeable than 100 barrer (1 barrer = 10^{-9} (cm^2/s) (cm^3 of O_2 /cm^3 of polymer/ mm Hg). However, even for thin samples (0.05-0.20 mm), it is necessary to correct permeability for both types of the non-idealities.

Appropriate formulas for thin samples with guard ring cell (according to Determination of oxygen permeability and transmissibility with the Fatt method in ISO 9913-1/1996) as well as using a permeometer with guard ring cell, (Rehder Development Co, http://www.rehder-dev.com/; 2003) can be used for elimination of edge effects. Nevertheless, the width of the outer guard ring is about 0.7 mm, therefore it is also suitable only for thin samples. The choice of a wider ring would bring another problem, because an increasing amount of ions at the cathode would have to migrate to an ambient electrolyte.

The electrochemical reaction that takes place at the gold cathode of the polarographic cell in the presence of a differential of voltage with the silver anode is described by equation 9.1. The electrons needed for this reaction to take place are produced when sliver atoms are reduced at the cathode according to equation 9.2 in the presence of oxygen:

$$O_2 + 2H_2O + 4e^- \rightarrow 4OH^- \quad \text{(Equation 9.1)}$$

$$4Ag \rightarrow 4Ag^+ + 4e^- \quad \text{(Equation 9.2)}$$

These electrons generate a small current that can be measured. The apparent oxygen transmissibility is related to the total current diffusion in the steady state (I) and will be described in further detail in the methods section.

Coulometric and gas-gas techniques work in a different way as the polymeric membrane is the only area that communicates two different chambers (some authors call these procedures as dual-chamber techniques). In the coulometric method one chamber is saturated with oxygen, while the other chamber is saturated with nitrogen. The amount of oxygen detected at the second chamber serves to evaluate the diffusion of oxygen thought the membrane. Both techniques are relatively free from boundary layer effects (only anterior boundary layer is present when measuring hydrophilic samples with coulometric technique) and the edge effect present in the polarographic method. A second type of edge effect is present with this techniques, but this can be neglected as only should under-estimate actual magnitudes of Dk/t and Dk by a minor amount within the range of the repeatability of measurements.[35] Gas to gas technique is not to be used with hydrophilic samples because one chamber is pressurized at 3 atm to force oxygen to pass through the lens, what will induce damage to the hydrophilic CLs.

The polarographic method is not recommended by ISO standards (ISO 9913-1) for measuring CLs whose Dk is above 100 barrer, and the coulometric method has been suggested as a more suitable method for lenses with Dk > 70 barrer.[36] Gas to tas method is only recommended by ISO 9913-2 for non-hydrogel materials as this method induces dehydration of the materials by direct contact with gas chambers. Despite this, both polarographic and coulometric methods had been used to obtain Dk/t and Dk of modern high-Dk (>100 barrer) Si-Hi CLs, with satisfactory results according to the nominal values given by the manufacturers.[12,33,37]

Morgan *et al.*[36] evaluated the oxygen transmissibility and permeability of lotrafilcon A (Focus Night & Day, CIBA Vision, Duluth, GA), obtaining some discrepancies between the coulometric in the liquid-gas configuration and polarographic techniques for lotrafilcon A and other RGP materials whose Dk were above 70 barrer. Discrepancies affected not only mean values but also standard error, being larger with the polarographic technique. Alvord *et al.*[37] compared results from the liquid-to-gas configuration with those from the gas-to-gas configuration of the coulometric technique for lotrafilcon A material. From their results we could see that the gas-to-gas configuration gave higher Dk values due to partial lens desiccation with this set up. Morgan *et al.*[36] and Alvord *et al.*[37] found similar Dk values for lotrafilcon A using the liquid-to-gas method in the coulometric device being 150 ± 4 barrer and 155 ± 5 barrer, respectively. Compan *et al.*[33] obtained Dk values of 141 ± 5 barrer for this material using the polarographic technique, probing that accurate and repeatable readings can be obtained with this technique even in high-Dk SCLs. The recent work of Young and Benjamin[34] and Compan *et al.*[12,33] also provided a term of comparison for balafilcon A (Purevision, Bausch & Lomb, Rochester, NY). Those authors reported values of transmissibility of 102 to 111 barrer and 107 ± 4 barrer, respectively.

Recently, new materials are being launched to the marketplace based on the Si-Hi technology. Although they are not intended to be worn on an extended or continuous wear schedule, their oxygen performance as labeled by their manufacturers seems to be very close to satisfy the more stringent criteria presently known. According to the different studies quoted above, it is not clear which methods should be used to measure the oxygen performance of theses lenses.

The purpose of this study was to measure the apparent oxygen transmissibility (Dk/t_{app}) of four Si-Hi CLs using the polarographic technique with edge effect correction and correction for boundary layer by stacking several lenses of the same material. The transmissibility value from a single sample was also obtained. From these two readings, the values of BOAT, EOP, p_{tc}, and j_c under open and closed eye conditions are derived and compared with those derived from nominal Dk/t values given by the manufacturers.

9.3. Materials and Methods

9.3.1. Contact lenses

Four Si-Hi CL materials currently available in the world market have been used in this study including Air Optix Night & Day (lotrafilcon A-24%) and Air Optix (lotrafilcon B-33%) from CIBA Vision Corporation, Duluth, GA; Acuvue Oasys (senofilcon A-38%) from Johnson & Johnson Vision Care, Jacksonville, FL and PureVision (balafilcon A-36%) from Bausch & Lomb, Inc., Rochester, NY. Technical details of Si-Hi are displayed in *table 9.1*.

Table 9.1. Technical details of Si-Hi CLs used in the study

	Air Optix Night&Day	Acuvue Oasys	Air Optix	Purevision
Material	Lotrafilcon A	Senofilcon A	Lotrafilcon B	Balafilcon A
Dk (barrer)	140	103	110	99
t_c (mm @-3.00)	80	70	80	90
t_c (measured)*	85 ± 6	72 ± 2	85 ± 4	96 ± 4
Dk/t (barrer/cm)	175	147	138	110
H_20 (%)	24%	38%	33%	36%
FDA	I	I	I	III
Power (D)	-3.00	3.00	-3.00	3.00
Diameter (mm)	13.8	14.6	14.2	14
Base Curve (mm)	8.6	8.7	8.6	8.6
Schedule/ Replacement	CW/ Monthly	DW/ Monthly	DW/ Monthly	CW/ Monthly

* This value is usually called Lav. In the present work, this will be represented by "t"

9.3.2. Measurements of apparent oxygen transmissibility (Dk/t_{app}). Stack method

Measurements were taken using a Clark-type fitted for the electrochemical determination of the oxygen transmissibility of hydrogel materials according to the technique originally described by Aiba *et al.*[31] for polymeric membranes. The amount of oxygen passing through the CL was computed from the measurement of the electric current generated by reduction of oxygen at the cathode of a modified polarographic electrode (Rehder Development Co., Castro Valley, CA) when the gold cathode is maintained at a 0.75 V with respect to the silver anode coupled to a Model 201T O_2 Permeometer (Createch, Albany, CA). The gold cathode had a surface area A=12.78 mm^2. The silver anode is positioned concentrically to the cathode, and these were isolated by an epoxy resin, altogether forming a spherical cap. In order to mimic ocular conditions, during measurements, the system was thermostated at 35 ± 1ºC. Five samples of each material were stacked and five repeated measures were taken with 1, 2, 3, 4 and 5 lenses in the stack. This procedure is used to eliminate the boundary layer effect as described previously.[33,38]

Mean values and standard deviation of intensity readings in nanoamperes (nA) were computed for subsequent analysis and calculations of Dk/t_{app} values. The electrochemical reaction that takes place at the cathode is described by equation 9.1. The apparent oxygen transmissibility $(Dk/t)_{app}$ is related to the total current diffusion in the steady state (I) by the following equation:

$$\left(\frac{Dk}{t_{av}}\right)_{app} = \frac{I}{n \cdot F \cdot A \cdot \Delta p} = B \cdot I \qquad \text{(Equation 9.3)}$$

where $B=(1/n{\cdot}F{\cdot}\Delta p)$ is a constant for each cell computed from n which is the number of electrons exchanged in the electrodes for each molecule of oxygen (n=4), F is the Faraday constant = 96.487 C/mol vol O_2(STp)=96.487·$A{\cdot}s$/22.400 cm^3O_2(STp). A is the surface area of the gold-plated cap in contact with the lens equal to 12.78 mm^2, and Δp is the oxygen partial pressure difference across the membrane = 15.5 cmHg (at sea level). For our cell, B is equal to 0.02929. *Figure 9.1* shows a graphical representation of the elements within the measuring cell. The harmonic average thickness of the CLs (L_{av}) was calculated from five measurements in five regions of the central zone of the lens within 2.5 mm radius (central 5 mm of diameter), corresponding to the active part of the lens in contact with the cathode. Despite "*t*" is usually used for central thickness and L_{av} or L will be considered as the average thickness at the central 5 mm of the CL, *t* will be used in the present work.

The value of oxygen transmissibility for polymacon (Soflens 38) was measured for calibration purposes as recommended by Compañ *et al.*[39] and adopted later by the ISO guidelines[40] given a value of 23 ± 1 barrer/cm which is agreement with the manufacturer values. The corresponding Dk value is 8 barrer, which is slightly below the accepted value of 9 ± 0.5 barrer given by Compañ *et al.*[39]

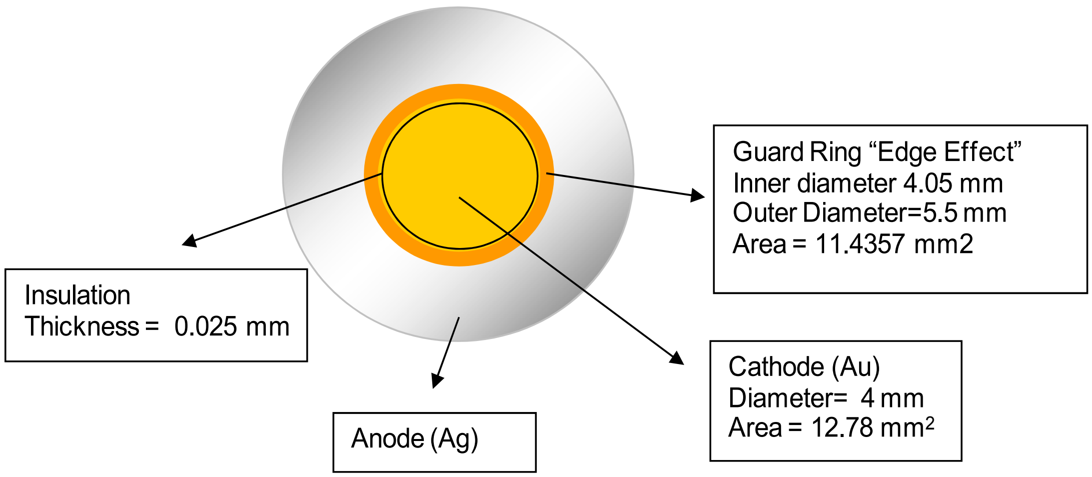

Figure 9.1. Representation of the measurement cell in the Rehder Permeometer.

9.3.3. Oxygen permeability determination (Dk). Stack method

After Dk/t_{app} values had been computed from the intensity values obtained from polarographic measurements, we obtained the apparent resistance of the system for each stack of 1-5 lenses as the reciprocal of the apparent transmissibility of each stack. Resistance is plotted against the cumulative thickness of the stacked samples. From the slope of the line adjusted to the relationship between the inverse of transmissibility or $(Dk/t)^{-1}$, we can obtain the inverse of permeability (1/Dk) of the test samples. The slope of the regression line divided by the cumulated thickness in the stack gives the inverse function of the oxygen permeability of the material. Accordingly, the Dk of the material will be computed as the inverse function of the slope.

$$slope = \frac{d(Dk/t)}{d(t)} = \frac{t}{Dk} \div \frac{t}{1} = \frac{1}{Dk} \qquad \text{(Equation 9.4)}$$

$$Dk = \frac{1}{\frac{d(Dk/t)}{d(t)}} \qquad \text{(Equation 9.5)}$$

The value of oxygen transmissibility obtained from the first lens in each stack will be also considered for later comparisons. This value, however, cannot be considered corrected for the boundary layer effect but it is interesting to know if this value (very rapid to obtain) is or is not significantly different from the value obtained with the stack method (more time consuming) and which impact will have this difference on the calculation of the physiological parameters (BOAT, EOP…).

The following sections of the methods will be devoted to the explanation of calculations of BOAT, EOP and oxygen flux (j_c). One critical point in these calculations is the need to know the partial pressure of oxygen at the cornea-CL interface (p_{tc}) under open and closed eye conditions. The work of Compañ *et al.*[12] allows determining these values under both situations directly using statistical relationships between p_{tc} and Dk/t_{app} obtained by the authors for a range of Dk/t_{app} values from 0 to 300 barrer/cm.

9.3.4. Oxygen tension at the lens-cornea interface (p_{tc})

This parameter is essential for BOAT and subsequent calculations of EOP and oxygen flux onto the cornea under open and closed eye conditions. Oxygen tension behind the CL (p_{tc}) as a function of instrument oxygen transmissibility (Dk/t_{app}) has been computed by Compañ *et al.*[12] In the present work, the equations that correlate those values have been obtained according the methodology described in the following two sections for open and closed eye conditions and then used to obtain BOAT, EOP and flux as a function of the Dk/t_{app} measured for each lens material. For their calculations, the authors used the second Fick's law, that relates the distribution of the pressure of oxygen across the thickness of the cornea with oxygen consumption ($Q \cong 6.6\cdot10^{-5}$ $cm^3O_2(STp)\cdot cm^{-3}\cdot s^{-1}$). Compañ *et al.* also took into account a value of corneal thickness of 0.05 cm and a Dk value for the corneal tissue of 24.7 barrer as reported by Fatt and Weissman.[41] Units of p_{tc} are mmHg.

9.3.4.1. Open eye conditions

According to the calculations of Compañ *et al.*,[12] we have fitted the following equation to their data in order to calculate p_{tc} from Dk/t_{app} obtained in our measurements. We used Table Curve 2D (Jandel Scientific) to obtain the graphic representation shown in *figure 9.2*.

9.3.4.2. Closed eye conditions

Using the same approach as in the previous section, now for closed eye conditions, we obtained the graphical representation in *figure 9.3*.

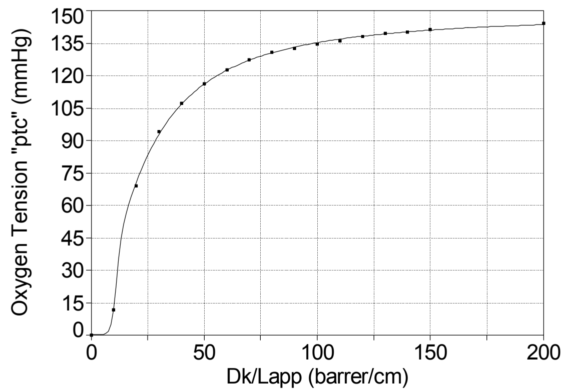

Figure 9.2. Model predicting the oxygen tension at the cornea-CL interface as a function of the measured Dk/t (Dk/L_{app}) under open eye conditions from the experimental values obtained by Compañ *et al.* (2004).[12]

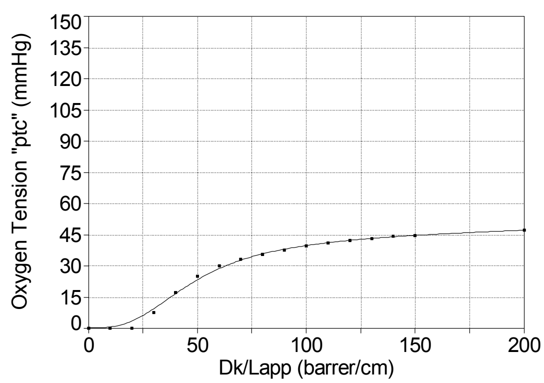

Figure 9.3. Model predicting the oxygen tension at the cornea-CL interface as a function of the measured Dk/t value (Dk/L_{app}) under open closed eye conditions from the experimental values obtained by Compañ *et al.* (2004).[12]

9.3.5. Biological oxygen apparent transmissibility (*BOAT*)

This parameter has been defined by Fatt and Ruben[42] as the relative variation of the partial pressure of oxygen between the front and back sides of a lens on the corneal multiplied by the Dk/t_{app}. Compañ *et al.*[12] also computed the biological oxygen apparent transmissibility (*BOAT*) as the multiplication of the instrument oxygen transmissibility (Dk/t_{app}) by the relative variation of the partial pressure of oxygen between the front (p) and the back sides (p_{tc}) of a lens placed onto the cornea.

$$BOAT = \frac{Dk}{t_{app}} \cdot \left(\frac{p - p_{tc}}{p} \right) \qquad \text{(Equation 9.6)}$$

The value of p is 155 mmHg under open eye conditions and 55 mmHg under closed eye conditions. BOAT units are the same as for Dk/t_{app}, $10^{-9} \cdot [cm^3 O_2 (STp)\ cm^{-2} \cdot s^{-1} \cdot mmHg^{-1}]$.

9.3.6. Equivalent oxygen percentage (*EOP*)

Using the equation of Turnbull *et al.*,[43] and assuming a percentage of oxygen at sea level under open eye conditions (p') of 20.93 % and 7.425 % for open and closed eye conditions, the equivalent oxygen percentage (EOP) can be calculated using equation 9.7 and 9.8. EOP has been the clinical parameter used to represent the oxygen reaching the cornea behind a CL and correlates the corneal swelling after wearing a specific lens with the swelling obtained in experiments involving the circulation of a series of hypoxic air of known oxygen concentration over eyes fitted with swimming goggles.[12]

$$EOP = \frac{p_{tc} \cdot p'}{p} \qquad \text{(Equation 9.7)}$$

Replacing the right values in the previous equation we obtain the same expression for open and closed eye conditions as a function of a constant and the corresponding p_{tc} value. EOP is obtained as a percentage (%).

$$EOP = 0.135 \cdot p_{tc} \qquad \text{(Equation 9.8)}$$

9.2.7. Oxygen flux to the cornea (j_c)

Using first Fick's law, Compañ *et al.*,[12] obtained the following equation to derive the oxygen flux to the cornea, which results from the multiplication of the BOAT value by the partial pressure of oxygen at the lens-air interface (p=155 and 55 mmHg for open and closed eye conditions, respectively).

$$j_c = \frac{BOAT \cdot p}{100} \qquad \text{(Equation 9.9)}$$

Oxygen flux according to previous calculations is given in $10^{-7} \cdot [cm^3 O_2 (STp) \cdot cm^{-2} \cdot s^{-1}]$ or converted into $\mu l(O_2) \cdot cm^{-2} \cdot h^{-1}$ by multiplying the previous value by 103 -to convert $cm^3 O_2 (STp)$ into $\mu l(O_2)$- and dividing the result by $2.7778 \cdot 10^{-4}$ -to convert seconds to hours-.

9.4. Results

Resistance to the oxygen flow defined as $(Dk/t)^{-1}$ by each stack from n=1 to n=5 was plotted against the cumulated thickness in the stack for different materials (*figure 9.4*). The linear relationship correlating resistance with stack thickness had correlation coefficients $r^2>0.99$ for all Si-Hi samples, except for lotrafilcon B ($r^2>0.98$) as shown in *figure 9.4*. From the inverse function of the slope, we obtained the permeability coefficients of different lenses using equations 9.4 and 9.5. Dk/t_{app} and Dk values obtained with this procedure, as well as Dk/t_{app} and Dk obtained from single sample and nominal values given by the manufacturers are given in *tables 9.2* and *9.3*, respectively.

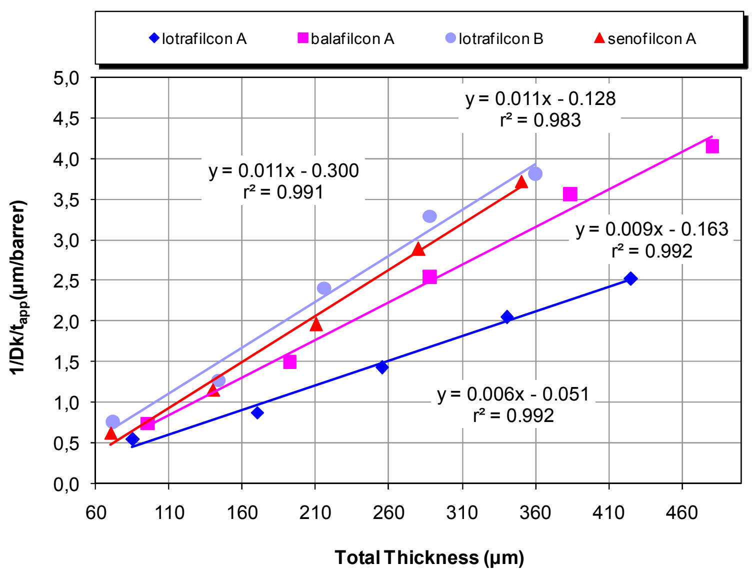

Figure 9.4. Inverse transmissibility vs. thickness of stacked lenses for Si-Hi materials. The average values are presented.

Apparent oxygen transmissibility measured in the study for the five Si-Hi materials ranged from 182 ± 8 barrer/cm for lotrafilcon A to 133 ± 5 barrer/cm for balafilcon A using the single sample method and from 195 barrer for lotrafilcon A to 117 barrer for lotrafilcon B using the stack method. In both cases measured and nominal parameters were correlated ($p<0.001$) although results from both methods are slightly different (*figure 9.5*). Overall, values of Dk/t_{app} derived from single measurements are higher than those obtained from the stack method (*figure 9.6*).

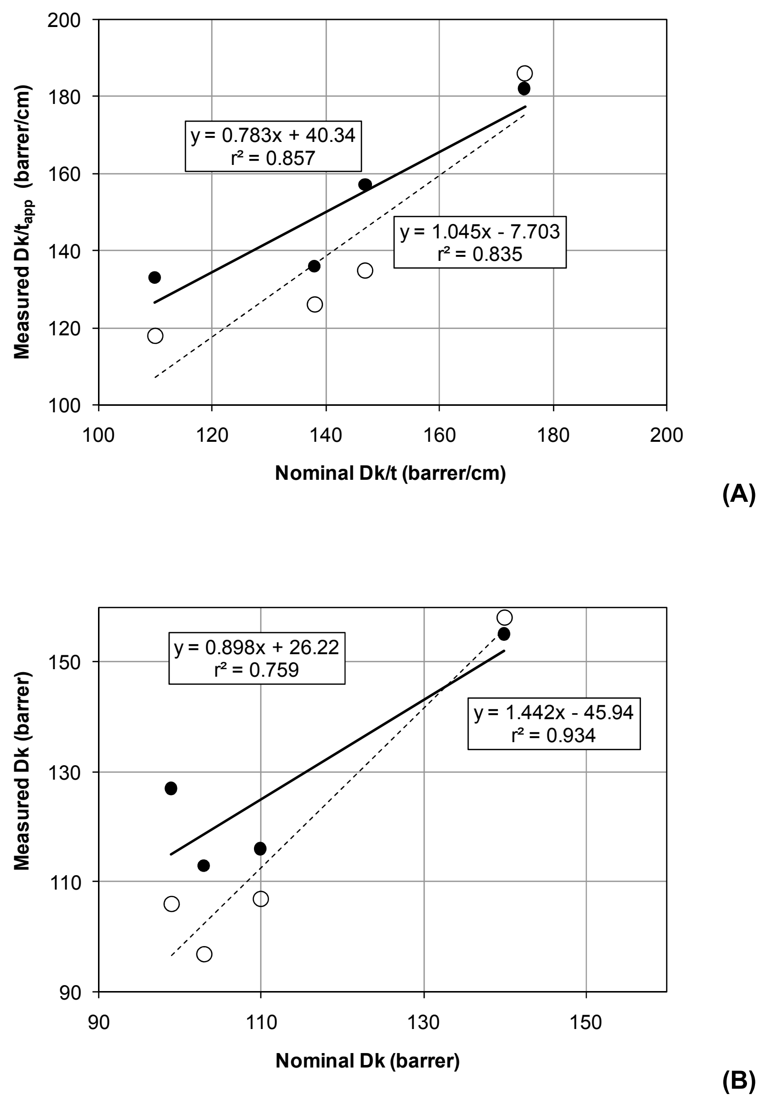

Figure 9.5. Regression of measured Dk/t (A) and Dk values (B) derived from single samples of each material (filled circles) and stack method (open circles) against the corresponding nominal values given by the manufacturers.

Table 9.4 presents the physiological values obtained by different methods and those reported by the manufacturers. Despite the differences observed in *tables 9.2* and *9.3* -for Dk/t_{app} and Dk values, respectively- depending on the method used, no significant differences are observed in the physiological parameters derived according to the methods described. Despite some deviations in the values obtained by the two methods and compared to the nominal values, the coefficient of variation (CV) is very low (highest is 2.8%).

Table 9.2. Oxygen transmissibility values obtained from different methods and values reported by the manufacturers for different Si-Hi CLs

	Lotrafilcon A	Balafilcon A	Lotrafilcon B	Senofilcon A
Nominal Dk/t*	175	110	138	147
Dk/t_{app} (barrer/cm)[a]	182 ± 8	133 ± 5	136 ± 18	157 ± 24
Dk/t_{app} (barrer/cm)[b]	186	118	126	135

Values ±SD are the values directly measured in the study. The average and SD are the result from 5 measurements. Units are barrer/cm = 10^{-09} (cm ml O_2)/(ml sec mmHg)
[a] derived from single measurement of Dk/t_{app}.
Corresponding Dk value result from the multiplication of this value by average thickness of the sample.
[b] derived from the slope in the stack method. Corresponding Dk/t is the value of Dk obtained from the stack divided by average thickness of the sample.
[*] nominal values given by the manufacturers

Table 9.3. Oxygen permeability values obtained from different methods and values reported by the manufacturers for different Si-Hi CLs

	Lotrafilcon A	Balafilcon A	Lotrafilcon B	Senofilcon A
Nominal Dk*	140	99	110	103
Dk (barrer)[a]	155	127	116	113
Dk (barrer)[b]	158 ± 13	106 ± 6	107 ± 11	97 ± 9

Values with SD (±) are the values directly measured in the study. The average and SD are the result from 5 measurements. Units are barrer = 10^{-11} (cm^2/sec)[ml O_2/(ml x mm Hg)])
[a] derived from single measurement of Dk/t_{app}. Corresponding Dk value result from the multiplication of this value by average thickness of the sample.
[b] derived from the slope in the stack method. Corresponding Dk/t is the value of Dk obtained from the stack divided by average thickness of the sample.
[*] nominal values given by the manufacturers

In *figures 9.7* to *9.10* the partial pressure of oxygen at the cornea-CL interface (p_{tc}), oxygen flux (j_c), BOAT and EOP values, respectively as a function of measured Dk/t_{app} according to formulations described in the methods section for the 4 Si-Hi lenses with Dk/t values of 110, 138, 147, 160 and 175 barrer/cm and two conventional SCLs with Dk/t values of 30 and 45 barrer/cm. The values in % reflect the amount of the corresponding parameter compared to the maximum value expected with a CL of infinite transmissibility.

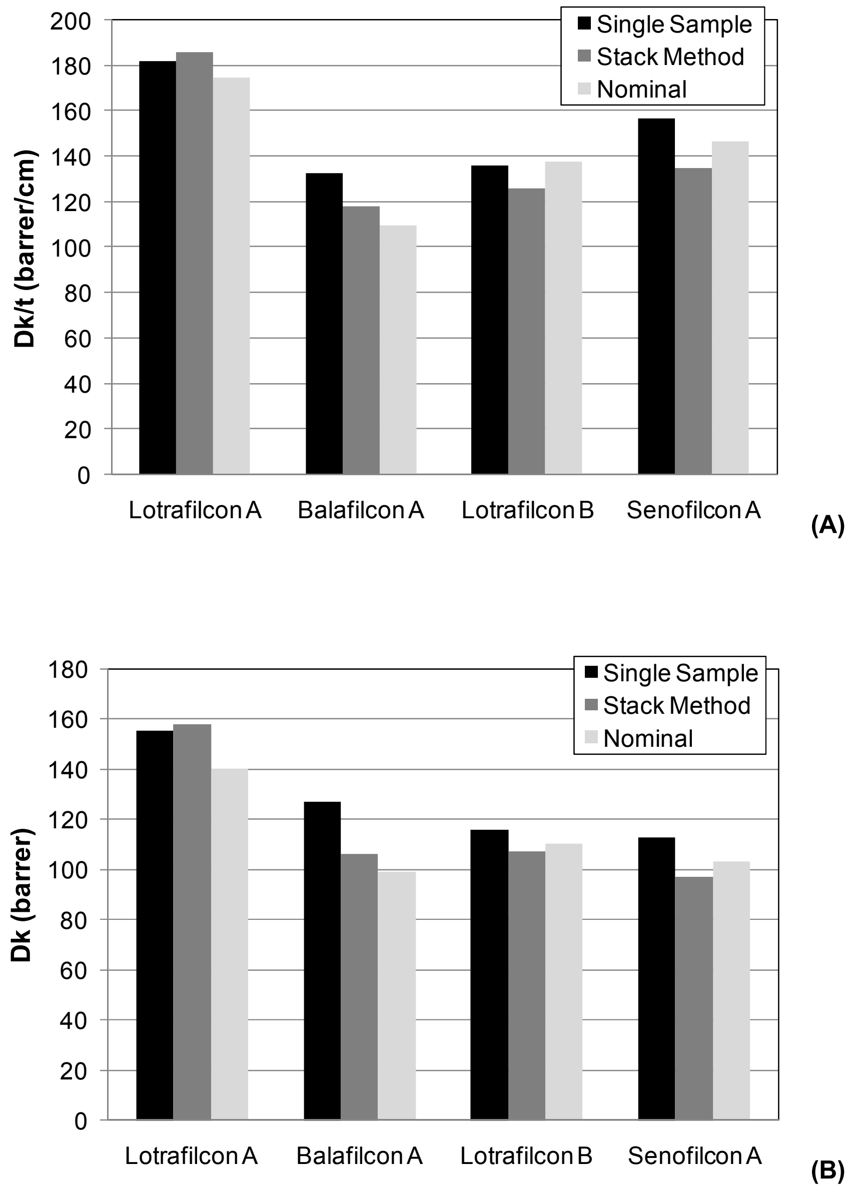

Figure 9.6. Comparative of Dk/t (barrer/cm) and Dk (barrer) values obtained from the two methods and the nominal values given by the manufacturer.

Table 9.4. Physiological parameters derived for different CLs from values of Dk/t_{app} derived from single sample method[a], stack method[b] and nominal values given by the manufacturers[c], respectively

	Lotrafilcon A		Balafilcon A		Lotrafilcon B		Senofilcon A	
$p_{tc\ open}$ (mmHg)	[a]143.6 [b]143.8 [c]143.1	0.24‡	[a]139.5 [b]137.6 [c]136.4	1.15‡	[a]139.8 [b]138.7 [c]140.0	0.53‡	[a]141.8 [b]139.7 [c]140.9	0.75‡
$p_{tc\ closed}$ (mmHg)	[a]46.1 [b]46.3 [c]45.8	0.57‡	[a]43.1 [b]41.6 [c]40.7	2.82‡	[a]43.3 [b]42.4 [c]43.5	1.28‡	[a]44.8 [b]43.2 [c]44.1	1.77‡
BOAT$_{open}$ (barrer/cm)	[a]13.4 [b]13.4 [c]13.4	0.10‡	[a]13.3 [b]13.2 [c]13.3	0.28‡	[a]13.3 [b]13.3 [c]13.3	0.13‡	[a]13.4 [b]13.3 [c]13.3	0.19‡
BOAT$_{closed}$ (barrer/cm)	[a]29.5 [b]29.5 [c]29.4	0.16‡	[a]28.9 [b]28.7 [c]28.6	0.56‡	[a]28.9 [b]28.8 [c]29.0	0.31‡	[a]29.2 [b]28.9 [c]29.1	0.50‡
EOP$_{open}$ (%)	[a]19.4 [b]19.4 [c]19.3	0.24‡	[a]18.8 [b]18.6 [c]18.4	1.15‡	[a]18.9 [b]18.7 [c]18.9	0.53‡	[a]19.1 [b]18.7 [c]19.0	0.75‡
EOP$_{closed}$ (%)	[a]6.2 [b]6.3 [c]6.2	0.57‡	[a]5.8 [b]5.6 [c]5.5	2.82‡	[a]5.9 [b]5.7 [c]5.9	1.28‡	[a]6.0 [b]5.8 [c]6.0	1.77‡
Flux$_{open}$	[a]20.8(7.5) [b]20.8(7.5) [c]20.8[c](7.5[d])	0.10‡	[a]20.6(7.4) [b]20.6(7.4) [c]20.5[c](7.4[d])	0.28‡	[a]20.6(7.4) [b]20.6(7.4) [c]20.6[c](7.4[d])	0.13‡	[a]20.7(7.5) [b]20.6(7.4) [c]20.7[d](7.4[e])	0.19‡
Flux$_{closed}$	[a]16.2(5.8) [b]16.3(5.9) [c]16.2[d](5.8[e])	0.16‡	[a]15.9(5.7) [b]15.8(5.7) [c]15.7[d](5.7[e])	0.56‡	[a]15.9(5.7) [b]15.8(5.7) [c]15.9[d](5.7[e])	0.31‡	[a]16.1(5.8) [b]15.9(5.7) [c]16.0[d](5.8[e])	0.50‡

Partial pressure of oxygen at the CL-cornea interface (p_{tc}), BOAT, EOP (%) and Flux values are provided considering Dk/t_{app} values obtained from single measurement, from the Dk value obtained from the slope in the stack method and from nominal values given by the manufacturer for open and closed eye conditions.

[a] derived from single measurement of Dk/t_{app}
[b] derived from the slope in the stack method
[c] derived from the slope in the stack method
[d] $10^{-7}\cdot[cm^3O_2(STp)\cdot cm^{-2}\cdot s^{-1}]$
[e] $\mu l(O_2)\cdot cm^{-2}\cdot h^{-1}$

barrer = 10^{-11} (cm^2/sec)[ml O_2/(ml x mm Hg)])
‡Coefficient of variation (CV%) of the three values as (SD/Mean)*100. CV for flux values is the same irrespective of the units.

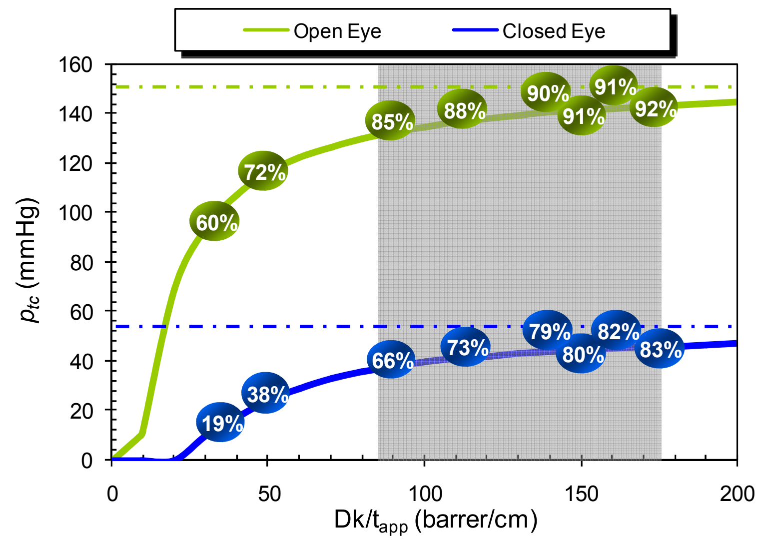

Figure 9.7. Oxygen tension (p_{tc}) at the cornea-CL interface under closed (dark line) and open eye conditions (light line) for CLs of different transmissibility. Shaded area corresponds to the actual range of Dk/t for Si-Hi materials.

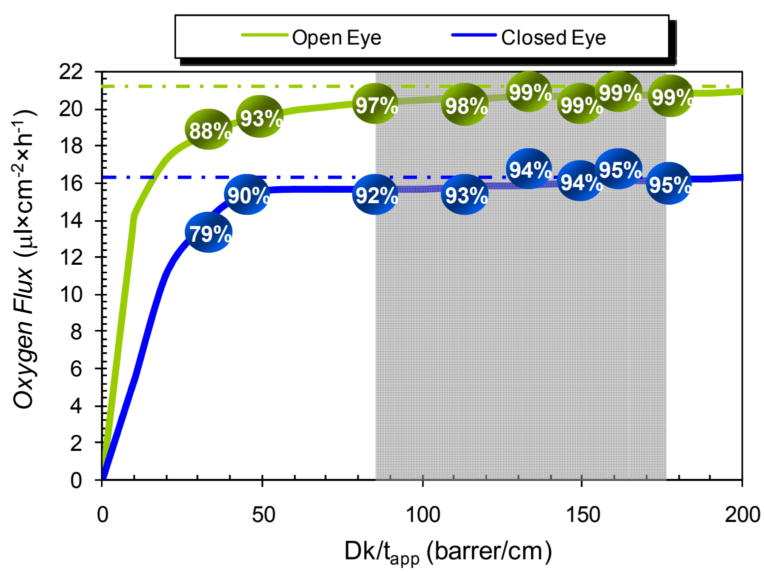

Figure 9.8. Oxygen flux (j_c) through CLs of different transmissibilities for closed (dark line) and open eye conditions (light line). Shaded area corresponds to the actual range of Dk/t for Si-Hi materials.

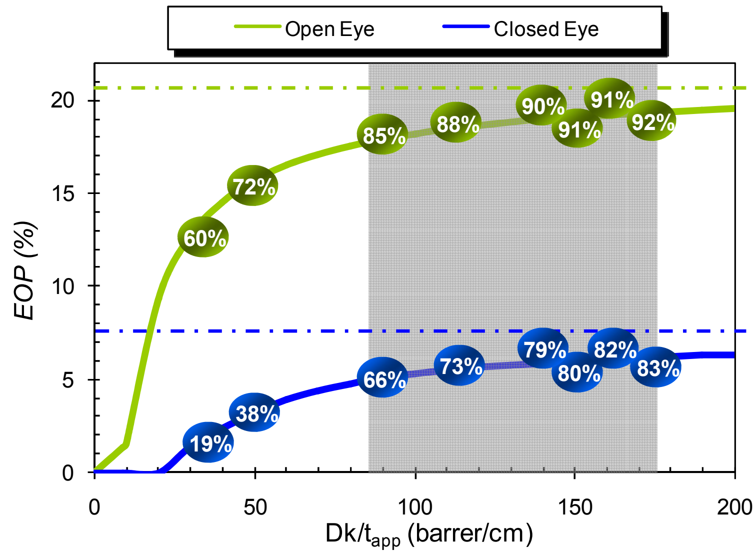

Figure 9.9. EOP available for CLs of different transmissibilities under closed (dark line) and open eye conditions (light line). Shaded area corresponds to the actual range of Dk/t for Si-Hi materials.

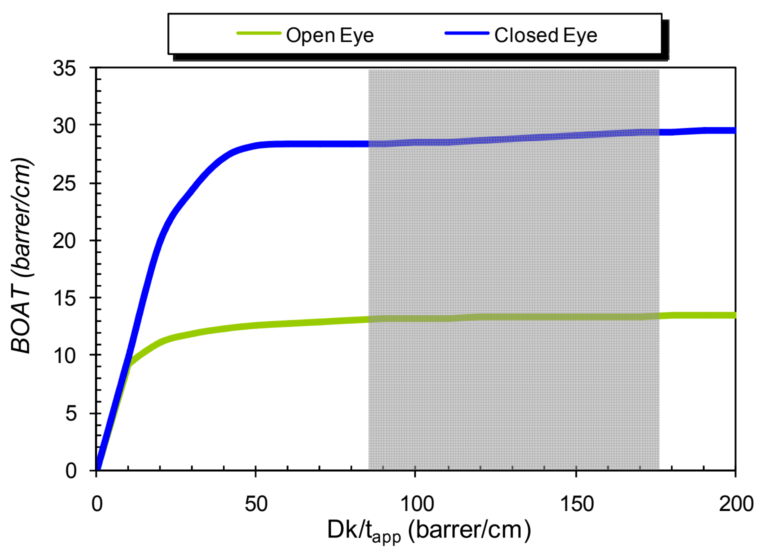

Figure 9.10. BOAT for CLs of different transmissibilities under closed (dark line) and open eye conditions (light line). Shaded area corresponds to the actual range of Dk/t for Si-Hi materials.

9.5. Discussion

With the advent of Si-Hi materials, the question of oxygen permeability became a hot topic in the scientific literature, but at the same time, nowadays, there is a current of thought that states that oxygen should not be a matter of concern anymore as all current Si-Hi materials warrant almost the same oxygenation levels to the eye. In fact, CLs made from hydrogels containing siloxane moieties in their structure present oxygen transmissibilities 5 to 10 times higher than those reported for previously used extended wear lenses made of conventional hydrogels. By conventional CLs we mean hydrogels made of polymers that do not contain siloxane moieties, so that oxygen permeation mainly occurs through the water content of the swollen hydrogel. On the other hand, oxygen permeation across Si-Hi takes place through siloxane-rich zones at substantially large rates of flow, compared with the conventional hydrogels.[12,33]

In the present study, the values of Dk/t and Dk of four Si-Hi materials was derived using two methods. The first one is the most simple and provides the value of Dk/t directly from measuring one sample of each material. Then by multiplication of this value by the average central thickness we obtain the Dk value. The second one is the stack method from which the Dk of the material corrected for the effect of boundary layers is directly obtained. Corresponding Dk/t is obtained by dividing the value by the average central thickness. In both methods, the edge effect is discarded by the guard ring available in the polarographic cell used.

The use of different measuring procedures to obtain Dk of CLs results in significantly different values. Even with the same measurement method, remarkable differences could be expected. Morgan *et al.*[36] found poor agreement between polarographic and coulometric technique as well as between polarographic and reference values for RPG CLs as well as for lotrafilcon A material. They explored different sources of error, without found a definitive explanation. Benjamin and The Dk Reference Study Group have recently assessed the oxygen permeability of the Permeability Reference Material Repository, consisting of 7 rigid gas permeable (RGP) materials with Dk values within the range of 10 to 161 barrer. They used the three different techniques currently available; the polarographic method corrected for boundary layer and edge effects according to the American National Standards Institute (ANSI) Z80.20 standard (9 instruments), coulometric method (4 instruments) and gas-to-gas method (2 instruments).[44] Although they found small average differences between repeated measurements, a detailed observation to data showed that similar values of oxygen permeability can be obtained using different methods as well as measurements taken with the same kind of equipment for the same reference material differ substantially.

Both methods used in this work render similar results in terms of correlation with nominal values when measuring Dk/t. However, the single sample method gave significantly higher values of Dk/t than the stack method. Conversely, when Dk values are required, the stack method showed a significantly better correlation with nominal values given by the manufacturer than the single sample method.

Despite these differences, the physiological values derived, partial pressure of oxygen at the CL-cornea interface (p_{tc}), BOAT, EOP and oxygen flux (j_c), did not change significantly for open and closed eye conditions for the materials evaluated in this work. This fact is better explained by the simulations given in *figures 9.7* to *9.10*. For all physiological parameters, their values would not be likely to change much with changes in Dk/t values. As a consequence, single measurements of Dk/t values could be acceptable when necessary to determine the physiological environment under a given Si-Hi CL within the range of 110 to 175 barrer. However, this could not be acceptable for lenses whose Dk/t values are below 70-100 units when p_{tc} and EOP are to be determined and below 50 units when oxygen flux and BOAT are to be computed. Also, when the actual Dk value of a material is to be determined, the stack method gives more reliable and accurate values.

Despite the values of Dk/t and Dk obtained in this study overestimate those given by the manufacturers, such overestimation agrees with values previously reported by other authors. Furthermore, some of the results obtained by us with the polarographic method are in agreement with those reported by other authors using the coulometric method that is supposed to be more appropriate to measure high Dk materials. Morgan *et al.*[36] and Alvord *et al.*[37] found similar Dk values for lotrafilcon A using the liquid-to-gas arrangement in the coulometric device being 150 ± 4 barrer and 155 ± 5 barrer, respectively. The extensive work carried out by Compañ *et al.* in the recent years with the first generation of Si-Hi materials using the stack method with a polarographic method also supports our measurements.[12,33] Compan *et al.*[33] obtained Dk values of 141 ± 5 barrer and 107 ± 4 barrer for lotrafilcon A and balafilcon A materials using the stack procedure with a polarographic sensor. Those values yield Dk/t_{app} of 183 ± 7 and 123 ± 5 barrer/cm, respectively. Our results demonstrated good agreement with their results, what could be expected as we used the same procedure.

In this study, we also simulated the relationships between Dk/t_{app} values and the physiological variables of partial pressure at the CL-cornea interface, BOAT, EOP or oxygen flux to the cornea. This data will assist clinicians to evaluate the conformity of the lenses they are fitting with the requirements of the cornea. For example, for open eye conditions, lenses with Dk/t values below 30 barrer/cm will only provide 60% of the partial pressure of oxygen provided by the "ideal CL" of infinite Dk/t. This supports the early estimations of

Holden and Mertz that at least 34 barrer/cm would be necessary to avoid corneal hypoxia under open eye conditions. For closed eye conditions, lenses with less than 80 barrer/cm will only provide about 60% of the partial pressure of oxygen provided by a ideal CL. The criteria of Holden and Mertz that required a Dk/t of at least 84 barrer/cm to limit the corneal edema to physiologic levels during overnight CL wear will only warrant about 65% of the ideal partial pressure at the contact-lens corneal interface. Thus, it makes sense to change the requirements to those stated by Harvitt and Bonnano.[9] According to their criteria, for closed eye conditions, a minimum of 125 barrer/cm will be necessary. This will warrant about 75% of the ideal partial pressure of oxygen at the cornea-CL interface.

At a first view, the BOAT relationship with Dk/t values could seem surprising for the reader, as BOAT values are higher for closed eye conditions than for open eye conditions. This is particularly evident for Dk/t values above 10 units. However, this is not surprising considering the definition of the BOAT as a representative parameter of the potential of diffusion of oxygen through the lens. According to the Fick's law, the potential of oxygen transport across a membrane will be higher as the transmissibility of the membrane increases and as the gradient of oxygen concentration increases. Thus, under closed eye conditions, the low partial pressure of oxygen at the CL-cornea interface increases the BOAT parameter. Another observation is that for Dk/t values below 20-25 barrer/cm, BOAT and Dk/t follow a 1:1 relationship for closed eye conditions. Above a certain level of transmissibility (20-30 barrer/cm for open eye and 50 barrer/cm for closed eye conditions), further increase in Dk/t will not have a significant positive reflection in the potential of diffusion of oxygen through the lens, as the partial pressure of oxygen at the cornea-CL will increase significantly thus decreasing the gradient of partial pressure (previously described as relative variation of the partial pressure of oxygen between the front (p) and the back sides (p_{tc}) of a lens onto the cornea). Any effect of stagnation of oxygen in the cornea-contact lens interface (oxygen not consumed by the cornea) will make the BOAT not to increase because the difference between p and p_{tc} will be reduced as p_{tc} will increase.

Both lotrafilcon A and senofilcon A CLs meet the more recent criteria for avoiding stromal edema during overnight wear. The high oxygen transmissibility of Si-Hi materials has provided substantial improvements in corneal physiology with almost no evidence of edema under overnight wear[45], and even allowing patients with active conditions in the ocular surface to wear them with therapeutic purposes.[20-23,46] Other situations that can potentially compromise ocular physiology as combined fitting of a RGP CL piggybacked over a soft CL have experienced remarkable improvements in terms of oxygen performance when highly permeable Si-Hi materials are used.[47-49]

In conclusion, with the present study we have observed that with the current highly transmissible CLs made of Si-Hi materials, we can expect significant differences in Dk values depending on the measuring approach used and even with respect to the nominal values given by the manufacturers. However, these differences are not likely to remain significant when translated into physiological variables of partial pressure at the CL-cornea interface, BOAT, EOP or oxygen flux to the cornea. The same would not apply to other CLs whose Dk/t remains below 50 to 100 barrer/cm.

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Chapter 10

Qualitative and Quantitative Characterization of the *In vitro* Dehydration Process of Hydrogel Contact Lenses†

10.1. Abstract

Purpose: To investigate the *in vitro* dehydration process of conventional hydrogel and silicone hydrogel (Si-Hi) contact lens (CL) materials.
Methods: Eight conventional hydrogel and five Si-Hi contact lenses (CLs) were dehydrated under controlled environmental conditions on an analytical balance. Data were taken at 1-min intervals and dehydration curves of cumulative dehydration (CD), valid dehydration (VD), and dehydration rate (DR) were obtained. Several quantitative descriptors of the dehydration process were obtained for further processing of the information.
Results: Duration of phase I ($r^2 = 0.921$), CD at end of phase I ($r^2 = 0.971$), time to achieve a DR of -1%/min ($r^2 = 0.946$) were strongly correlated with equilibrium water content (EWC) of the materials. For each individual sample, the VD at different time intervals can be accurately determined using a 2nd order regression equation ($r^2 > 0.99$ for all samples). The first 5 min of the dehydration process show a relatively uniform average CD of about -1.5%/min. After that, there was a trend towards higher average CD for the following 15 min as the EWC of the material increases ($r^2 = 0.701$). As a consequence, average VD for the first 5 min displayed a negative correlation with EWC ($r^2 = 0.835$), and a trend towards uniformization among CL materials for the following periods ($r^2 = 0.014$). Overall, Si-Hi materials display a lower dehydration, but this seems to be primarily due to their lower EWC.
Conclusions: DR curves under the conditions of the present study can be described as a three-phase process. Phase I consists of a relatively uniform DR with a duration that ranges from 10 to almost 60 min and is strongly correlated with the EWC of the polymer as it is the CD during this phase. Overall, HEMA-based hydrogels dehydrate to a greater extent and faster than Si-Hi materials. There are differences in water retention between lenses of similar water content and thickness that should be further investigated.

10.2. Introduction

First introduced by Wichterle and Lim[1] hydrogel materials have experienced a great expansion in healthcare industry, particularly for CL manufacture. However, despite the numerous improvements in their composition and manufacturing technology, the ocular performance of hydrogel CLs continues to be compromised by dehydration.

† Gonzalez-Meijome JM, Lopez-Alemany A, Almeida JB, Parafita MA, Refojo MF. Qualitative and quantitative characterization of the *In vitro* dehydration process of hydrogel contact lenses. *J Biomed Mater Res B Appl Biomater.* 2007 (*in press*)

Dehydration begins immediately after a CL is placement on the eye and continues further during the day depending more or less on the material properties, lens thickness, environmental conditions and tear composition, and blink function.[2,3] End of the day complaints of dryness and other related symptoms, are at least in part attributed to dehydration of the lens on the eye.

In hydrogels, water uptake and release depend primarily on the chemical composition and cross-linking density of the polymer, thus determining the equilibrium water content (EWC) of the hydrogel. The thickness of the material also affects the degree of dehydration of CLs. But dehydration also affects other important properties of hydrogel CLs, such as oxygen permeability. In HEMA-based hydrogels oxygen permeability decreases as the lens dehydrates,[4] while in Si-Hi lenses oxygen permeability increases as the polymer partially dehydrates.[5] Changes in lens parameters with dehydration have also been documented, as well as changes in lens movement on the eye.[6,7] Dehydration of hydrogel CLs has an impact on the ocular surface, since it is associated with surface deposit build-up, dryness symptoms, and dehydration of the corneal epithelium. Lens dehydration also has the potential to affect ionic and hydraulic permeability, thus reducing lens movement, promoting lens binding, and increasing the chance for microbial colonization due to limiting tear turnover and debris removal from the cornea-CL interface. Andrasko confirmed some of these effects as he observed that after lens insertion a new hydration equilibrium was reached, and the lenses became less flexible, less permeable to oxygen, and its base curve radius became steeper.[8]

Different approaches have been used to maximize water uptake and to minimize water release in hydrogel CL. Initially, the most common method was the introduction of other hydrophilic monomers into the base polymer, particularly into HEMA base hydrogels, such as, methacrylic acid, vinyl-pyrrolidone, and glyceryl methacrylate.[9] However, was subsequently found that the higher the water uptake, the faster the water release while the lens is on the eye.[10] Biological deposit formation was also found to be a major factor in highly hydrated hydrogels CLs whether they are ionic or nonionic.[11,12] For this reason, modern materials include specific formulations claiming to prevent rapid dehydration from high water content materials, apparently with some clinical benefits.[13-16]

Despite this diversity of options, clinicians do not have objective indicators of the ability of different CLs to remain fully hydrated while they are on the eye and this limits their criteria to choose the right material for each patient. This is more important in patients complaining of ocular CL discomfort related to dryness,[17,18] such as patients working in environments that could potentially exacerbate ocular symptoms,[19] older females, because of their higher risk to experience dryness with CLs,[20] and those with tear deficiency upon pre-fitting examination.[21]

Dehydration of CLs is usually measured by manual or automatic commercial refractometers.[22,23] However, the gravimetric method used in this study has been credited to be more precise for *in vitro* studies on the water content of hydrogel CLs.[24]

It has been reported that *in vitro* studies failed to explain the clinical observations that high water content lenses dehydrate more than low water content materials.[25] However, more recently, Jones *et al.*[26] qualitatively characterized the dehydration process of hydrogel CLs under *in vitro* conditions. Unfortunately, their work included fewer conventional hydrogel CLs, than the present study, and only the two silicone-hydrogel lenses available at the time the study was carried out. Also, they limited experiments to specific portions of the lenses, and the dehydration process was carried out under varying airflow conditions.

The present study was developed to investigate the dehydration process of eight HEMA-based hydrogel CLs, within more frequent EWC available, and the five Si-Hi lenses also currently marketed. Different qualitative and quantitative indicators were developed to characterize the dehydration process of the samples and to compare against each other and to their respective EWC. The main goal was to obtain those parameters that more specifically characterize the *in vitro* dehydration process of conventional and Si-Hi CL materials.

10.3. Material and Methods

10.3.1. Contact lens materials

Thirteen different commercial hydrogel CLs were used. Those materials were chosen to include the five Si-Hi materials currently available and eight conventional HEMA-based hydrogel lenses; among these, including four hydrogel lenses claimed to maximize water uptake and minimize water release (omafilcon A, hioxifilcon A, B and pGMA+HEMA+MA copolymer). Their technical details are summarized in *table 10.1*. Three samples of each material from the same batch were measured.

10.3.2. Sample preparation and gravimetric measurements

A digital analytical balance (AT 210, Metler Toledo, Giessen, Germany) with a six-figure scale capable of measuring within 0.001 mg was used to continuously measure the weight of the CLs while they dehydrate at a controlled temperature of (22.4 ± 0.46)ºC and a relative humidity (RH) of (49.1 ± 1.45)%. The accuracy of the instrument monitoring temperature and RH was ±1ºC and ± 5%, respectively. The weight of the lens was registered each 60 s with a microgram resolution ($\pm 1\cdot10^{-6}$ grs.).

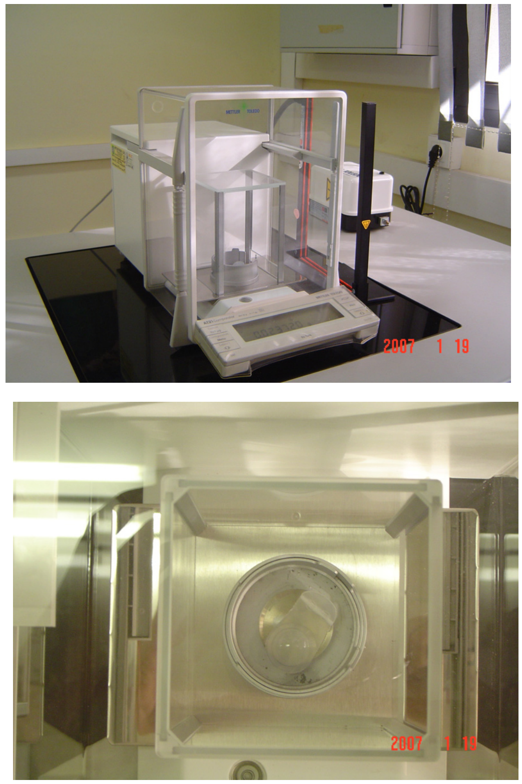
Table 10.1. Nominal parameters of CLs used in this study. All lenses are produced with cast-molding technology except lenses made in Hioxifilcon A, B and p(GMA)+HEMA+MA copolymer, produced by lathe-cut. Some of the principal hydrophilic monomers included in each material are also quoted along with the main monomeric chain

Brand	USAN Generic name	Material (main monomers)	EWC (%)	Ionic (FDA)	Dk (barrer)	Surf. Treat.	CT (mm)
Air Optix Night & Day	Lotrafilcon A	TRIS+DMA+siloxane monomer	24	No	140	Plasma coating	0.080
Air Optix	Lotrafilcon B	TRIS+DMA+siloxane monomer	33	No	110	Plasma coating	0.080
Purevision	Balafilcon A	TRIS+NVP+TPVC +NCVE+PBVC	36	Yes	99	Plasma oxidation	0.090
Acuvue Oasys	Senofilcon A	HEMA+PDMS+ DMA+PVP	38	No	103	No	0.070
Soflens 38	Polymacon	HEMA	38.6	No	8.5	No	0.065
Acuvue Advance	Galyfilcon A	HEMA+PDMS +DMA+PVP	47	No	60	No	0.070
Equis 60	Hioxifilcon A	HEMA+GMA	59	No	24	No	0.130
Acuvue 2	Etafilcon A	HEMA+MA	58	Yes	28	No	0.084
SPH4UV	Hioxifilcon B	HEMA+GMA	49	No	15	No	
Proclear	Omafilcon A	HEMA+PC	62	No	32	No	0.065
Osmo 2	-	p(GMA)+ HEMA+MA	72	Yes	45	No	0.140
Actifresh 400	Lidofilcon A	MMA+VP	73	No	36	No	0.110
Precision UV	Vasurfilcon A	MMA + VP	74	No	39	No	0.140

USAN: United States Adopted Names Council; EWC: equilibrium water content; Dk: oxygen permeability; ST: surface treatment; CT: central thickness. Dk units are 10^{-11} (cm^2/sec)[ml O_2/(ml x mm Hg)]).
DMA: *N,N*-dimethyl acrylamide; GMA: glycerol methacrylate; HEMA: 2-hydroxyethyl methacrylate; MA: methacrylic acid; MMA: methyl methacrylate; NCVE: *N*-carboxyvinyl ester; PC: phosphorylcholine; TRIS: 3-methacryloxy-2-hydroxypropyloxy propylbis(trimethylsiloxy) methylsilane; TPVC (tris-(trimethylsiloxysilyl) propylvinyl carbamate); PBVC: poly[dimethysiloxy] di [silylbutanol] bis[vinyl carbamate]); VP: *N*-vinyl pyrrolidone.

Lenses were allowed to equilibrate for at least 24 h before testing in preservative-free saline solution meeting the criteria of BS EN ISO 10344:1998.[27] A number under each vial identified each lens and the investigator performing the measurements was not aware or the lens being measured.

After taking the lens from the vial, the excess water was removed by blotting with a slightly dampen Whatman nº1 filter paper. The lens was then placed on a convex plastic holder with the approximate curvature of the CLs in order to simulate the lens on the ocular surface with only the anterior surface directly exposed to air. The total time the samples were exposed to air prior to measurements were initiated was less than 5 seconds in order to minimize dehydration before first reading could be obtained. After the lens and holder were placed on the balance, there was an additional 2-3 s until the digital scale of the balance stabilized. For repeated measures of the same lens, a minimum time interval of 72 h was left for the lenses to fully re-hydrate.


(A)

(B)

Figure 10.1. Lateral (A) and top view (B) of the analytical balance with CL in the holder during the dehydration process.

10.3.3. Quantitative descriptors and dehydration curves

Different quantitative parameters were derived from the curves of percentage cumulative loss of weight (CD) according to Equation 10.1 (*figure 10.2*), dehydration rate (DR) computed from Equation 10.2 (*figure 10.3*), and valid percentage dehydration (VD) computed from Equation 10.3 (*figure 10.4*). These parameters are described in detail in the following sections. To get a more reliable idea of the short-term dehydration process, the first 20 min of the dehydration process for the three dehydration curves (averaged at intervals of 5 min) will be analyzed in the last part of the results section. *Figure 10.5* shows examples of repeated readings for three different CL materials.

10.3.3.1. Cumulative dehydration as [%]

This parameter represents the accumulated loss of weight experienced by each lens at 1-min intervals during the dehydration process. It is computed using Equation 10.1, where

$W_{T(n)}$ is the sample weight at time *n* with intervals of 1 min, and $W_{T(0)}$ the initial sample weight. Negative values are obtained for this parameter. An example of this curve is shown in *figure 10.2.*

$$CD = \left[\frac{\left(W_{T(n)} - W_{T(0)}\right)}{W_{T(0)}} \right] \cdot 100 \qquad \text{(Equation 10.1)}$$

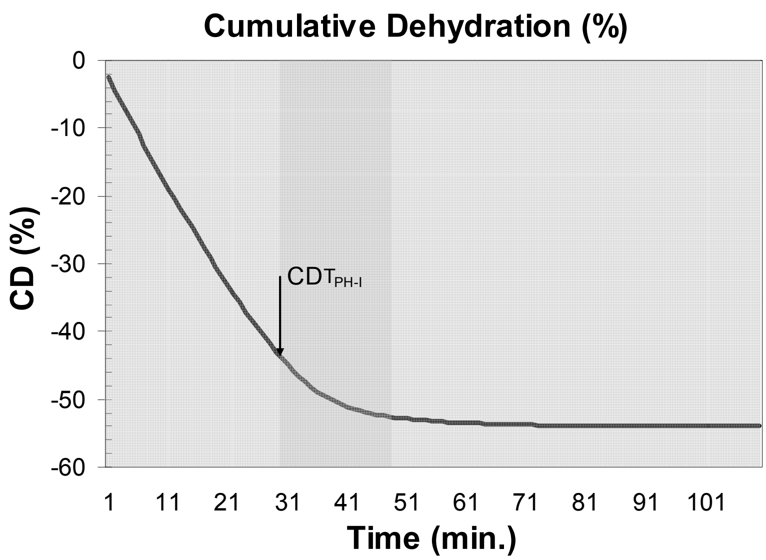


Figure 10.2. Curve displaying cumulative dehydration (CD). Units of CD are percentages. The parameter T_{PH-I} is deduced from the profile of the DR curve showed in figure 10.3.

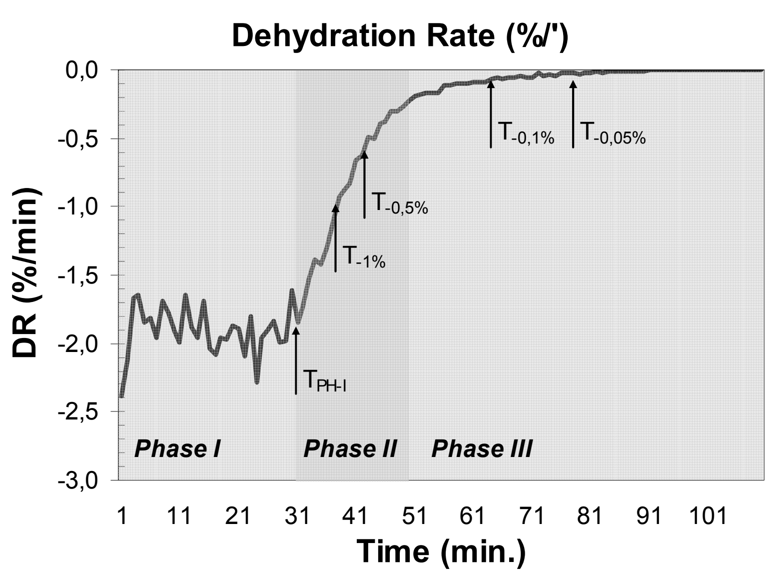


Figure 10.3. Curve displaying dehydration rate (DR) until stabilization. Units of DR are percentage per minute.

10.3.3.2. Dehydration rate as [% per minute]

This parameter represents the DR per minute for each lens at a certain time during the dehydration process. It is computed using Equation 10.2, where $W_{T(n)}$ is the sample weight at time *n* with intervals of 1 min, and $W_{T(n-1)}$ the sample weight at time n-1 with intervals of 1 min. An example of this curve is shown in *figure 10.3*. Times to achieve DR of -1, -0.5, -0.1 and -0.05% per minute are identified for each DR curve along with other quantitative descriptors.

$$DR = \left[\frac{\left(W_{T(n)} - W_{T(n-1)} \right)}{W_{T(n)}} \right] \cdot 100 \qquad \text{(Equation 10.2)}$$

In *figure 10.3*, three phases are identified for the majority of the lenses. Phase I is the part of the dehydration curve (in DR units) characterized by a high and relatively stable average DR. Phase II is the part of the dehydration curve (in DR units) characterized by a rapid and progressive decrease in the DR. End of phase II was arbitrary established when DR reaches -0.25% per minute. Phase III is the part of the DR curve characterized by DR approaching to zero. $T_{PH\text{-}I}$ and $T_{PH\text{-}II}$ are duration of phase I and phase II, respectively. During phase II and phase III four additional parameters have been defined: $T_{-1\%/min}$, $T_{-0.5\%/min}$, $T_{-0.1\%/min}$, and $T_{-0.05\%/min}$ are the time to reach a DR of -1%/min, -0.5%/min, -0.1%/min, and -0.05%/min, respectively.

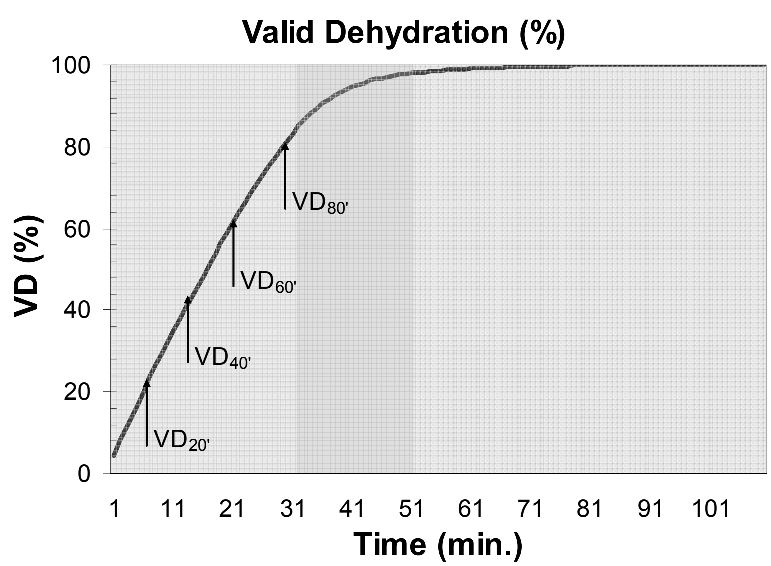


Figure 10.4. Curve displaying valid dehydration (VD). Units of VD are percentages.

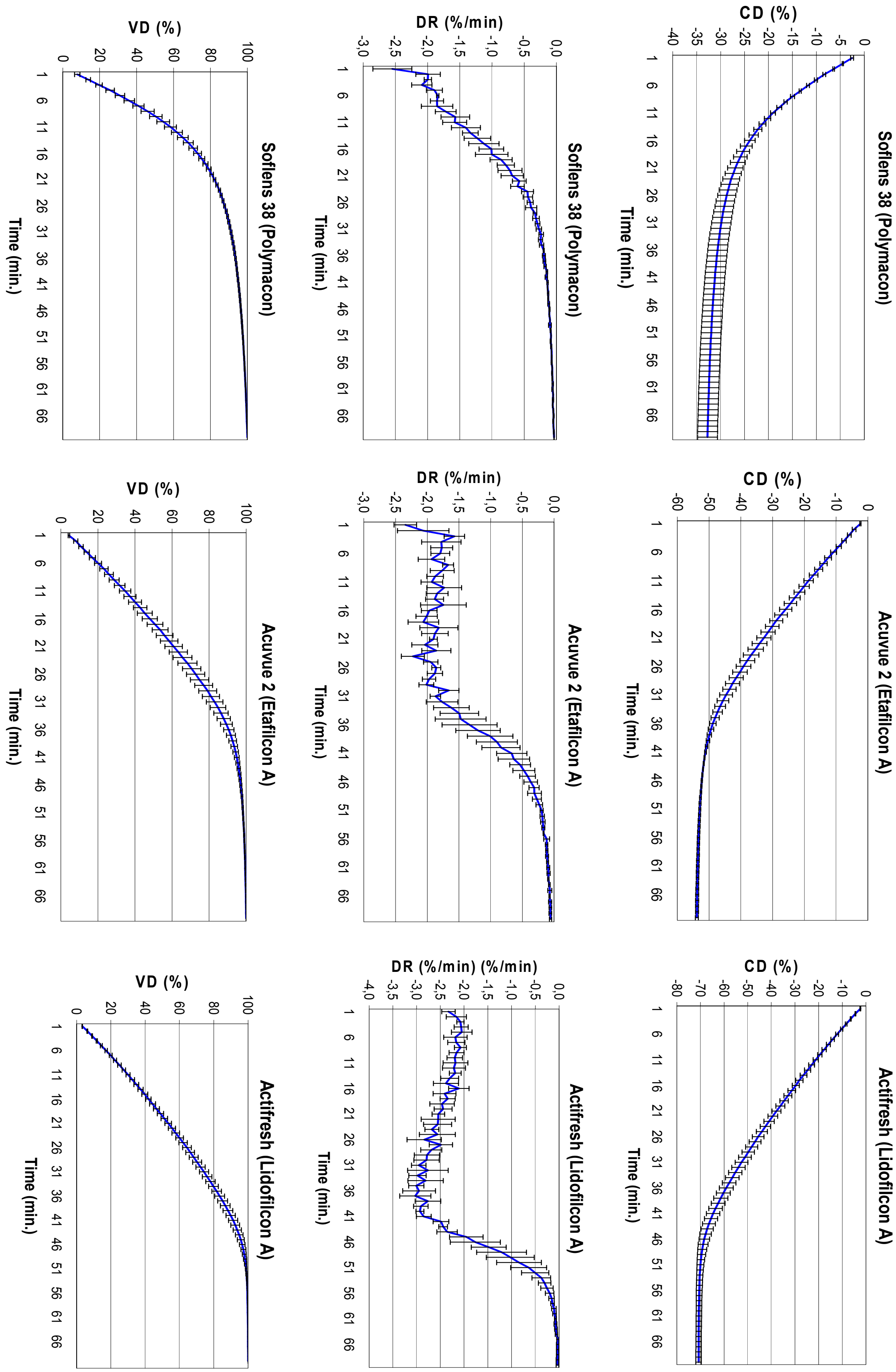


Figure 10.5. Repeatability of the dehydration process and the corresponding dehydration curves derived for three lenses of different EWC. Error bars are standard deviation of three repeated measurements of three samples.

10.3.3.3. Valid dehydration as [%]

This parameter represents the loss of weight of each lens at a certain time during the dehydration process compared to its total loss of weight. It is computed using Equation 10.3, where $W_{T(0)}$ is the initial sample weight, $W_{T(n)}$ is the sample weight at time *n* with intervals of 1 min, and $W_{T(f)}$ the final lens weight. Positive values are obtained because this value is calculated with respect to the final weight of the sample. An example of this curve is shown in *figure 10.4*. Time to achieve VD of 20 (VD_{20}), 40(VD_{40}), 60 (VD_{60}), and 80% (VD_{80}) was determined for each lens.

$$VD = \left(\frac{W_{T(0)} - W_{T(n)}}{W_{T(0)} - W_{T(f)}} \right) \cdot 100 \qquad \text{(Equation 10.3)}$$

10.3.3.4. Water retention index

This parameter represents the difficulty of water to leave the CL. As a preliminary approach we have derived two values of WRI. The first one (WRI_1) was obtained from the slope of the straight line that defines the VD at 20, 40, 60 and 80 (dVD/dT) for each lens (Equation 10.4). The second one (WRI_2) was derived from the inverse function of the mean CD during the first 5 min ($Mean_{CD}$) of the dehydration process (Equation 10.5). This parameter will be taken as an indicator of the dehydration resistance.

$$WRI_1 = \left(\frac{dVD}{dT} \right) \cdot 100 \qquad \text{(Equation 10.4)}$$

$$WRI2 = \left(\frac{1}{MeanCD} \right) \cdot 100 \qquad \text{(Equation 10.5)}$$

10.3.4. Statistical analysis

Values of CD, DR, and RD were compared for different CLs according to their EWC (low EWC, 24–38%; medium EWC, 39–60%; and high EWC, 61–74%), and type of material (conventional hydrogel, hydrogels that supposedly minimize water release, and Si-Hi) using one-way ANOVA test. Before statistical tests could be applied, normal distribution of variables was assessed by Kolmogorov-Smirnov test.

Regression analysis was used to plot the quantitative values obtained in this work against EWC in order to detect statistical relationships that describe dehydration process as a function of the material EWC. Statistical significance of those correlations was assessed by

Pearson correlation. Most graphical representations were made against the EWC of the CLs. This has a double advantage providing a quantitative reference value for statistical comparisons and at the same time identify each lens on graphical plots (except for two different lenses that have the same EWC = 38%).

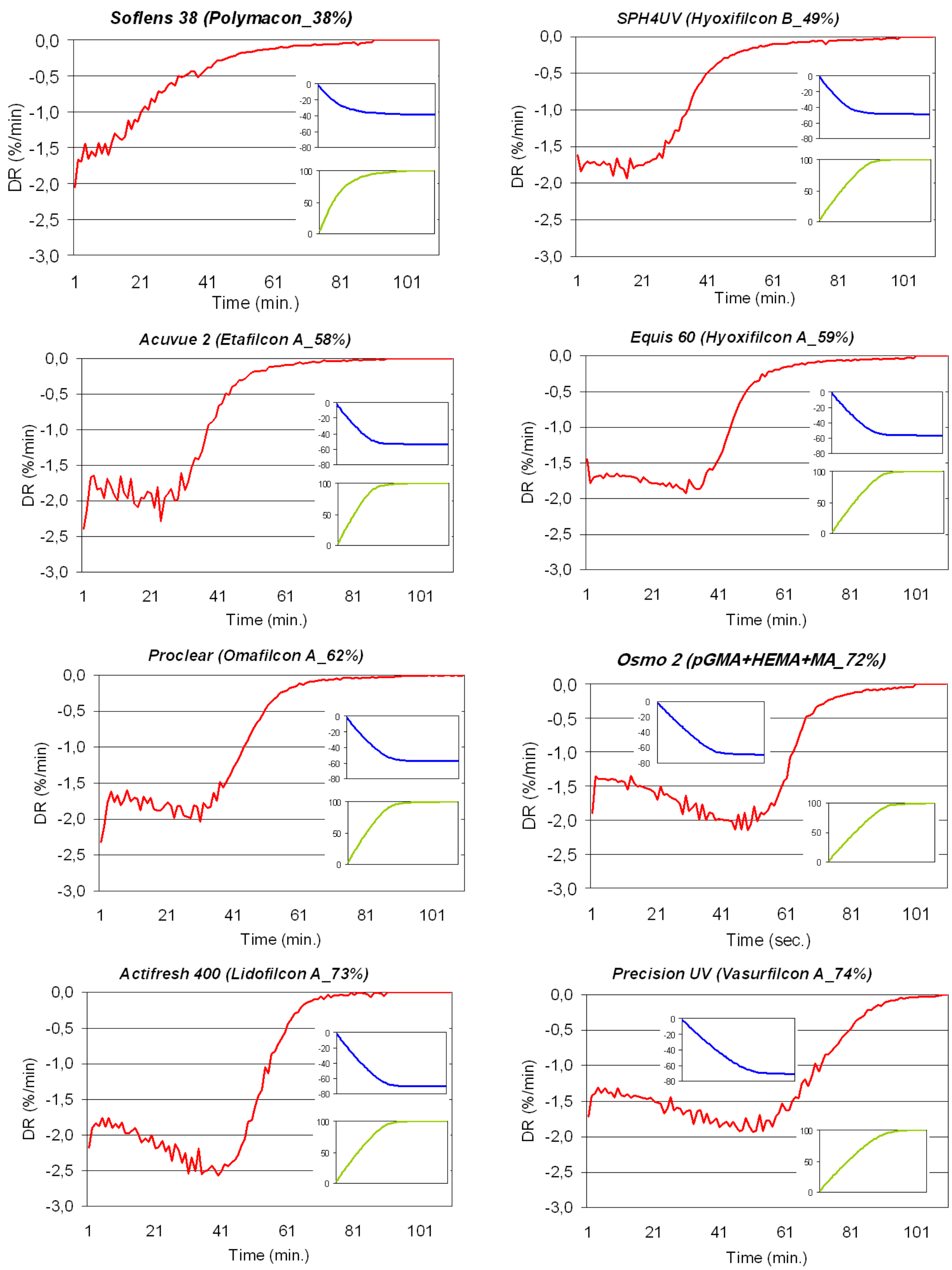


Figure 10.6. Curves of DR for conventional hydrogel materials. Insets represent CD (0 to -80% scale) and VD (0 - 100% scale).

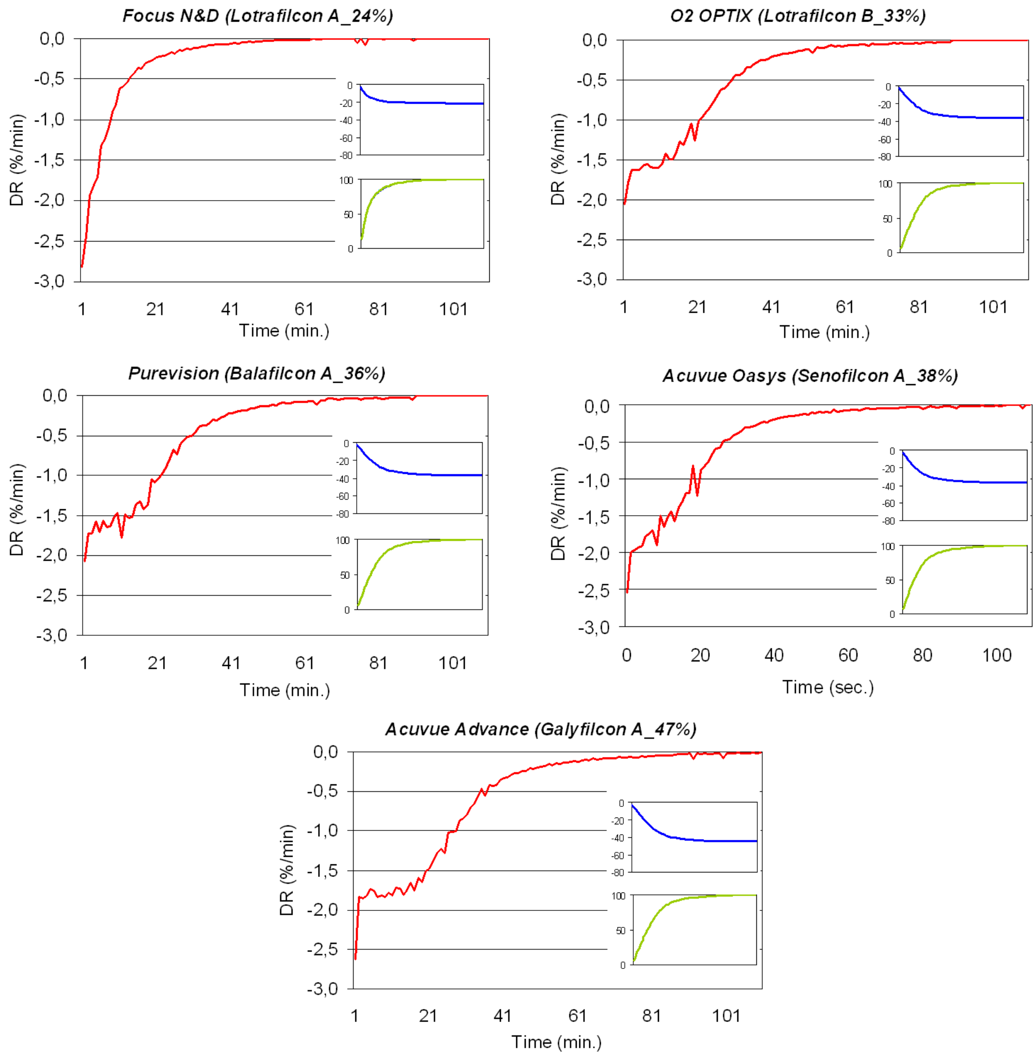


Figure 10.7. Curves of DR for Si-Hi materials. Insets represent CD (0 to -80% scale) and VD (0 - 100% scale).

10.4. Results

Curves of DR are characteristic of each CL, apparently depending on their EWC and polymeric composition. In those curves a three-phase pattern is observed. Phase I is characterized by a relatively uniform DR, and has a limited duration. An exception to this behavior is lotrafilcon A lens, with no defined phase I. Phase II is characterized by a rapid and almost linear decrease in the DR. Phase III represents the final period of time in which the lens approaches a zero DR. There is not a distinct change between phase II and III, so this point was set arbitrarily as the point where DR achieves a value of -0.25 %.

Figures 10.6 and *10.7* present the DR curves for conventional hydrogels and Si-Hi materials, respectively. From the DR curves, we determine the duration of phase I as the point where DR begins to decrease. High EWC materials presented a significantly longer phase I (44.5 ± 10.97 min) compared to medium EWC (22.75 ± 7.32 min) and low EWC (12.0 ± 3.91 min). These differences were statistically significant between low and high EWC materials (ANOVA; $p = 0.001$).

Duration of phase I is plotted in *figure 10.8A* against the EWC of the lenses displaying a strong relationship ($r^2 = 0.921$). A second order polynomial function fits to this relationship ($T_{PH\text{-}I}$ vs. EWC) showing a rapid increase in duration of this phase as EWC of the lenses increase. The minimum value of the function seems to be around an EWC of about 20%. CD and VD at the end of phase I are strongly correlated with EWC as seen in *figures 10.8(B,C)*. Mean DR during phase I is plotted against EWC in *figure 10.8D*; in this case despite a trend towards higher DR during phase I for lenses with higher EWC, the correlation was not significant (Pearson coefficient = -0.536; $p < 0.072$). These parameters and their relationship with EWC over the first 20 minutes of the dehydration process will be further analyzed later in this section.

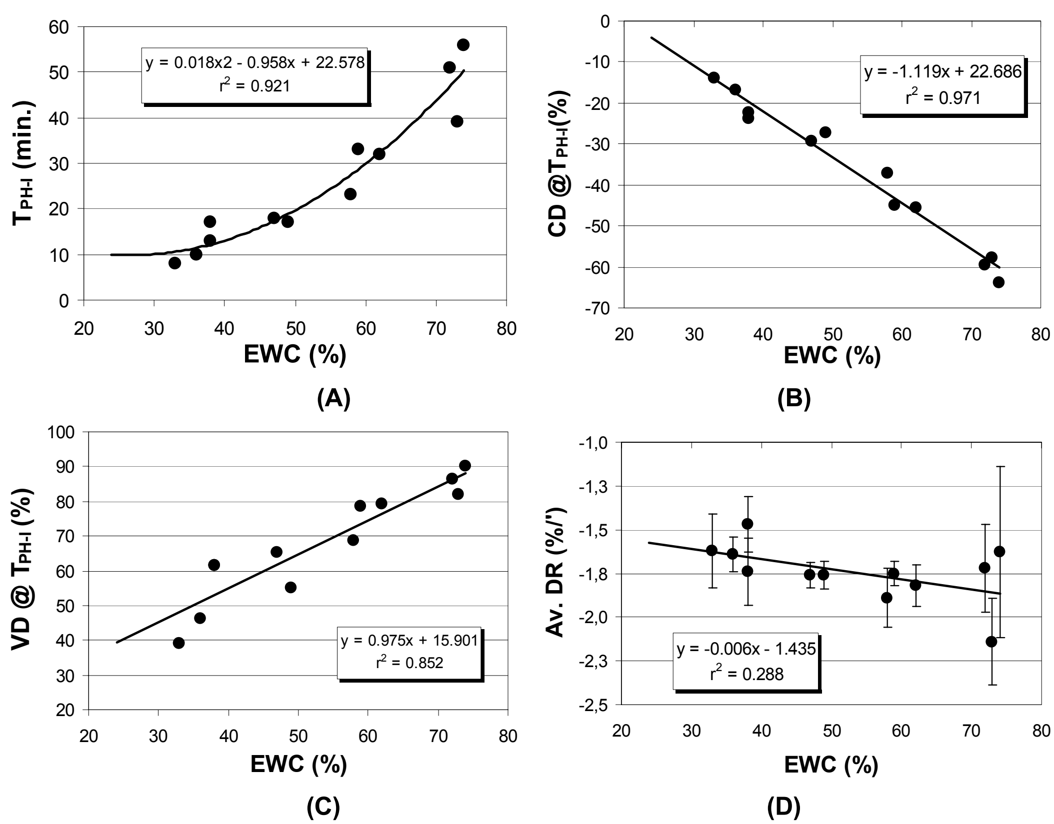


Figure 10.8. Relationship of EWC of CL materials with duration of phase I (A), CD (B), VD at the end of phase I (C) and mean DR during phase I (D). Bars represent standard deviation.

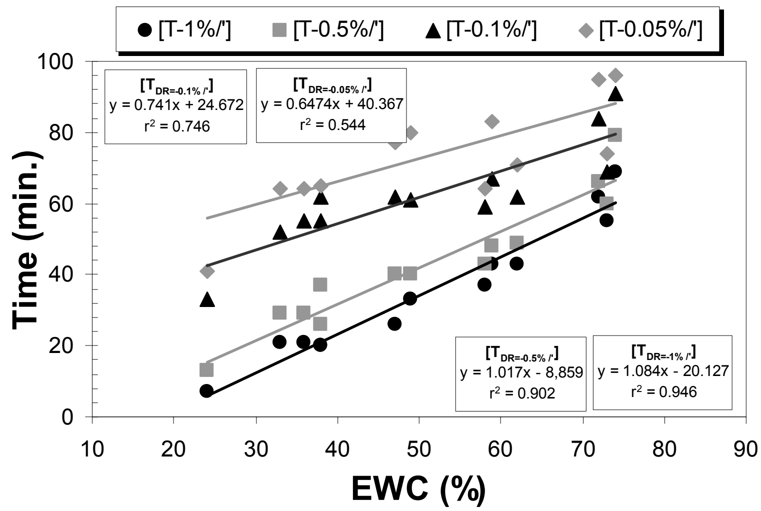


Figure 10.9. Time to achieve a DR of -1, -0.5, -0.1 and -0.05 %/min against EWC.

Times to achieve a DR of -1, -0.5, -0.1 and -0.05 % per minute during phases II and III, were plotted against EWC and fitted to linear models as independent variable in *figure 10.9*. According to this figure, the time to reach each DR landmark follows a more predictable linear relationship for the first two parameters ($T_{-1\%/min}$ and $T_{-0.5\%/min}$) than the other two ($T_{-0.1\%/min}$ and $T_{-0.05\%/min}$).

We also evaluated the time required to achieve a VD of 20, 40, 60 and 80 for each material tested. Time values follow almost ideal correlations ($r^2 \geq 0.99$) when fitted to a 2nd order regression equation for all the materials under investigation. *Figure 10.10* shows that differences are evident among different materials. It is also evident that differences become larger for higher values of dehydration. Two lines are hidden by others as SPH4UV exactly matches values of Acuvue 2 while Air Optix exactly matches values of Purevision. Coefficients of determination are 0.999 or 1.0 for all materials except lotrafilcon A (r^2 = 0.995). Values of time to reach VD of 20, 40, 60 and 80% were highly correlated with EWC ($r^2 = 0.921$; $r^2 = 0.944$; $r^2 = 0.940$; $r^2 = 0.914$) and with high statistical significance ($p < 0.001$ in all cases). As expected, the most significant difference was observed between the least hydrated Si-Hi lens (lotrafilcon A, 24% EWC), and the most highly hydrated hydrogel lens (vasurfilcon, 74% EWC). While the least hydrated Si-Hi (lotrafilcon A) reached each VD landmark the fastest, vasurfilcon (74% EWC), and GMA/HEMA/MA (72% EWC) showed a significantly slower progression towards the higher VD values than the remaining materials, including one with similar EWC, lidofilcon A (73% EWC).

These differences are further explored by grouping the lenses by their EWC and polymeric composition as shown in *figures 10.11* and *10.12*, respectively. On average, the parameters described in the previous paragraph have lower average values for the Si-Hi materials than for HEMA-based hydrogels. *Figure 10.11* shows this trend, with Si-Hi materials displaying shorter time periods to achieve each valid dehydration (VD) value and lower DRs, respectively. Conversely, the mean behavior of all the conventional hydrogels, including those claimed to retard dehydration, is almost indistinguishable regarding these parameters.

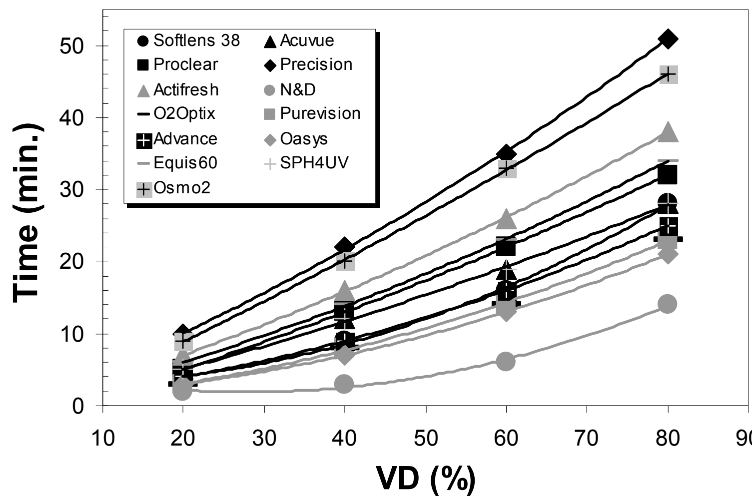


Figure 10.10. Time to achieve VD of 20, 40, 60 and 80% for different CL materials.

In *figure 10.12* the mean values for the same parameters are now represented for lenses grouped by their EWC in low EWC (24–38%), medium EWC (39–60%), and high EWC (61–74%). As expected from the previous analyses, all differences were statistically significant (ANOVA, $p<0.05$) except for time to achieve DR of -0.1%/min ($p = 0.072$) and -0.05%/min ($p = 0.074$).

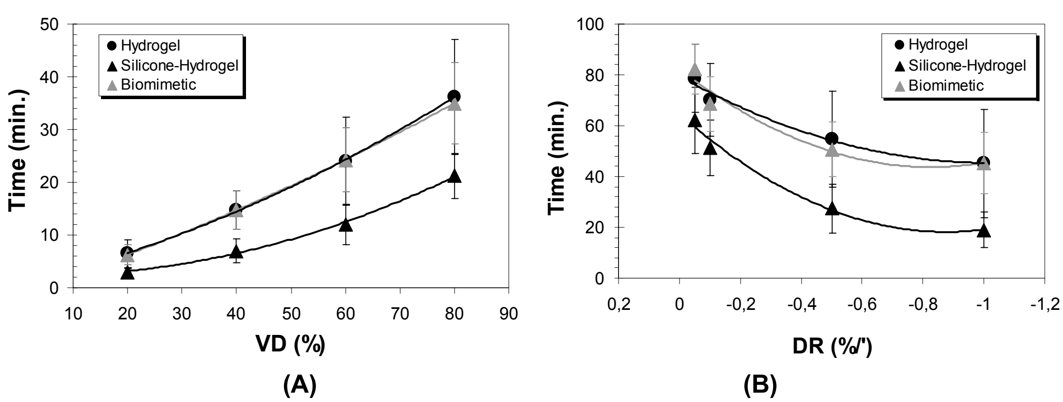


Figure 10.11. Mean and standard deviation values of time at VD of 20, 40, 60, and 80% (A) and time for DR of -1, -0.5, -0.1 and -0.05%/min (B) for Si-Hi lenses, lenses claimed to reduce on-eye dehydration (biomimetic), and conventional hydrogels. Bars represent standard deviation.

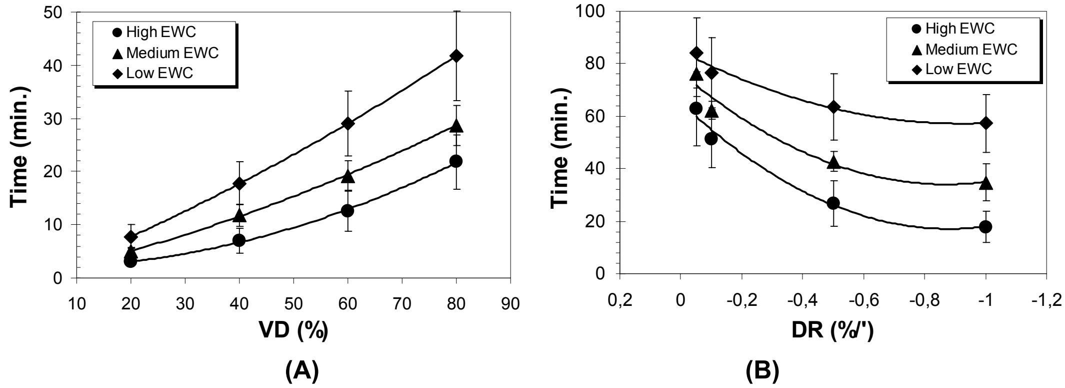


Figure 10.12. Mean and standard deviation values of time at VD of 20, 40, 60, and 80% (A) and time for DR of -1, -0.5, -0.1 and -0.05%/min (B) for lenses within the three groups according to their EWC. Bars represent standard deviation.

To get more precise knowledge of the short-term dehydration process for each particular lens, we divided the first 20 min of the dehydration process into 5 min periods, and CD, VD and DR were averaged within those periods. Mean values and standard deviation are presented in *figures 10.13 (A-C)*, and plotted against the EWC in *figures 10.14, 10.15 and 10.16*, respectively. Average CD and VD decreased for all lenses between the first period (1–5 min) and the fourth period (16–20 min). This decrease was the most obvious for Si-Hi materials, and less marked for high EWC PUV and OSM lenses *(figures 10.13A,B)*. The mean DR is fairly uniform for HEMA-based hydrogels. However, decrease is seen for some Si-Hi materials *(figure 10.13C)*.

For average CD (see *figure 10.14*), significant correlations with EWC were found only for the 3rd (11–15 min, Spearman coefficient = 0.682, p=0.010) and 4th period (16–20 min, Pearson coefficient = 0.837, p < 0.001). Conversely, for VD, significant correlations with EWC were found during the 1st (1–5 min, Pearson coefficient. = 0.914, p < 0.001) and 2nd period (6–10 min, Pearson coefficient = 0.901, p < 0.001) as shown in *figure 10.15*. *Figure 10.16* shows that DR is quite similar during the first 5 min, and thereafter shows a trend for higher dehydration at higher EWC.

Figures 10.17 (A,B) show two different approaches to the determination of the water retention index (WRI) or index of dehydration resistance. The first one is clearly correlated with CL EWC (r = 0.897; p < 0.001) while the second one is not (r = 0.128; p = 0.676). Values of both WRI indices were also evaluated for potential correlations with central lens thickness. Again, WRI computed using the first model showed a correlation with lens thickness (r = 0.653; p < 0.015) while the second one is not significantly correlated with lens thickness (r = 0.419; p = 0.154).

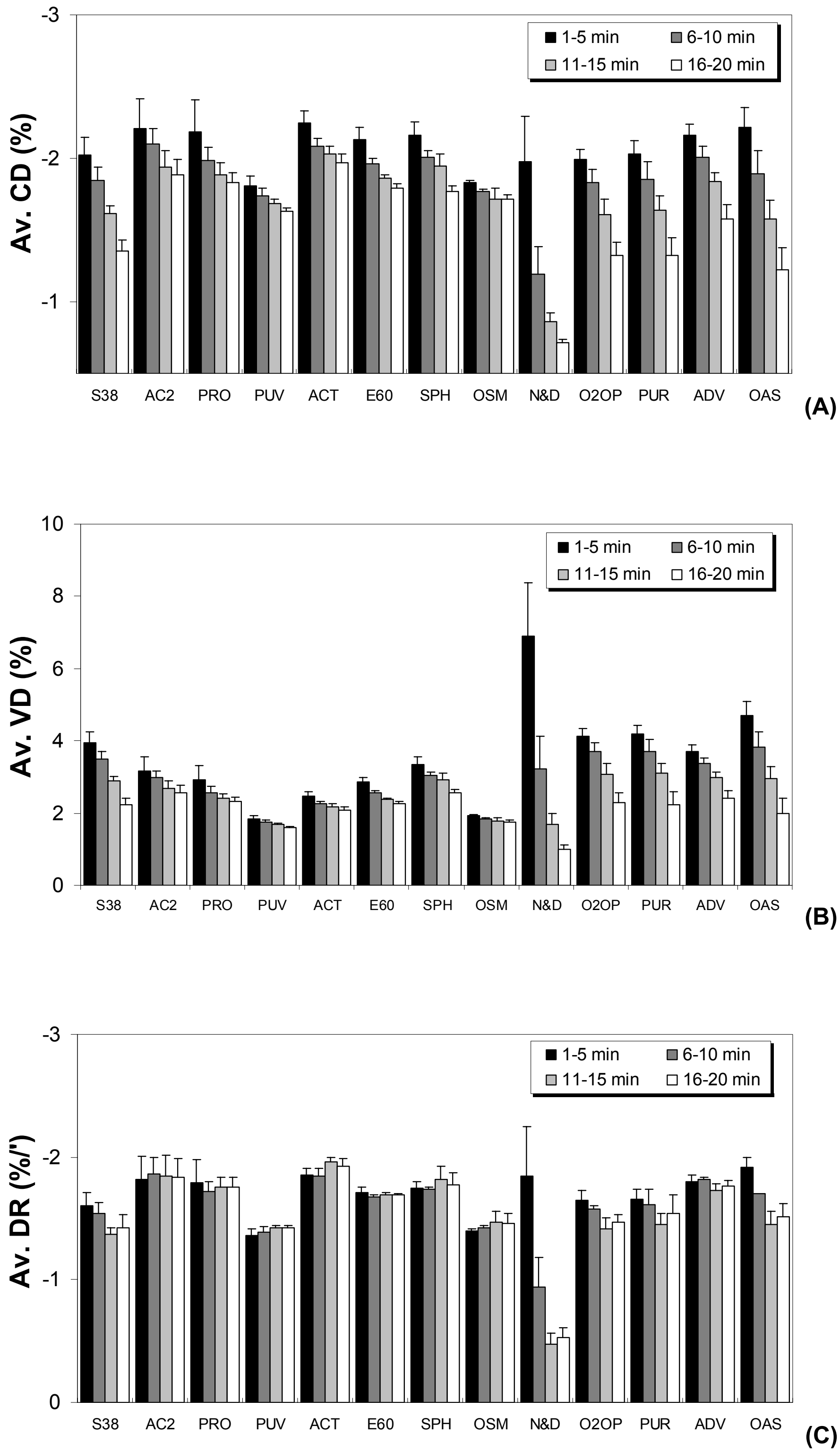


Figure 10.13. Average and standard deviation of CD (A), VD (B), and DR (C) at intervals of 5 min for the first 20 minutes. Bars represent standard deviation.
HEMA-based lenses: S38 (Soflens 38-38%); AC2 (Acuvue 2-58%); PRO (Proclear -62%); PUV (Precision UV -74%); ACT (Actifresh 400 - 73%); E60 (Equis 60 - 59%); SPH (SPH4UV -49%); OSM (Osmo 2-72%). Silicone-hydrogel: N&D (Air Night & Day - 24%); O2OP (Air Optix -33%); PUR (Purevision-36%); ADV (Acuvue Advance-47%); OAS (Acuvue Oasys-38%)

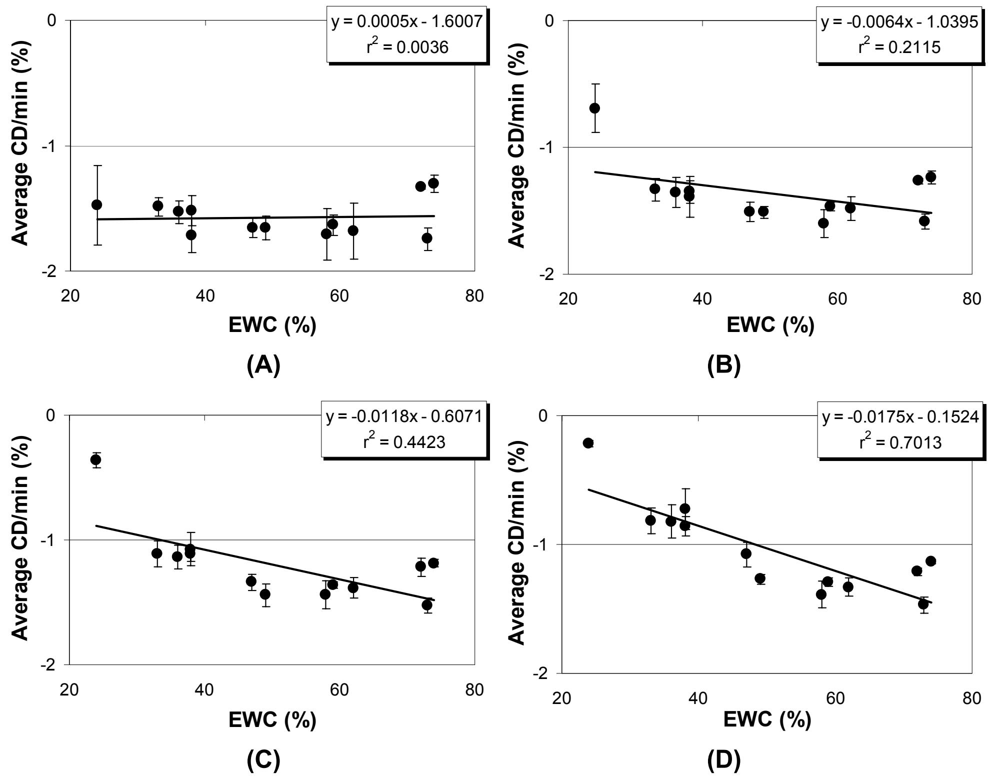


Figure 10.14. Relationships between EWC of the CLs and mean CD at intervals of 5 min for the first 20 minutes of the dehydration process during 1–5 min (A), 6–10 min (B), 11–15 min (C), and 16–20 min (D). Bars represent standard deviation.

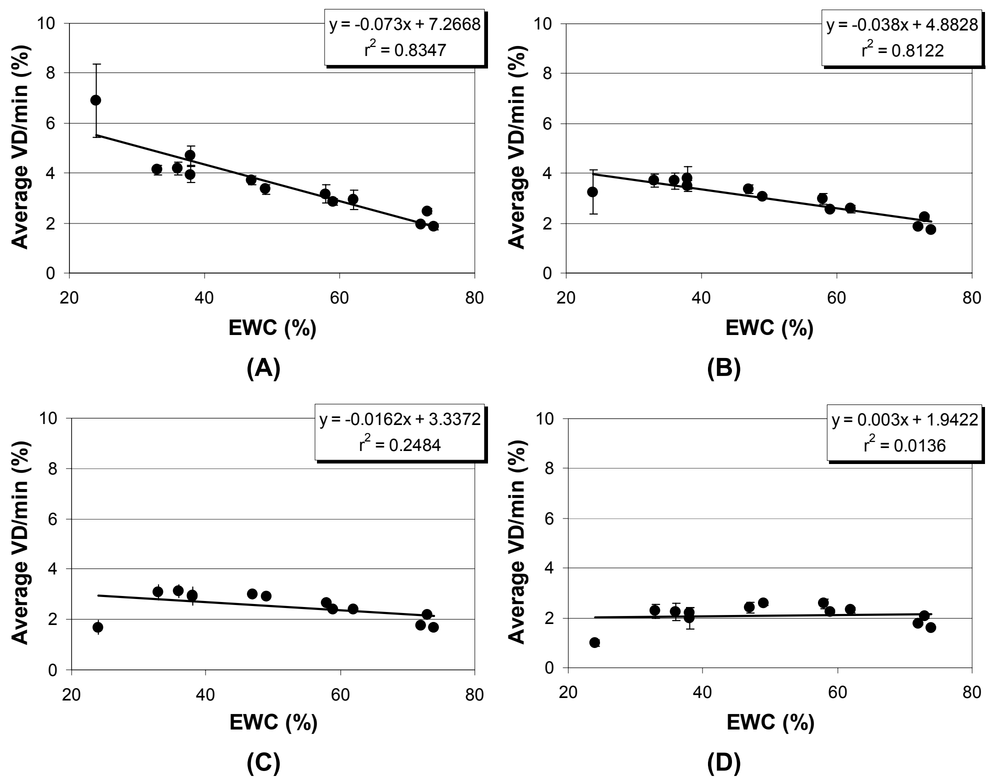


Figure 10.15. Relationships between EWC of the CLs and mean VD at intervals of 5 min for the first 20 min of the dehydration process during 1–5 min (A), 6–10 min (B), 11–15 min (C), and 16–20 min (D). Bars represent standard deviation.

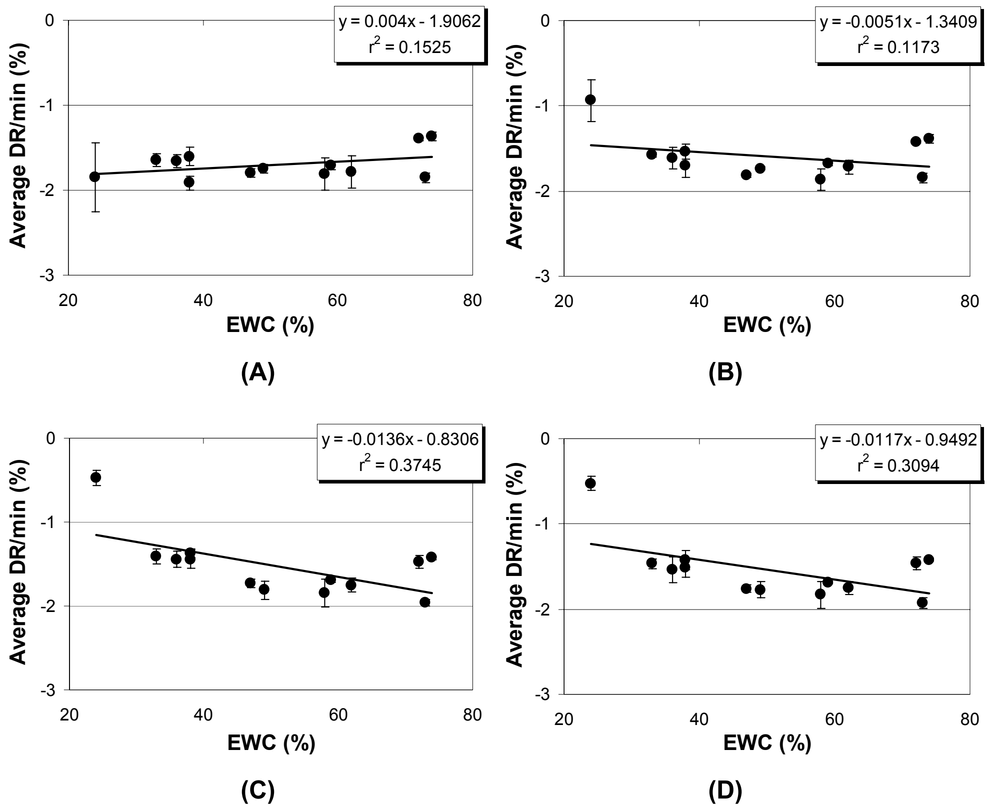


Figure 10.16. Relationships between EWC of the CLs and mean DR at intervals of 5 min for the first 20 min of the dehydration process during 1-5 (A), 6-10 min (B), 11-15 (C), and 16-20 min (D). Bars represent standard deviation.

10.5. Discussion

The ability of CLs to maintain its hydration during wear is considered as one of the most important parameters involved in CL tolerance. Currently, different materials are available, with low, medium and high EWC. Most HEMA-based conventional hydrogels have an EWC ranging from 38 to 74%. This group includes lenses which claim to retain normal hydration better than other types of hydrogel lenses. Silicone-based hydrogel lenses, which differ in proportion and types of siloxane moieties and hydrophilic components, have an EWC ranging from 24 to 47%.

Within a polymer, water molecules can be "bound" to each other and to hydrophilic groups on the polymer backbone by hydrogen bonds, or can be "free", only loosely associated with each other and without any polymeric structural effects. However, the reported amount and proportion of "bound" and "free" water depends largely on the method used for determination. According to Refojo,[28] in one high EWC hydrogel (EWC 70%) more than half was "free" water, while within low to medium EWC hydrogels (EWC 41–45%) the proportion of "free" to "bound" water was inverted (high EWC materials have more than 50% of free water, while low EWC materials have more than 50% bound water). Despite, all the water in a hydrogel can be removed by evaporation under the right conditions, in clinical terms, only the "free" water is physiologically relevant to CLs. Current research has showed that the proportion of not-bound or freezable water is positively correlated to the EWC of the material.[29,30]

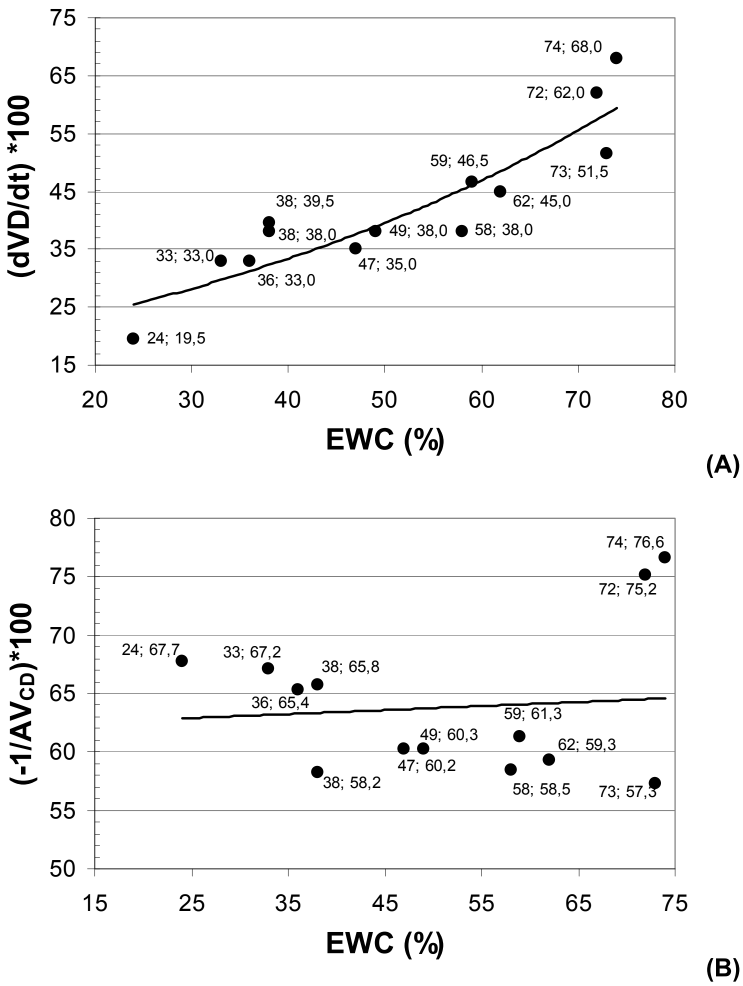


Figure 10.17. WRI as a function of EWC. First calculation was computed from the slope of straight lines fitted to the VD at 20, 40, 60, and 80 minutes for each lens (A). Second calculation was computed as the inverse function of the mean CD during the first 5 min (B).

This is one of the first studies presenting qualitative and quantitative descriptors of the *in vitro* dehydration process of such a wide range of currently available CLs in their original design. In our opinion, graphs presenting DRs are the best way to characterize the dehydration process of hydrogel CLs. Those graphs show a three-phase profile with an initial phase I of rapid and relatively constant DR, a phase II of rapid and progressive decrease of DR and a final phase III characterized by a slow decrease of DR approaching to zero.

However, during phase I, DR experiences constant variations within a maximum and minimum range around the average DR reported here. A similar feature is observed in the % dehydration curves reported by Jones *et al.*[26] In our opinion this acceleration and slow-down in DR would be related to the water loosely bound to the surface of the polymer.

Only one Si-Hi lens, lotrafilcon A, displayed a different dehydration behavior compared to all the other hydrogel lenses examined in this study. There was no phase I observed in its DR curve. This phenomenon could be explained on the basis of its higher content of siloxane moieties compared to the other Si-Hi lenses tested and its lower EWC. The cause of the water retention in this lens could also be due to the hydrocarbon-plasma coating that, by reacting with air, results in a thin hydrophilic membrane over the surface of the lens.[31] As this thin layer of water dehydrates, the internal dehydration of the polymer will begin thus passing directly to phase II with no apparent phase I. Other potential explanation to this fact is that silicone rubber has been shown to have high water pervaporation, but this does not appear to contribute to liquid water transport though Si-Hi lenses.[9] Also, although Si-Hi CL contain polysiloxane (silicone) and/or other siloxane moieties, they do not contain silicone rubber per se.

The other Si-Hi materials have a brief but defined phase I, which lengthens as the EWC increases (siloxane content decreases). Thus the presence of phase I is a characteristic of all conventional hydrogels, but not of Si-Hi containing high proportions of siloxane moieties.

The results and relationships presented in this work support many of the observations of previous clinical and experimental studies. According to our results, the higher the EWC of hydrogels the higher the DR and the longer the duration of phase I. This means that the higher the EWC of the hydrogel lenses, the higher cumulative and VD within the same time periods compared to hydrogels with lower EWC.

The higher dehydration of more hydrated hydrogels, despite not admitted by all authors, is the most commonly accepted relationship between EWC of hydrogels and DR.[10] Andrasko[8] concluded that at same lens thickness, hydrogel lenses with higher EWC dehydrate more during the same time period of *in vivo* lens wear than lenses of lower EWC. McConville and Pope[32] studied the diffusivity of water in hydrogels and concluded that this property was well predicted by their EWC. The authors suggested that the mobility of water within the hydrogel is associated with the probability of the water to leave the bulk of the hydrogel, thus supporting the commonly accepted fact that high EWC CLs dehydrate more in the eye than the lower hydrated lenses. Jones *et al.*[26] used a methodology similar to ours to evaluate the dehydration of three conventional hydrogels and two Si-Hi CLs. However, they used different environmental conditions of RH and airflow than airflow. They observed that *in vitro* dehydration of hydrogels was closely related to the EWC, and as a consequence, Si-Hi dehydrated less than high EWC hydrogels. The results derived from our *in vitro* dehydration curves support these observations.

In a study with etafilcon A (HEMA/VP, and 58% EWC) and omafilcon A (HEMA/phosphorylcholine (PC) moieties, and 62% EWC) under arid and arctic environments, significantly higher in-eye dehydration was found for the etafilcon A lens.[33] Another study found similar results under normal wearing conditions.[34] Our results predict a difference of DRs of about 0.07 % per minute between these two lenses, supporting the higher dehydration of etafilcon A despite its slightly lower EWC compared to omafilcon A, probably due to the PC moieties in the former material. However, considering the present results alone, we cannot predict that such a small difference will have significant implications from the clinical point of view.

Another experimental study carried out by Maldonado-Codina and Efron[30] concluded that hydrogel CLs with lower EWC had lower free-to-bound water ratio than the more hydrated lenses. The same conclusions were previously reported by Tranoudis and Efron.[29] Although, the present study did not specifically measured the free and bound portions of water in the hydrogel lenses, it is reasonable to conclude that free water would be lost first, during the rapid phase I within the dehydration process. This is supported by the higher dehydration (both CD and VD) and longer duration of phase I obtained for hydrogels with higher EWC. Our dehydration curves display a different behavior between phase I, at a sustained higher rate of dehydration, and phase II, with a rapid decay in DRs approaching zero at end of phase III. The first two phases could be in some way related to the evaporation of freezable and non-freezable water.

A clinical study from Morgan and Efron, compared the dehydration of etafilcon A (conventional hydrogel, 58% EWC) and balafilcon A (Si-Hi, 36% EWC). After a period of 2 weeks of lens wear, EWC of etafilcon A decreased by 10.3% while the balafilcon lens decreased by only 8% of their initial EWC. Considering the higher EWC of the etafilcon A compared to the balafilcon A, the result of the *in vivo* study could be expected. Nevertheless, if we consider the VD values , greater differences are found, between the results of etafilcon A and balafilcon A with VD values of 6.0 and 2.8% of their respective EWC.[5] In this regard, our results predict an almost double average cumulative dehydration (CD) of etafilcon Acompared to balafilcon A, thus are in total agreement with their results.

In the work of Tranoudis and Efron,[35] the authors evaluated lens centration, up-gaze lag, post-blink movement, total diameter and subjective assessment of comfort for eight hydrogel lenses made of different materials. They found that all lenses exhibited a reduction in lens total diameter and most of the lenses exhibited less movement on blinking and less lag after a 6-h wearing period. All these facts can be directly related to on-eye CL dehydration.

In the present study, we have obtained significantly different results of dehydration of lenses at the mid-term (end of phase I and phase II, 30-50 minutes) and long-term (phase III, 100 min), but we have observed a quite similar average CD during the first 5 min for all lenses, irrespective of their composition and EWC. The initial dehydration observed under *in vitro* conditions could be the most representative of the *in vivo* dehydration of the CLs. Thus, despite a sharp trend towards higher dehydration as the materials increase their EWC, such differences could not be as sharp at the first stages of the process. This fact, and the different experimental conditions used by different authors, could explain some of the controversies surrounding the ability to confirm statistically significant differences in dehydration among different CL materials.[36]

In conclusion, most of the dehydration parameters obtained here support a lower DR of Si-Hi materials, which is in agreement with other recent studies.[5] However, there is no significant difference in dehydration when we compare Si-Hi lenses and conventional hydrogels of similar EWC (i.e. senofilcon A, balafilcon A and polymacon), suggesting that the EWC more than the polymeric composition governs the ability of CLs to sustain their hydration.

Regarding the comparison between conventional hydrophilic lenses and lenses claim to retain water better than the other HEMA based lenses, we only have observed differences between omafilcon A, containing PC, and etafilcon A, both of have a similar EWC. We observed that omafilcon A displayed a lower average DR during phase I and slightly longer time periods to achieve certain degrees of VD. This observation is agreement with clinical and experimental results presented by Young *et al.*[13]

The parameter we have designated as WRI can be used as a quantitative indicator of the lens resistance to dehydration. The second equation used in the present work obtain WRI (WRI_2) seems to be more useful in terms of lens physiological performance because it expresses the average dehydration (in absolute values) within the first five minutes of the dehydration process. The water evaporated during this phase is more likely to be related with the evaporation process while the lens is on the eye. Additionally, values of WRI_2 obtained have demonstrated not to depend on EWC or lens thickness. For this parameter, we can have significant differences in evaporation rates even for lenses with similar EWC. Thus, contrary to most of the previous quantitative parameters, this could reflect some differences in polymeric composition irrespective of lens EWC and thickness profile. For example, lidofilcon A (73% EWC) has shown a WRI significantly lower than lenses of similar thickness and EWC. Also, senofilcon A showed a lower WRI than polymacon, despite their similar EWC. Omafilcon A and hioxifilcon A showed WRI values slightly above etafilcon A, but those differences were too small to be statistically or clinically significant. This parameter should be further investigated and the model should be probably refined in order to better reflect the ability of the CL to retain its hydration in the short-term (i.e. short periods of time between blinks …). WRI could be improved by considering parameters as time to DR of -1, -0.5, -0.1 and -0.05% as well as duration, average DR and VD at end of phase I.

Despite some limitations, the results presented have demonstrated to be in agreement with other clinical and experimental observations made in several previously published studies regarding comfort and on-eye dehydration of hydrogels. Considering these facts, the methodology discussed in the present study has demonstrated to be sensitive and able to show significant differences in water release between lenses of similar EWC, but with different chemical composition.

The present study has provided several objective quantitative parameters to characterize the *in vitro* dehydration process of different currently used CL materials. Some of these parameters help us to understand certain behaviors observed in clinical and other experimental investigations. They have also showed objective differences in the behavior of conventional hydrogels compared to hydrogels which claim to retain hydration more efficiently, and to Si-Hi materials of similar EWC and thickness. In addition, this approach will be useful in carrying out further experiments simulating different environmental conditions, without exposing human subjects to adverse conditions of temperature or RH.

However, the actual significance of each parameter obtained will have to be evaluated in more applied experiments in order to evaluate which ones more adequate to characterize CL degradation with use or the ability of CL solutions to improve lenses hydration and prevent dehydration, just to cite some potential applications.

Acknowledgments:

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Chapter 11

Analysis of the Deterioration of Contact Lens Polymers. Part I: Surface Topography

11.1. Abstract

Purpose: To evaluate the qualitative and quantitative topographic changes in the surface of worn contact lenses (CLs) of different materials, using atomic force microscopy (AFM).
Methods: The topography of 5 different CL materials was evaluated with AFM over a surface of 25 μm^2 according to previously published experimental setup. The topographic appearance of worn CLs was compared qualitatively against unworn samples of the same materials. Average roughness (*Ra*) and root mean square (*Rms*) values from roughness analysis facility of the microscope were also obtained and compared between new and worn samples.
Results: The *Ra* value increased for balafilcon A (11.62 nm to 13.68 nm for unworn and worn samples, respectively), lotrafilcon A (3.67 nm to 15.01 nm for unworn and worn samples, respectively), lotrafilcon B (4.08 nm to 8.42 nm for unworn and worn samples, respectively), galyfilcon A (2.81 nm to 14.6 nm for unworn and worn samples, respectively) and comfilcon A (2.87 nm to 4.63 nm for unworn and worn samples, respectively). Differences were statistically significant for all lenses except comfilcon A (*Rms* and *Ra*) and *Ra* parameter for balafilcon A ($p > 0.05$). The least relative increase was observed for some balafilcon A samples and for some of these samples the roughness decreased after the lenses had been worn, apparently due to partial coverage of the macropores seen at the surface of unworn balafilcon A lenses.
Conclusion: Overall, all CLs increased the degree of surface roughness after being worn, even for very short periods of time. Surprisingly, the opposite could be observed in some samples of balafilcon A, whose roughness increases at a lower extent or even can decrease compared to unworn samples. This fact could be related with the filling of the macropores that increase the surface roughness of unworn lenses. The changes in surface roughness between unworn and worn lenses are different for different Si-Hi materials.

11.2. Introduction

The concept of surface topography of the material has been rarely considered in SCL research in the past decades. However, the surface of the CL can be a key factor determining ocular surface tolerance. This is particularly important with the advent of some modern CL materials whose surfaces are treated to improve their wettability as in first generation Si-Hi materials. Some of these lenses show more irregular surfaces when observed by microscopic methods as AFM.[1] This technique offers the unique possibility to quantify the roughness of the surface, and to observe the qualitative appearance at a nanometric level with high resolution.

Deposit formation has been described as a major factor of deterioration on current contact lenses, including Si-Hi materials, as described in chapter 4 and it has been shown that lipids and denaturized proteins could be particularly relevant in these kind of materials.

The surfaces of unworn lenses had been evaluated by AFM in different studies.[1-3] The same technique has been also used by several authors to evaluate the surface of worn lenses.[4,5] However, the application of such methodology to worn samples of Si-Hi materials is lacking at present. Given potential role of mechanical impact of some of these materials on the ocular surface, due to their higher elastic modulus,[6] it is important to evaluate which kind of changes can be expected at the surface of Si-Hi CL. This information could be relevant to understand the mechanisms of interaction between worn CLs and the ocular surface and to find better explanations for the ocular response to CL wear.

The present study was carried out to investigate the characteristics of worn CLs from the qualitative and quantitative point of view of different Si-Hi materials in the hydrated state using the high resolution capability of the AFM.

11.3. Material and Methods

Worn samples of Air Optix Night & Day and Air Optix (Ciba Vision, Duluth, VA), Purevision (Bausch & Lomb, Rochester, NY), Acuvue Advance (Johnson & Johnson, Jacksonvile, FL), and Biofinity (Coopervision, CA) were observed with AFM in Tapping Mode using the experimental protocol described in chapters 5 and 6 to obtain CL surface roughness in the hydrated state. Ten samples of each material were used. All lenses had refractive power between -2.50 and -3.50 D. All lenses were used for 30 days on a daily wear basis and the same multipurpose solution (Renu Multiplus, Bausch & Lomb, Rochester, USA) was used for daily care purposes with all lenses. Acuvue Advance was worn only for 15 days as recommended by the manufacturer. Only the anterior surface of each sample was evaluated. Values of average roughness (*Ra*) and root mean square roughness (*Rms*) were compared against those obtained for 10 unworn samples of the same materials with a refractive power of -3.00 D. Technical details of the lenses used in this study are listed in *table 11.1*.

Statistical analysis was performed using SPSS Software v.15.0 (SPSS Inc, IL). Normal distribution of variables was previously assessed by Kolmogorov-Smirnov test. When normal distribution of data could not be assumed, Mann-Whitney non-parametric test for independent samples was carried out in order to compare mean values of roughness (*Rms* and *Ra*) between worn and unworn samples. Comparisons involving normally distributed variables were performed using independent samples T-test. In this case, Levene test was used to assess equality of variances. The level of statistical significant was set at α=0.05.

Table 11.1. Details of the contact lenses used in the study

Brand	USAN Generic name	EWC (%)	Ionic (FDA)	Dk (barrer)	Power‡ (D)	Surface Treatment	CT (mm)
Air Optix Night & Day	Lotrafilcon A	24	No(I)	140	-3.00	Plasma coating	0.08
Purevision	Balafilcon A	36	Yes(III)	99	-3.00	Plasma oxidation	0.09
Air Optix	Lotrafilcon B	33	No(I)	110	-3.00	Plasma coating	0.08
Acuvue Advance	Galyfilcon A	47	No(I)	60	-3.00	No	0.07
Biofinity	Comfilcon A	48	No(I)	128	-3.00	No	0.08

‡ Worn lenses had powers between -2.50 and -3.50 D; CT: central thickness

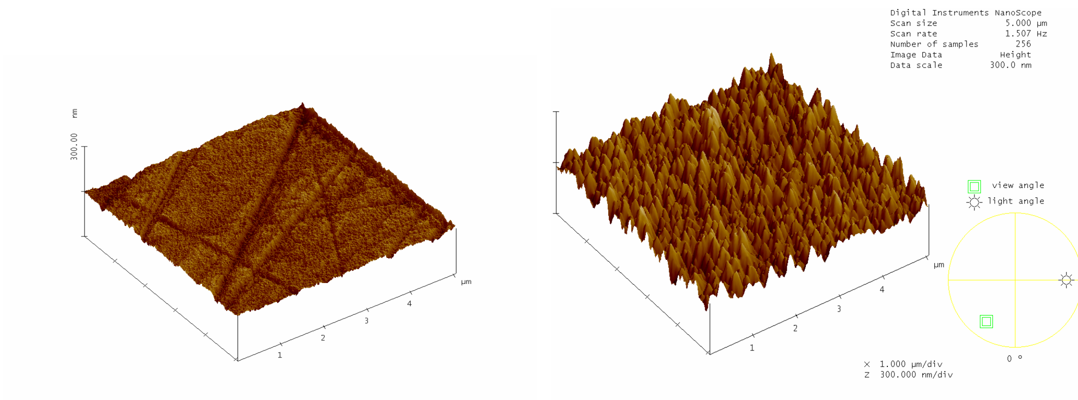
11.4. Results

Figure 11.1 displays examples of the qualitative appearance of worn samples of lotrafilcon A, balafilcon A, lotrafilcon B, galyfilcon A and comfilcon A materials. On the right side of each image, a microtopograph of an unworn sample is also shown for comparison purposes.

Figure 11.2A and *11.2B* display the values of *Rms* and *Ra* for the unworn and worn samples. *Tables 11.2* and *11.3* show the results of the statistical comparison for values of *Rms* and *Ra*, respectively, between unworn and worn lenses.

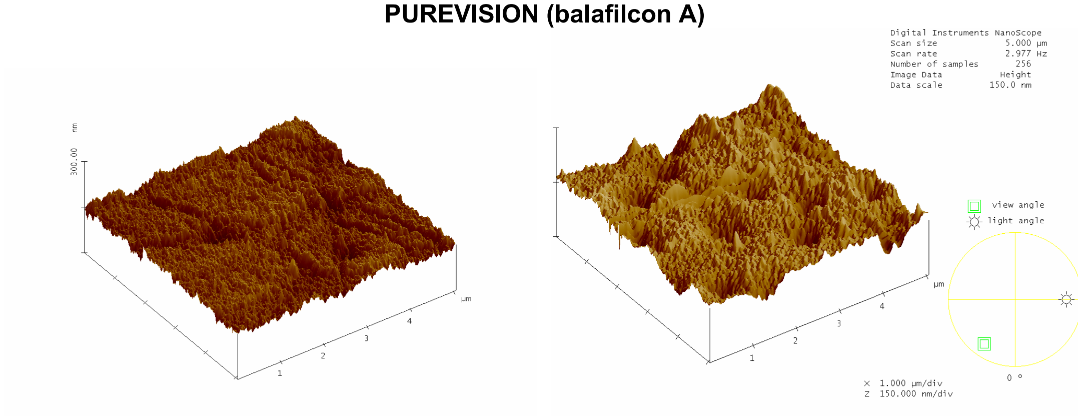
Overall, all worn lenses presented higher values of *Rms* and *Ra* than their unworn reference samples. However, the lens with the initial higher values of roughness (balafilcon A) displays only a modest increase in the roughness parameters compared to the remaining samples whose *Rms* and *Ra* parameters increase by approximately 2 to 5 times of the initial value. Balafilcon A *Rms* and *Ra* values increase only by 1.25 and 1.17 times, respectively. Moreover, balafilcon A was the only material with a worn sample having lower surface roughness than the unworn reference values. This sample is shown in *figure 11.3* along with a reference image from an unworn sample. This example is provided to demonstrate that with this lens, it is possible to obtain lower values of roughness in worn lenses than in some unworn samples. It is evident that the reduction in the roughness parameters is due to the partial filling of the macropores usually seen in new samples of this material.[1,7] This effect and the large variability in the roughness values of this sample (see error bars for unworn samples) made possible that the *Rms* and *Ra* values for the unworn sample had been higher (*Rms* = 26.59 nm; *Ra* = 20.22 nm) than those obtained for the worn sample (*Rms* = 22.01 nm; *Ra* = 17.55 nm).

AIR OPTIX NIGHT & DAY (lotrafilcon A)



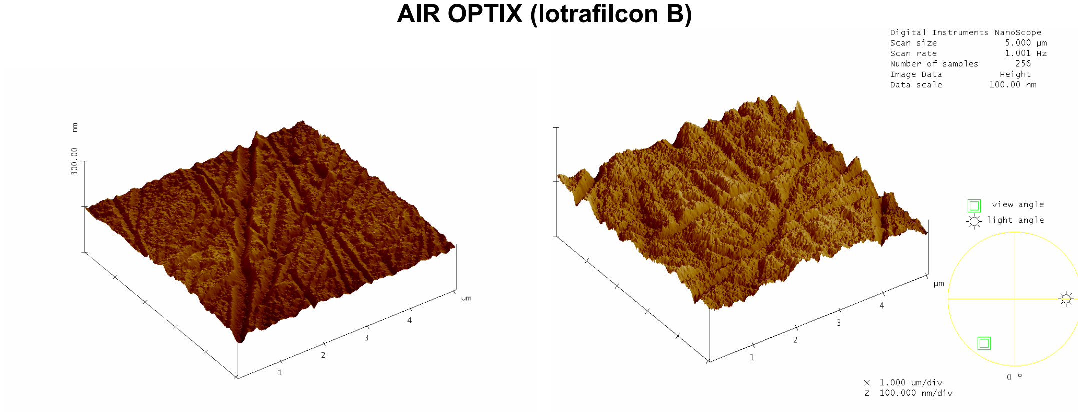
(A) **(B)**

PUREVISION (balafilcon A)



(A) **(B)**

AIR OPTIX (lotrafilcon B)

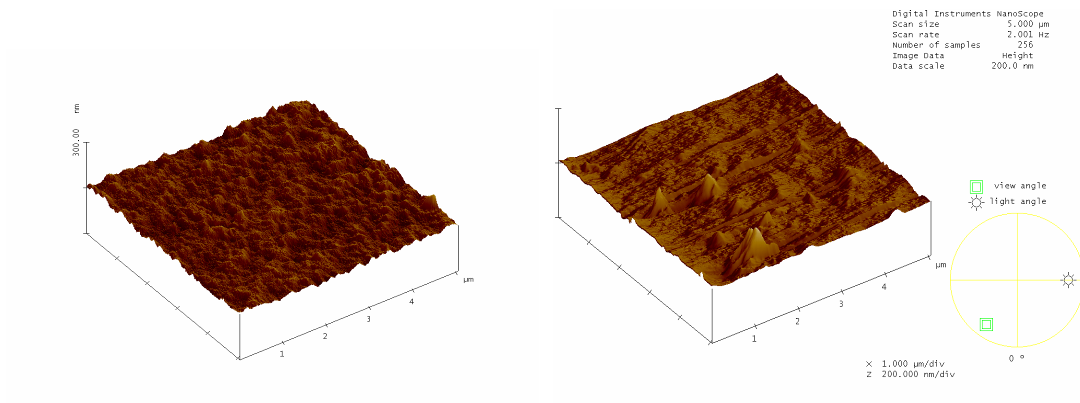


(A) **(B)**

Figure 11.1. Examples of the qualitative appearance of unworn lenses (A) and worn samples (B) for different materials.

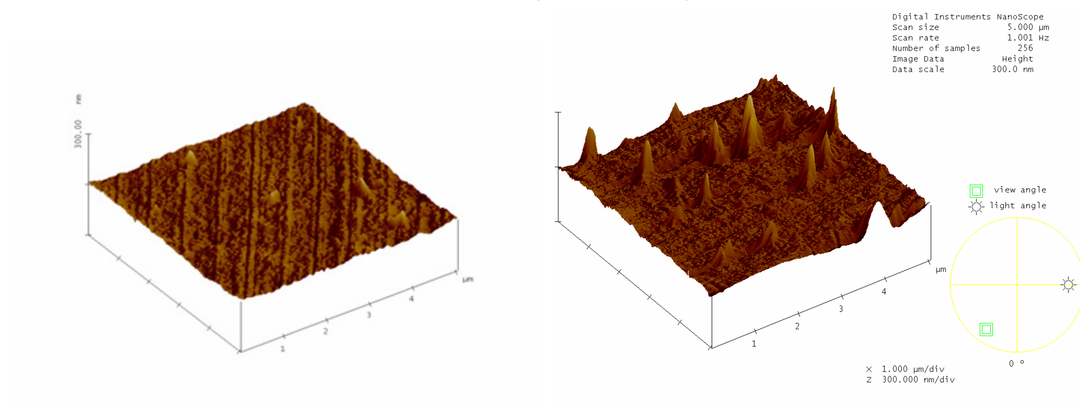
José Manuel González-Méijome

ACUVUE ADVANCE (galyfilcon A)



(A) **(B)**

BIOFINITY (comfilcon A)



(A) **(B)**

Figure 11.1*(cont)*. Examples of the qualitative appearance of unworn lenses (A) and worn samples (B) for different materials.

Table 11.2. Comparison of values of root mean square roughness parameter (*Rms*) for worn and unworn samples of the same CL materials. Values in nm

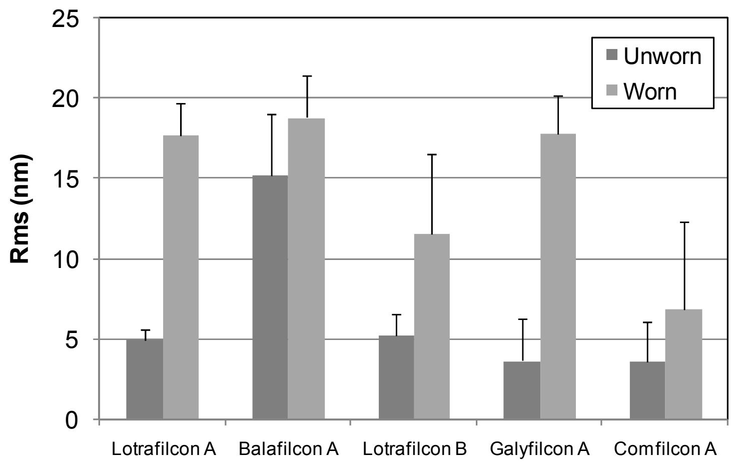
Contact Lens *(Material)*	**Unworn Samples (n=10)**	**Worn Samples (n=10)**	**Statistical Significance‡**
Air Optix Night & Day *(lotrafilcon A)*	4.98 ± 0.60	17.68 ± 1.98	<0.001‡
Purevision *(balafilcon A)*	15.19 ± 3.81	18.8 ± 2.56	0.021†
Air Optix *(lotrafilcon B)*	5.27 ± 1.31	11.59 ± 4.91	0.002†
Acuvue Advance *(galyfilcon A)*	3.68 ± 2.61	17.79 ± 2.43	<0.001†
Biofinity *(comfilcon A)*	3.62 ± 2.39	6.89 ± 5.42	0.237‡

† Independent Sample T-Test; ‡ Mann-Whitney non-parametric test for independent samples

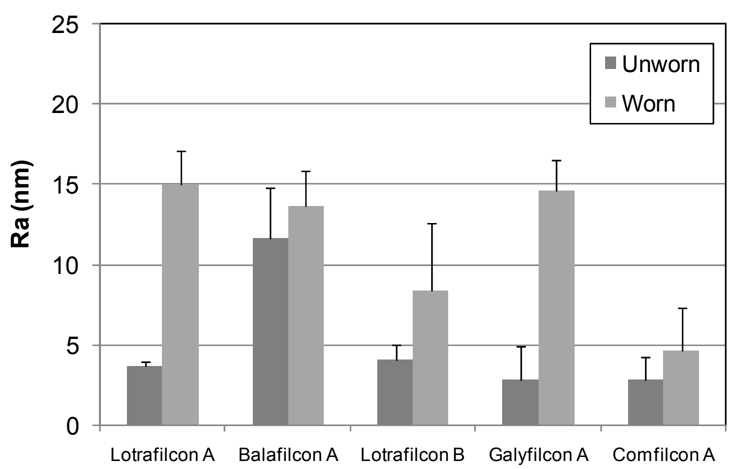
Table 11.3. Comparison of values of average roughness parameter (*Ra*) for worn and unworn samples of the same CL materials. Values in nm

Contact Lens	Unworn Samples (n=10)	Worn Samples (n=10)	Statistical Significance‡
Air Optix Night & Day *(lotrafilcon A)*	3.67 ± 0.35	15.01 ± 2.13	<0.001†
Purevision *(balafilcon A)*	11.62 ± 3.22	13.68 ± 2.21	0.157†
Air Optix *(lotrafilcon B)*	4.08 ± 0.92	8.42 ± 4.14	<0.001‡
Acuvue Advance *(galyfilcon A)*	2.81 ± 2.12	14.6 ± 1.93	<0.001†
Biofinity *(comfilcon A)*	2.87 ± 1.47	4.63 ± 2.74	0.151†

† Independent Sample T-Test; ‡ Mann-Whitney non-parametric test for independent samples

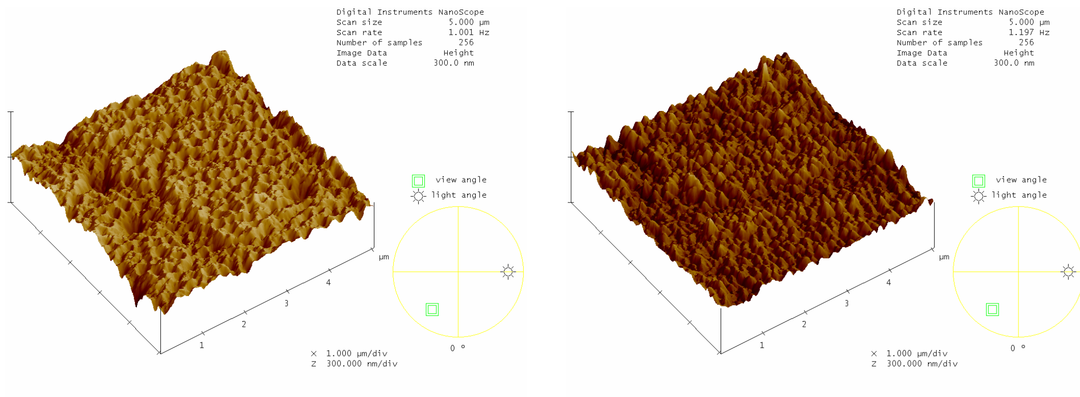


(A)



(B)

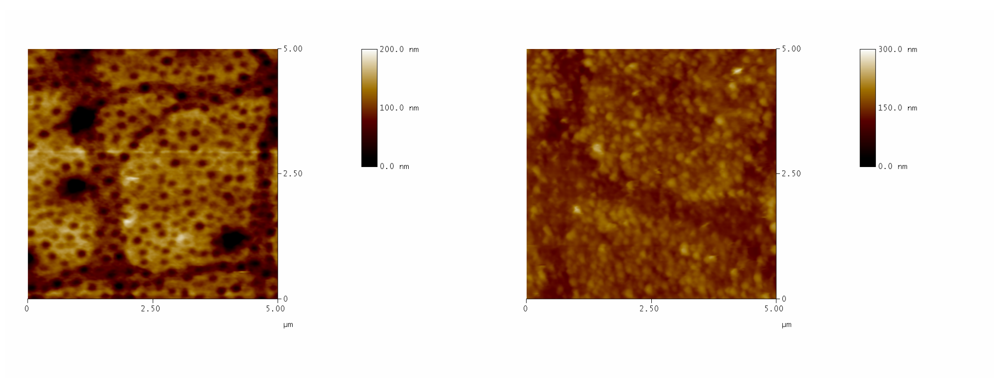
Figure 11.2. Quantitative parameters of *Rms* (A) and *Ra* (B) for unworn and worn samples of the five CL materials.



(A) (B)

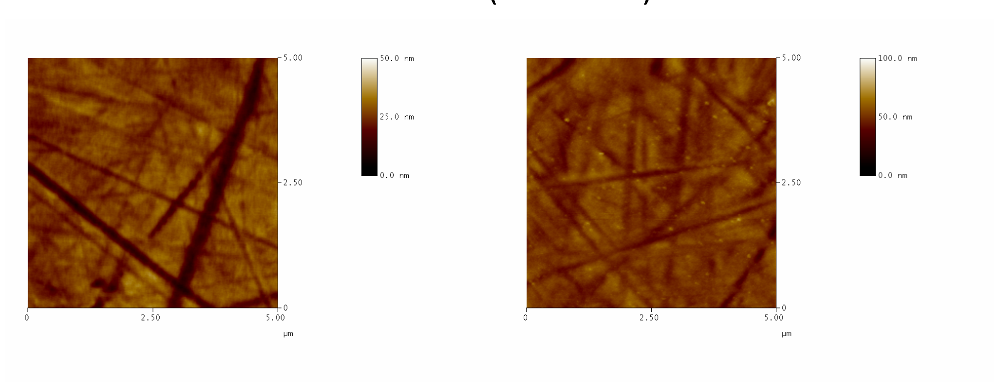
Figure 11.3. Microtopographic images of the surface of unworn (A) and the corresponding worn sample (B) of balafilcon A.

PUREVISION (balafilcon A)



(A) (B)

AIR OPTIX (lotrafilcon B)



(A) (B)

Figure 11.4. Examples of the qualitative appearance of unworn (A) and worn samples (B) of two different materials (balafilcon A –top– and lotrafilcon B –bottom–).

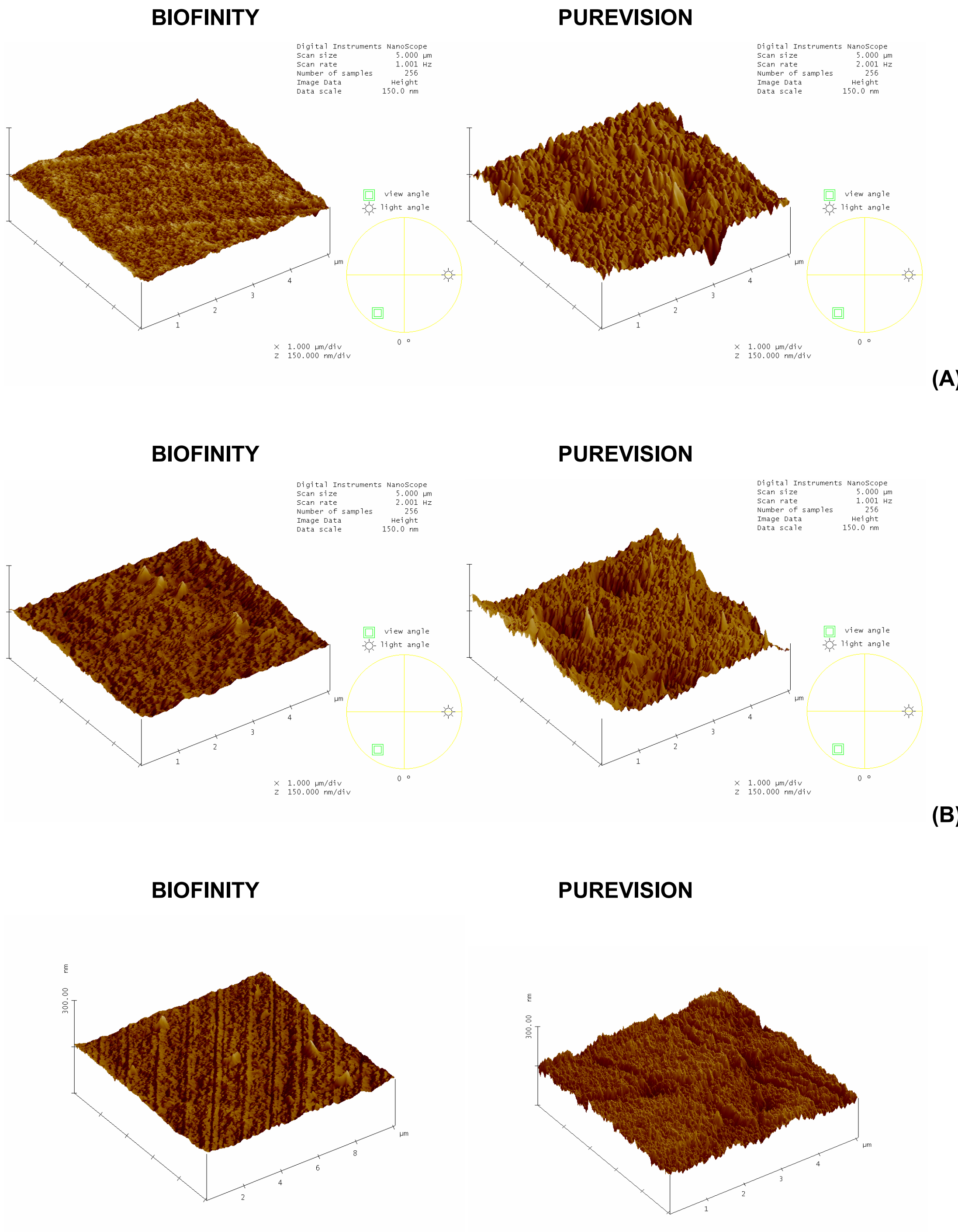


Figure 11.5. Samples of the same CL material worn for 20 minutes (A) and 30 days (B) by the same patient and reference unworn sample (C).

Images in *figure 11.4* show how the deposit formation on the CL surface do not have to distort the characteristic appearance of some CLs. This is illustrated on this figure for balafilcon A and lotrafilcon B materials. This effect can also be observed in three-dimensional images provided in *figure 11.1*.

Figure 11.5 shows the qualitative appearance of samples of two different contact lens material worn by the same patient for 20 minutes in one case and for 30 days in other case. It is apparent that the qualitative aspect of both samples is not much different. In fact, the quantitative values of roughness are very similar. Five balafilcon A samples worn for 20 minutes showed $Rms = 16.31 \pm 2.52$ nm and $Ra = 11.47 \pm 1.38$ nm against $Rms = 18.80 \pm 2.56$ nm and $Ra = 13.68 \pm 2.21$ nm for the ten samples of the same material worn for 1 month. On the other side, five samples of comfilcon A worn for 20 minutes displayed $Rms = 4.86 \pm 2.15$ nm and $Ra = 3.72 \pm 1.47$ nm against $Rms = 6.89 \pm 5.42$ nm and $Ra = 4.63 \pm 2.74$ nm for the ten samples of the same material worn for 1 month.

11.5. Discussion

AFM is becoming a powerful tool for the fine characterization of CL material surface. This is particularly important in SCL because this technology allows us to evaluate the lens in the hydrated state without further preparation or dehydration of the sample. In the most recent study conducted using this technique, Guryca *et al.*[8] have found a close relationship between the maximum roughness (*Rmax*) and the EWC of the material, with the *Rmax* value decreasing as the EWC increased. In fact, in previous studies, we have found that certain Si-Hi materials with lower EWC (lotrafilcon A, B and balafilcon A) present a higher surface roughness than Si-Hi materials with higher EWC. However, even lenses with similar EWC as balafilcon A (36% EWC) and senofilcon A (38% EWC) have markedly different surface roughness values. So, the findings of Guryca *et al.*[8] can be more directly related with the surface treatment of certain low-EWC Si-Hi lenses (and these are those with surface treatment) than with the EWC itself. Rather than a direct effect of low EWC on surface roughness, our published results and unpublished experiences with AFM suggest that conventional hydrogel materials and Si-Hi without surface treatment have smoother surfaces than Si-Hi with surface treatment. The same authors[8] found that spin-casting lenses present smoother surfaces compared to cast-mold lenses.

However, beyond the characterization of new materials, other relatively unexplored field is the application of AFM technology to worn CLs. In the few studies conducted with this purpose, Goldberg, Bathia and Enns,[5,9] observed significant changes in the surface of worn CL. However their studies were conducted in conventional hydrogel materials while the growth of present contact lens practice relies strongly on Si-Hi materials.[10]

Our results show that surface roughness of Si-Hi CLs increases significantly after wear. There was a trend towards lower relative increase in roughness parameters for those lens surfaces that were initially more irregular.

Trying to transpose the topographic data to the clinical field, previous studies conducted by Baguet *et al.*[4] found that the higher roughness of the materials made it more prone to bind deposits. However, our results do not suggest that fact as balafilcon A was the lens that demonstrated the lower relative increase in surface roughness. Along with comfilcon A material, balafilcon A was the only material that did not demonstrated significant changes in *Ra* parameter. This could also be explained because of the higher variability in roughness values for the unworn samples but also to the lower relative increase in roughness values (≈1.2x) compared to the other samples (≈2-5x). The lower values of roughness in comfilcon A and the high variability are also responsible for the absence of statistically significant changes between unworn and worn lenses of this material. On the other hand, galyfilcon A, with a smoother surface in new lenses displayed a significantly increase in the roughness after wear. This could be related with the fact that CLs containing NVP increase the adhesion of deposits because the chemical configuration of monomers as NVP has been associated with a higher incidence of lipid deposits in FDA group II hydrogel CL.[11] This could explain the large relative increase in roughness in galyfilcon A material as this material incorporates a derivate of NVP as an internal wetting agent which along with the hydrophobic nature of siloxane, could increase the amount of lipid deposits and the roughness of the material. In fact, despite the present did not evaluate the biochemical nature of the surface deposits, recent studies support the higher lipid deposition on Si-Hi materials,[12] so lipids could be an important part of the materials encountered on the lens surface after wear and be responsible for the increase in surface roughness.

The variability (SD) in the results of roughness (*Ra* and *Rms*) also increased after the lenses had been worn. This was particularly evident for lotrafilcon A, lotrafilcon B and comfilcon A CLs. Jones *et al.*, observed that once lens material is taken into account, protein deposits display a small inter- and intra-subject variation. Conversely, the same study showed that lipid deposits display a higher patient-related variability.[13] Considering that lipids are the main source of deposits on Si-Hi materials, this could explain the higher inter-lens variability encountered for roughness parameters in worn lenses.

Despite the formation of deposits over the CL surface increases the roughness of the surface, the typical pattern of certain lenses is kept after the deposit build-up and this suggests that the deposit layer should be relatively thin. Otherwise, the pattern of lenses as lotrafilcon A and B or balafilcon A won't be observed after deposit formation. Such a thin layer of deposits could be responsible for the clinically observed lack of wettability of some of these materials. This is particularly evident in some Si-Hi lenses at first insertion before lenses are worn for several hours. In the case of balafilcon A, it is evident in some worn samples that the surface of the material is relatively more uniform after lens wear, and this fact is related to the total or partial filling of the macropores observed with microscopy techniques in unworn samples.[1,7] This is in agreement with the fact that certain contaminants penetrate within the polymer bulk, as is the case for certain proteins whose small molecular weight (i.e. lysozyme) makes them able to penetrate beyond the outer material surface.[14,15]

The impact of surface roughness on significant aspects as bacterial adhesion is far from being understood. For example, there is interest on elucidate if the increase in surface roughness as a consequence of wear as found in the present study, could be a risk factor to increase the risk of ocular infection by means of a higher bacterial attachment to the CL. Some authors found a higher bacterial adhesion to some Si-Hi materials[16] and the roughness of surfaces seems to be accepted as a factor to potentiate bacterial adhesion which has been explained with the fact that organisms on rough surfaces are better protected against shear forces and cleaning procedures.[17] However, these facts could be somewhat contradicted by the current finding of Vermeltfoort *et al.* that observed a higher rate of bacterial transfer from different contact lenses to surfaces with lower roughness than more rough surfaces.[18] Considering that first generation Si-Hi materials present more rough surfaces and that they increase roughness with use as we report in the present work, it will be interesting to know how this could affect bacterial adhesion and potential contamination of the ocular surface. However the relationship between surface roughness, bacterial adhesion and the potential impact of contact lens wear is far from being a simple question.

In another study, Vermeltfoort *et al.* did not find significant changes in the surface roughness of Si-Hi materials after 1 and 4 weeks of wear, while a reduction in the wetting angle was observed. These facts were accompanied by a general decrease in the adhesion of bacteria to worn lenses compared to new samples.[19] These results agree with the findings of Boles *et al.* who concluded that worn disposable CLs restricted the attachment of *Pseudomonas aeruginosa* compared to new lenses.[20] Early studies from Duran *et al.* also support the affinity of new CL materials for bacterial adhesion.[21] Regarding the lack of significance of increase in surface roughness found by Vermelfoort *et al.*[19] in their study, this seems not to be supported by previous research that demonstrated a significant increase in roughness.[4,22] Our results are very clear in supporting this increase in surface roughness with use. Results of Bruinsma *et al.*[22] agree with previous studies that wear and overwear of CL do not imply an increase in bacterial adhesion, despite the increase in surface roughness that they have observed, particularly in lenses that had been used beyond the intended life-time.

Results from a recent study showed that Si-Hi lenses with surface treatment showed a higher level of bacterial attachment than other non-treated Si-Hi materials.[16] The materials compared in that study showed in successive studies conducted by us that balafilcon A presents a significantly higher roughness value than galyfilcon A (see chapters 5 and results of unworn samples in present study). In fact, Beattie *et al.* demonstrated a lower bacterial attachment to second generation Si-Hi lens without surface treatment (galyfilcon A) compared to first generation surface treated lotrafilcon A.[23] Even if surface treatment could be a source or surface irregularity, we cannot ensure that the presence of surface treatment itself could be a risk factor for bacterial adhesion. On the light of previous research, this factor seems not to be a determinant one.[24]

The fact that lenses worn for some minutes do not present a significantly different pattern of appearance of surface topography compared with those worn for up to 30 days agrees with the previous evidences that deposit formation is a rapid process after the lens is inserted on the eye. In fact, galyfilcon A lenses, worn only for 15 days presented one of the higher relative change in roughness parameters between unworn and worn samples. This evidence also demonstrates that with adequate care, the surfaces of the lenses can be kept in good state regarding to surface roughness for the whole period of 30 days of wear or at least do not induce marked differences from those lenses being worn for very short periods of time. However, this should not be understood as a loss of relevance of length of wear on material deterioration. The question of overwear of CLs beyond the periods recommended by the clinician is also a matter of concern. In a study conducted by Michaud *et al.*, overwear of group IV hydrogel CL was associated with an increased level of protein deposits. This increase could be somewhat responsible for the exacerbation of several clinical signs and decrease in visual acuity found by the authors.[25] Bruinsma *et al.*, investigated directly the impact of overwear of SCL on surface properties, demonstrating an increase in surface roughness parameters in lenses worn beyond the intended period of time.[22]

Another interesting observation to be considered in future studies is that when a lens presents focal deposits, these can increase much the *Rms* parameter, while the *Ra* parameter reflects this change in more moderate way. So, *Ra* could be a more reliable parameter to evaluate the changes in surface roughness of worn CLs than *Rms* which is more sensible to local defects. Despite *Rmax* has been used by Guryca *et al.*,[8] it seems unlikely that this parameter could be used as a reliable form to characterize surface changes after the lenses had been worn. This is more important considering that with AFM we are observing a small portion of the lens and *Rmax* and to a lower extent *Rms* can be significantly affected by focal deposits or surface irregularities being less representative of the whole image topography than *Ra*. Anyway, we have found a good agreement between *Rms* and *Ra* for the majority of the samples being analyzed.

In summary, the present study shows that deposit formation over disposable Si-Hi materials create a relatively thin layer that in some cases is unable to mask the typical pattern of some CLs. Overall this deposit build-up increases the roughness of the surface by twofold but can be also a factor of regularization of the surface in certain samples characterized by high roughness prior to being worn. After short periods of wear the lenses do not show significantly different patterns of surface topography than lenses worn for longer periods of time. In lenses with prominent focal deposits, *Ra* is a more reliable parameter to obtain an "average" measure of the surface roughness within the image while *Rms* parameter is much increased by the presence of focal elevations on the surface, resulting in higher inter-sample variability (SD) when several lenses of the same material are analyzed. Despite new lenses with higher roughness could be more prone to bacterial adhesion prior to being worn, when these lenses have been worn, their relatively lower increase in roughness when compared with other materials, initially less irregular, could make differences in bacterial attachment less evident, if surface roughness could be considered as a risk factor for bacterial attachment.

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Chapter 12

Analysis of the Deterioration of Contact Lens Polymers. Part II: Surface Mechanical Properties

12.1. Abstract

Purpose: To evaluate the impact of contact lens wear on the mechanical properties of contact lens (CL) surface measured with atomic force microscopy (AFM) in the hydrated state.
Methods: Nanoindentation with AFM was done and the values of mechanical properties were obtained from new samples of five silicone hydrogel (Si-Hi) CLs, and from ten samples of the same material that had been worn under daily wear conditions. For each sample, three repeated indentation curves had been processed to obtain Young modulus.
Results: Some lenses displayed statistically significant changes in the surface modulus measured with the AFM. Some lenses experienced a slight decrease but the general and more significant trend was towards increasing the modulus in the worn lenses. For two lenses (lotrafilcon A and lotrafilcon B) the increase was more evident and the variability of the results also increased in the worn samples when compared with the results of the new samples.
Conclusion: Contact lens wear induces significant changes in the mechanical properties of the contact lens surface. These changes have the potential to alter the interaction between the contact lens and the ocular surface. If these changes are significant enough to induce or exacerbate physiological changes in the corneal and conjunctival epithelium or in the tarsal conjunctiva, it should be evaluated.

12.2. Introduction

Mechanical interaction between soft contact lenses (SCLs) and the ocular surface, particularly at the corneal level is one of the main critical aspects of modern contact lens materials. It is well known the close relationship between first generation Si-Hi materials and changes in the anterior corneal surface as superior epithelial arcuate lesion (SEAL), corneal flattening or debris in the retrolental space.[1-5]

However, the significance of the mechanical behavior of a CL material could be also reflected at the cellular level deep in the corneal stroma, not in direct contact with the contact lens surface. For example, Kallinikos *et al.*[6] have observed a loss of keratocytes in the corneal stroma with the use of Si-Hi contact lenses. The authors hypothesize that the mechanical stimulation of the corneal surface by the presence of the CL is able to release inflammatory mediators able to induce keratocyte apoptosis. The potential implication of mechanical stimulation of the corneal surface, due to the physical presence of a CL, in the release of inflammatory mediators as the likely cause of reduced keratocyte density or keratocyte redistribution associated with lens wear is being investigated.[6-8] On a similar line of thought but probably with different significance, Ladage *et al.*[9] have reported the proliferation of keratocytes under the corneal surface affected by the presence of post-lental debris in the form of mucin balls in rabbit corneas. This mechanism could also be the reflection of the mechanical impact of the mucin balls compressed under the contact lens and could be interpreted as a form of corneal response to localized mechanical interaction between the CL and the external epithelium.

The goal of this study was to evaluate the mechanical properties of the contact lens surface before and after being worn on a daily wear schedule. These properties had been analyzed by nanoindentation with AFM and should not be interpreted as the classical mechanical properties reported by the industry concerning to the properties of the bulk of the lens usually obtained with macroscopic indenters or with instruments that induce a deformation on the whole sample, measuring the force needed to induce such a deformation, at a macroscopic scale.

12.3. Material and Methods

Ten samples of five silicone hydrogel materials were used in order to measure their mechanical properties in response to nanoindentation with AFM in Contact Mode before and after being worn. This process has demonstrated a high repeatability in qualitative terms.[10] *Figure 12.1* shows a 25 μm^2 microtopographic image with the approximate points of the indentation highlighted.

Ten worn samples of each lens material were evaluated by indentation analysis in Tapping Mode according to the experimental protocol showed in chapter 6. All lenses had between -2.50 and -3.50 D of refractive power. All lenses were used for 30 days on a daily wear basis and the same multipurpose solution (Renu Multiplus, Bausch & Lomb, Rochester) was used with all lenses. Acuvue Advance was worn for 15 days only. Values of Young modulus for worn lenses were compared against those obtained for 10 samples of the same unworn materials (-3.00 D). Technical details of the lenses used in this study are listed in *table 12.1*. Purevision lens (balafilcon A) has been recently improved, including a slight change in the modulus of the material. However, all lenses used in the study (worn and unworn samples) corresponded to the older design.

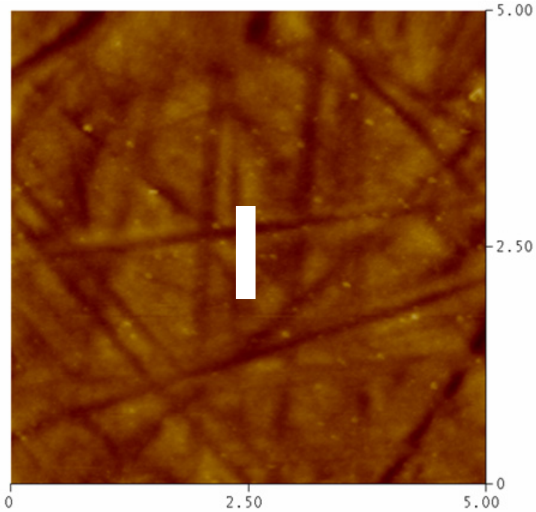


Figure 12.1. Microtopographic image of the contact lens surface with the area of indentation highlighted as white rectangle (0.100 x 0.500 µm).

Statistical analysis was performed using SPSS Software v.15.0 (SPSS Inc, IL). Normal distribution of variables was previously assessed by mean of the Kolmogorov-Smirnov test. Because of the non-normal distribution of data, Mann-Whitney non-parametric test for independent samples was carried out in order to compare mean values of Young Modulus between worn and unworn samples. Comparisons involving normally distributed variables were performed using independent samples T-test. In this case, Levene test was used to assess equality of variances. The level of statistical significant was set for $\alpha = 0.05$.

Table 12.1. Details of the lenses used in the study

Brand	USAN Generic name	EWC (%)	Ionic (FDA)	Dk (barrer)	Power‡ (D)	Surface Treatment	CT (mm)
Air Optix Night & Day	Lotrafilcon A	24	No(I)	140	-3.00	Plasma coating	0.08
Purevision	Balafilcon A	36	Yes(III)	99	-3.00	Plasma oxidation	0.09
Air Optix	Lotrafilcon B	33	No(I)	110	-3.00	Plasma coating	0.08
Acuvue Advance	Galyfilcon A	47	No(I)	60	-3.00	No	0.07
Biofinity	Comfilcon A	48	No(I)	128	-3.00	No	0.08

‡Worn lenses had powers between -2.50 and -3.50 D; CT: central thickness

12.4. Results

Figures 12.2 to *12.6* present examples of the indentation curves for unworn and worn samples of the five contact lenses. For all of them (worn and unworn samples) it is evident that the process of indentation is highly repeatable, despite the evidenced differences in surface topography that can be present in the small area under analysis (*figure 12.1*). As observed in previous work,[11] the pattern of each material is highly repeatable and is characteristic of each CL material. Also at the qualitative level, there are differences in some samples regarding the paths of trace and retrace curves. This reflects different interactions in unworn and worn materials, with a less elastic behavior (lack of parallelism between trace and retrace paths) and more adhesion of the tip to the surface in the retrace curve of some samples (i.e. *figure 12.3B*).

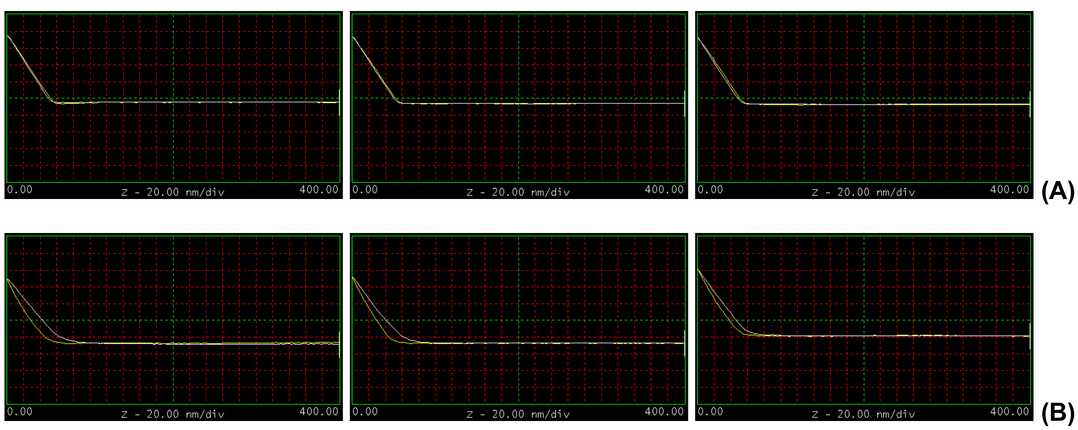


Figure 12.2. Indentation profiles of unworn (A) and worn (B) samples of Air Optix Night & Day (lotrafilcon A).

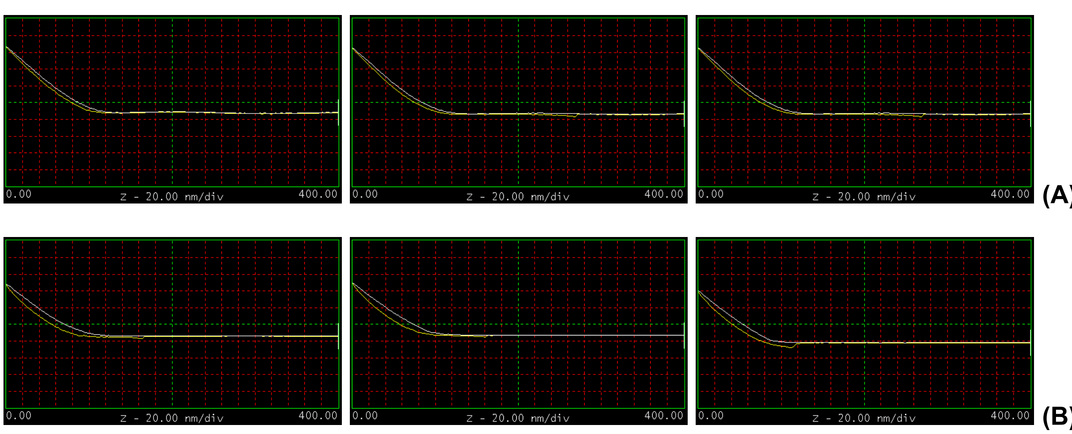
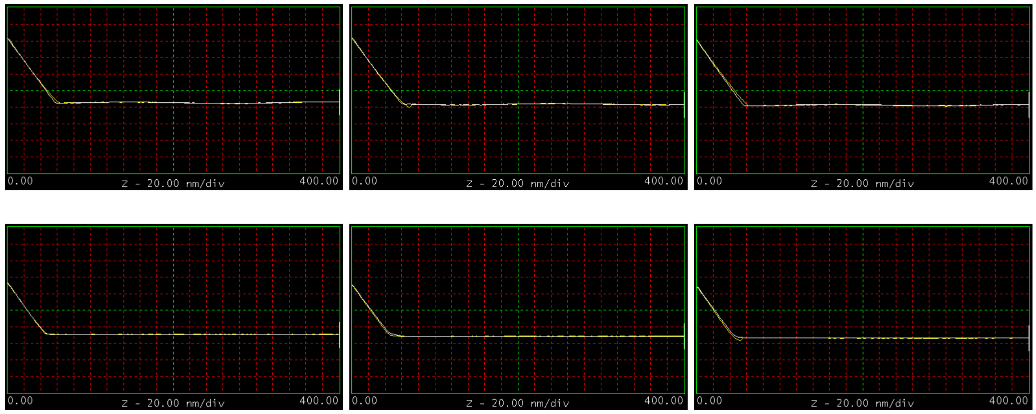


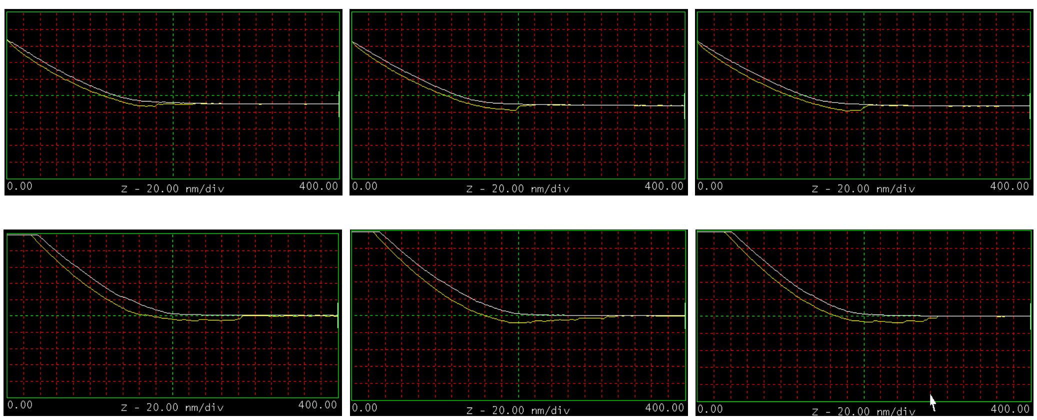
Figure 12.3. Indentation profiles of unworn (A) and worn (B) samples of Purevision (balafilcon A).



(A)

(B)

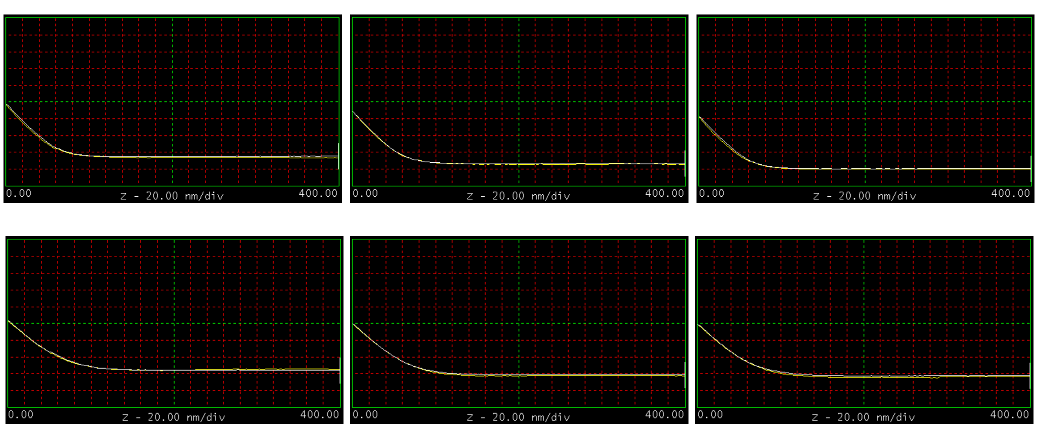
Figure 12.4. Indentation profiles of unworn (A) and worn (B) samples of Air Optix (lotrafilcon B).



(A)

(B)

Figure 12.5. Indentation profiles of unworn (A) and worn (B) samples of Acuvue Advance (galyfilcon A).



(A)

(B)

Figure 12.6. Indentation profiles of unworn (A) and worn (B) samples of Biofinity (comfilcon A).

Table 12.2 and *figure 12.7* present the average modulus of unworn and worn samples of the five materials. All materials displayed statistically significant differences between both groups suggesting an effect of lens wear on the mechanical properties of the surface. However, the effect is not the same for all lenses as can be seen in *figure 12.7*. The lenses with the higher EWC displayed a trend towards a decrease in modulus, while the opposite trend is observed in the remaining samples. Moreover, these changes are highly evident for the less hydrated samples lotrafilcon A and lotrafilcon B.

Table 12.2. Comparison of values of modulus for worn and unworn samples of the same CL materials. Units are MPa

Contact Lens ***(Material)***	**Unworn Samples (n=10)**	**Worn Samples (n=10)**	**Statistical Significance**
Air Optix Night & Day *(lotrafilcon A)*	8.48 ± 1.08	15.28 ± 5.61	0.012†
Purevision *(balafilcon A)*	2.25 ± 0.19	3.85 ± 0.19	0.005†
Air Optix *(lotrafilcon B)*	6.96 ± 0.32	14.44 ± 3.16	<0.001‡
Acuvue Advance *(galyfilcon A)*	1.42 ± 0.04	1.06 ± 0.01	0.001‡
Biofinity *(comfilcon A)*	3.85 ± 0.11	2.47 ± 0.15	<0.001†

† Independent samples T-test; ‡ Mann-Whitney

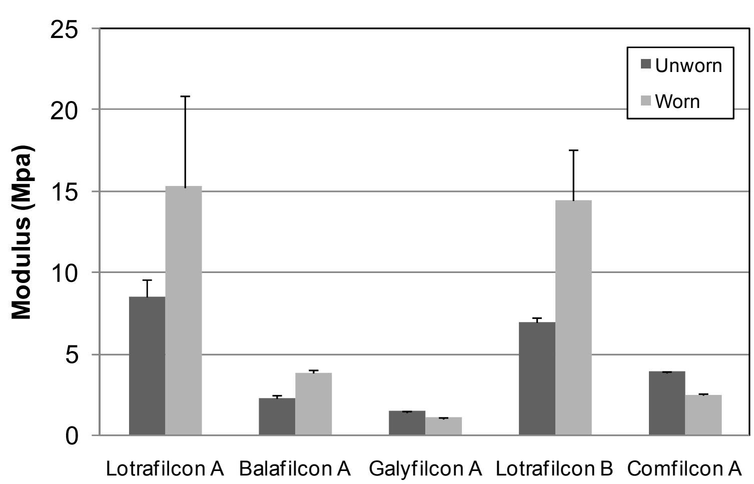


Figure 12.7. Comparison of modulus of unworn and worn samples of the same CL materials.

12.5. Discussion

It is accepted that the singular mechanical properties of the Si-Hi contact lenses of the first generation are responsible, or at least important predisposing factors to explain several changes at the ocular surface level[12] including superior epithelial arcuate lesions,[1,13] mucin balls formation,[14] or slight topographic and refractive changes in the anterior corneal surface.[4,5] New Si-Hi materials have tried to address this evidence by lowering the modulus in order to reduce the impact of these changes and improve initial comfort. This is the case for second generation materials as galyfilcon A and senofilcon A (Johnson & Johnson, Jacksonville, FL), lotrafilcon B (Ciba Vision, Duluth, GA) and comfilcon A (Coopervision, Virginia). Recently, the lens made of balafilcon A has also been recently improved by the manufacturer (Bausch & Lomb, Rochester) in order to improve comfort.

Despite the important relevance of the Young modulus, it is presently unknown if the mechanical properties of the contact lenses can change overtime as a result of lens wear or different situations that can cause stress in the material as the use of certain care regimes. It could be hypothesized that rigidity of the CL surface could increase as a result of CL wear due to partial dehydration of the material overtime, an effect that has been observed with conventional hydrogels.[15] However, this assumption is not well supported because galyfilcon A and comfilcon A that would be expected to suffer more dehydration as a result of their higher EWC demonstrated in fact a lower modulus in worn samples. However, it is unknown the effect that could have the materials deposited on the contact lens surface on the mechanical relationship between the CL and the more superficial histological layers of the ocular surface, the corneal and conjunctival epithelium or even the underlying stroma. On this regard, the main concern with Si-Hi materials is with lipid deposits[16] and the impact of this contaminants on the contact lens surface mechanical properties are also unknown.

An increase in the rigidity of the contact lens, with reflection at the surface could be due to molecular changes at this level with reorientation of the hydrophobic elements to the outer surface that could lead to a dryer surface and consequently a more rigid interaction with the corneal epithelium. However, some authors argue that CL wear and the associated tear deposits can in fact increase the surface wettability of the contact lens, rather than decrease it. In this case, the nanoindentation procedure could reflect the mechanical properties of the deposits rather than the polymer. However, considering the depth of penetration in nanoindentation, that reaches 150 to 200 nm, it is hard to believe that deposited layers on disposable contact lenses reach such a thicker structure if properly care is taken by the patient according to the recommendations of the clinician. Moreover, our previous results showed how contact lens topography still reflect the surface issues that characterize new lenses, suggesting the thin structure of films deposited on the contact lens surface. For this reason, we could hypothesize that we are in fact measuring the properties of the surface of the contact lens, although an effect of the films deposited on it or those that had penetrated into the more superficial pores cannot be discarded. Furthermore, the presence of lipid deposits on the CL surface makes that less hydrophilic radicals are available to bind water at the surface, so, the presence of deposits itself certainly affect the mechanical response of the lens surface, and the CL surface should be considered as the combination of the CL surface properties (substrate for deposit formation) but also as the films deposited on it as well.

This study has revealed an increase in the elastic modulus of some Si-Hi CLs after being worn. This effect has been particularly evident in lenses with plasma treatment on their surfaces, but we cannot establish a direct link between both facts until further investigations could be conducted. However, this increase could be relevant because of the potential implications of mechanical presence of the CL on the ocular surface to explain some physiological facts at the level of the histology of the cornea.

It has been demonstrated that the presence of CL is able to induce an increase in concentration of Langerhans cells in the corneal epithelium of guinea pigs, and this effect has been attributed in part to a mechanical effect caused by the presence of the CL.[17] Also, Efron *et al.* in different studies conducted using confocal microscopy supported the mechanical aetiological factor to explain the lower keratocyte density in the stroma of corneas wearing Si-Hi CL.[6-8]

This effect of the physical presence and the enhanced mechanical effect of certain CLs in the ocular surface has been postulated as an aetiological factor in the loss of keratocyte in the corneal stroma during lens wear had also been suggested in earlier investigations.[6,18] This fact could also be related with the stromal thinning[19] and overall corneal thinning[20] observed in long-term CL wearers. Long-term thinning of the stroma has been evidenced in low-Dk SCL wearers by modified optical pachometry (*unpublished data* from González-Méijome and Perez). The proof for this link will need to demonstrate this effect in long-term Si-Hi CL wearers, as the thinning effect on the cornea with low-Dk CL materials has been attributed to hypoxia in low-Dk CLs.

Another area of interest related with the mechanical impact of CL is contact lens giant papillary conjunctivitis (CLGPC). This is a relatively common contact lens complication and despite deposits on the surface are frequently considered as the etiological cause, and particularly denaturized protein deposits, it has also been suggested that mechanical trauma caused by the contact lens to the upper tarsal conjunctiva could be also an important factor to develop CLGPC in CL wearers. Donshik[21] stated that in addition to the chemistry of the CL polymer, other factors such as edge design and surface properties are also important variables in the pathophysiology of CLGPC. If we consider modulus as a potential factor to induce CLGPC in contact lens wearers in addition to the presence of denaturized lisozyme which has been considered as one of the main factors for the occurrence of this adverse response, we can find both entities converging in Si-Hi materials. The mechanical effect of CLs has also been pointed as a causative effect of CL-related corneal infiltrates.[22]

It is accepted that protein deposition on SCL is a material dependent process.[23] The ionic nature of FDA group IV containing methacrylic acid (MA) significantly adhere more proteins (particularly lisozyme) than copolymers of HEMA with NVP or acrylamide,[24] and this has been explained on the basis of an electrostatic affinity between the anionic material and the positively charged lysozyme at physiological pH.[25] Furthermore, the level of ionicity in the CL surface seems to be related with the amount of proteins deposited.[26] Despite higher levels of lipid deposits and lower levels of protein deposits have been found in Si-Hi materials, it has been also been observed that these new materials induce a higher degree of lysozyme denaturation.[16] Surprisingly, the higher incidence of lysozyme deposits on ionic materials compared to Si-Hi materials was associated with a lower incidence of denaturation in the same study. Despite lower deposits of protein in Si-Hi materials, the higher proportion of denaturized proteins, could be considered together with the higher modulus of first generation Si-Hi considered as the main factor for CLGPC in Si-Hi materals[27] to explain the increased occurrence of this entity with some Si-Hi materials.[28]

Although we were not able to know which reflection on the mechanical behavior of the CL surface could be expected from different types of deposits deposited on the lens surface, it could be hypothesized that denaturized proteins forming plaques could increase the rigidity of the contact lens surface beyond any level of superficial dehydration. An additional explanation to dehydration will be probably needed to explain the increase in surface modulus found in worn lenses as galyfilcon A and comfilcon A (materials with higher dehydration potential because of their higher EWC) did in fact decrease the modulus.

In summary, surface material changes due to contact lens wear of Si-Hi materials is commonly associated with some degree of increase in surface modulus. The results of the present study could be relevant to understand the mechanisms of certain ocular reactions to lenses covered with proteins, particularly when they are made of Si-Hi materials whose modulus could be increased as a consequence of wear. If these changes are significant enough to induce a higher incidence of papillary conjunctivitis or other reactions with a mechanical component on its etiology is still to be investigated.

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Chapter 13

Analysis of the Deterioration of Contact Lens Polymers. Part III: *In vitro* Dehydration of Contact Lenses

13.1. Abstract

Purpose: To evaluate the effect of wear on contact lens (CL) dehydration process under in vitro conditions using a previously described gravimetric procedure.
Methods: Different silicone hydrogel (Si-Hi) materials have been evaluated after being worn by patients under daily wear conditions, and conditioned and disinfected with a multipurpose solution. Equilibrium water content (EWC) was measured with a manual refractometer and compared with previous data obtained under the same conditions for unworn lenses. After refractometry, lenses were left to dehydrate in an analytical balance at known levels of temperature and relative humidity and the results compared with data from new lenses using the same procedure under the same experimental and environmental conditions.
Results: Overall, all worn samples showed lower values of EWC compared to the new samples. However, these differences were not statistically significant. The quantitative parameters derived from the dehydration curves showed statistically significant differences between worn and unworn lenses. Worn lenses showed shorter phase I duration, a significantly faster initial dehydration rate and lower water retention index as derived from the initial cumulative dehydration.
Conclusion: The initial dehydration rate demonstrated to be significantly increased in all CL after wear. This could be of clinical interest because it will represent the average initial dehydration during the first instants when the lens is left to dehydrate after a blink. This fact along with the lower EWC measured with refractometry suggests that even after the lenses had been equilibrated in saline solution for several days, the lenses loss in part their ability to bind and retain water.

13.2. Introduction

Evaporation of tears from the ocular surface is a natural process and has been extensively analyzed.[1-3] However, the evaporation rate is increased when a contact lens is placed on the eye, having negative effects for the integrity of the ocular surface.[1] Dehydration of CLs begins soon after the lens is placed on the eye to reach a new equilibrium of hydration given the different environmental conditions of the ocular surface of temperature, pH, osmolarity, exposure to atmosphere... However, this process could be even faster when the lens has been worn. However there is not common agreement on the relationship between lens wear and lack of hydration and wettability of the lens surfaces. We could expect that soiled lenses will resist better the dehydration process because the deposits covering the surface will protect the water to leave the material. On the other hand, we could also expect that less wettable surfaces will result in more rapid dehydration process once the most superficial hydrated portion of the lens will dry out. This seems to be the more likely mechanism, particularly in lenses with medium and high hydration as we have observed this effect in a recent study involving high EWC SCLs.[4] In this study, it has been observed that for high EWC lens materials, the dehydration rate becomes more accentuated after the most superficial water has evaporated.

Results from previous studies are somewhat controversial. While some studies showed a significant decrease in surface wetability with time of wear,[5] other authors found an increase in surface wettability with time of wear as it was found by Shirafkan *et al.*[6] after short periods of wear of HEMA-based hydrogel materials and Vermelfoort *et al.*[7] after 1 and 4 weeks of wear of two Si-Hi contact lenses. These authors found a continuous reduction of the wetting angle for the first 30 minutes of wear with no further improvement in wettability thereafter. A similar effect of improvement in wettability has also been found under in vitro conditions by Cheng *et al.*[8] Clinical observations seem to partially support both options (increase and decrease in surface wettability in the presence of tear components) as it is frequently observed that silicone hydrogel materials show an improvement in surface wettability in the short term (hours to first days of wear), but once that deposits are formed on the surface the opposite effect is observed, with lower tear stability on the contact lens surface.

Some studies had evaluated the dehydration of CL materials after being worn, and most of them agree that CL hydration decreases after days or weeks of wear.[9] However, to date, most of the *in vitro* dehydration studies had been carried out only with unworn materials and the potential changes that could happen in worn CLs as a result of lens contamination are not presently known. Due to the close relationship between the EWC of the materials and the quantitative parameters derived from the *in vitro* dehydration process according to a experimental procedure previously described,[4] it is expected that worn lenses present a significantly different pattern of dehydration compared with unworn samples of the same materials.

With these facts in mind, the present study was carried out to know if there is any measurable change in the dehydration process of Si-Hi soft contact lenses after had been worn on a daily wear. The in vitro dehydration process was analyzed using a previously described gravimetric method to compute dehydration rates and several other quantitative parameters. We are particularly interested on the parameters that describe initial dehydration.

13.3. Material and Methods

13.3.1. Sample materials

Samples of different CLs (*table 13.1*) were collected from patients. In all cases, lens care was done with multipurpose solution only (Renu Multiplus, Bausch & Lomb, Rochester), and all the lenses were worn on a daily wear schedule for one month. In order to limit the differences in dehydration pattern because of the refractive power of the samples[10] all worn lenses had a power between -2.50 and -3.50 D, while the reference materials (unworn samples) had a power of -3.00 D. All lenses were worn for one month except for Acuvue Advance, worn for 15 days only according to the manufacturer's recommendations.

Table 13.1. Details of the lenses used in the study

Brand	USAN Generic name	EWC (%)	Ionic (FDA)	Dk (barrer)	Power‡ (D)	Surface Treatment	CT (mm)
Air Optix Night & Day	Lotrafilcon A	24	No(I)	140	-3.00	Plasma coating	0.08
Purevision	Balafilcon A	36	Yes(III)	99	-3.00	Plasma oxidation	0.09
Air Optix	Lotrafilcon B	33	No(I)	110	-3.00	Plasma coating	0.08
Acuvue Advance	Galyfilcon A	47	No(I)	60	-3.00	No	0.07
Biofinity	Comfilcon A	48	No(I)	128	-3.00	No	0.08

‡Worn lenses had powers between -2.50 and -3.50 D; CT: central thickness

13.3.1. Equilibrium water content

Refractometric measurements were taken with a manual refractometer Atago N2E. This instrument showed to be able to measure lenses within the range of 38 to 74% EWC with good repeatability and good agreement with the values reported by the manufacturers. For Si-Hi materials, although their EWC will be expected to be out of the scale of this instrument, their peculiar behavior in terms of the relationship between refractive index and EWC allow that they can be measured with the same instrument.[11]

We have shown in a previous work that the power of the lens does not affect the value of the EWC measured with a manual refractometer, so the power of the lenses won't be a limitation to compare the results of worn lenses against the reference unworn materials.[12] However, because of the dehydration process could change with the power of the lens, all lenses had a power between -2.50 and -3.50 D. If the actual EWC of Si-Hi materials is to be obtained, the value measured with the refractometer has to be converted by using specific conversion relationships because the value obtained directly from the refractometer is higher than expected.[13]

Figure 13.1 shows the relationship between the nominal EWC given by the manufacturer (EWC_N), here considered as the actual EWC of the material, and the value measured with a manual refractometer (EWC_R). This relationship fits well to a linear relationship of the form:

$$EWC_N = 2.162 \cdot EWC_R - 77.10 \qquad \text{(Equation 13.1)}$$

This equation will be used to convert measured values of EWC into the actual values. This relationship has been obtained from previously published work (see chapter 7)[11] adding the values of comfilcon A material that had not been previously measured, and the graphical representation of this conversion is showed in *figure 13.1*. The experimental conditions to evaluate the EWC of the CLs are the same as in previous work conducted in this field (see chapters 7 and 8).[11-13]

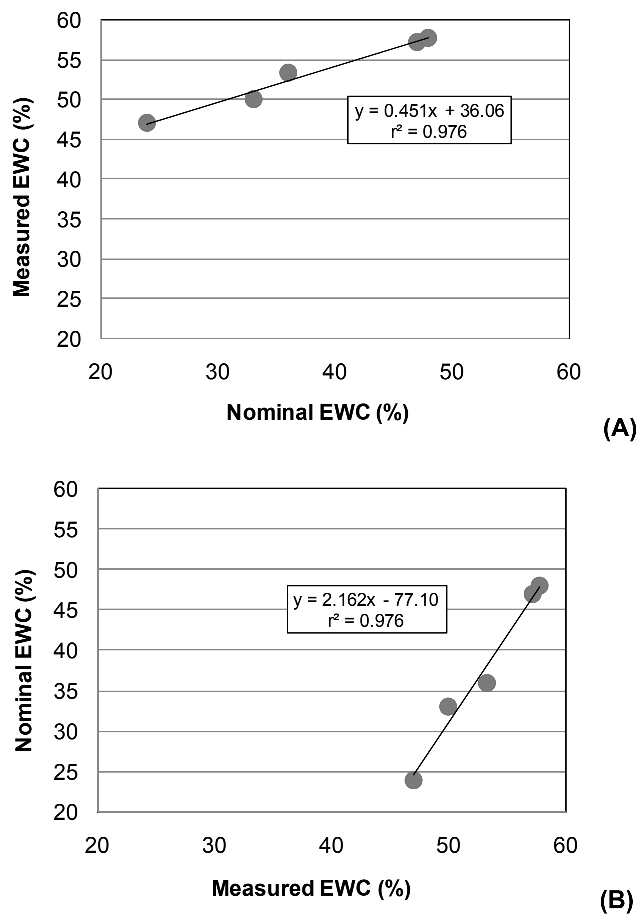


Figure 13.1. Relationship for conversion between the nominal EWC given by the manufacturer and the EWC obtained with the manual refractometer.

13.3.2. Dehydration process

Evaluation of the *in vitro* dehydration process of CLs was performed using a gravimetric method that has been extensively reported in a recent publication.[4] This process has been shown to be reproducible and reliable for repeated measures of the same sample and for different samples of the same material. The repeatability of the *in vitro* dehydration process for lenses of the same material and same refractive power has been confirmed, and is illustrated in *figure 13.2* for lenses of low, medium and high EWC regarding the time progression of the DR parameter (see chapter 10 for further details).

In this study the times of dehydration in the experimental protocol were shorter. While in previous studies lenses were left to dehydrate for 70 to 110 minutes, in the present study, lenses were left to dehydrate for 50 minutes in order to shorten the experimental measurements. This fact will affect those parameters that depend on the final lens weight ($W_{T(f)}$), this is, those parameters derived from the curve of valid dehydration (see chapter 10). However, in the present study, we will concentrate on the initial part of the dehydration rate (DR) curve and in the cumulative dehydration curve (CD). Neither of these curves or the parameters derived from them depends on the final weight of the lens, so the results won't be affected by shortening of the experimental time.

Ten worn samples of each lens were left to dehydrate for 50 minutes following the protocol presented in chapter 10 and average dehydration rate (DR) curves have been obtained for each lens from three repeated measurement sequences (see examples in *figure 13.2*). All lenses had between -2.50 and -3.50 D of refractive power. All lenses were used for 30 days on a daily wear basis and the same multipurpose solution (Renu Multiplus, Bausch & Lomb, Rochester) was used with all lenses. Different quantitative parameters related with DR and CD curves from the worn lenses were compared against those obtained for 10 samples of the same unworn lenses (-3.00 D). Technical details of the lenses used in this study are presented in *table 13.1*. Examples of two repeated DR curves for unworn and worn samples of two different materials are shown in *figure 13.3*.

Statistical analysis was performed using SPSS Software v.15.0 (SPSS Inc, IL). Normal distribution of variables was previously assessed by mean of the Kolmogorov-Smirnov test. When normal distribution of data could not be assumed, Mann-Whitney non-parametric test for independent samples was carried out in order to compare values of EWC, initial dehydration rate during the 1st minute ($DR_{1'}$), average dehydration rate during the first 5 minutes ($AvDR_{5'}$), duration of phase I ($T_{PH\text{-}I}$), cumulative dehydration at the end of phase I ($CD_{PH\text{-}I'}$) and water retention index (WRI_2) between worn and unworn samples. Comparisons involving normally distributed variables were performed using independent samples T-test.

In this case, Levene test was used to assess equality of variances. The level for statistical significance was established for $\alpha = 0.05$.

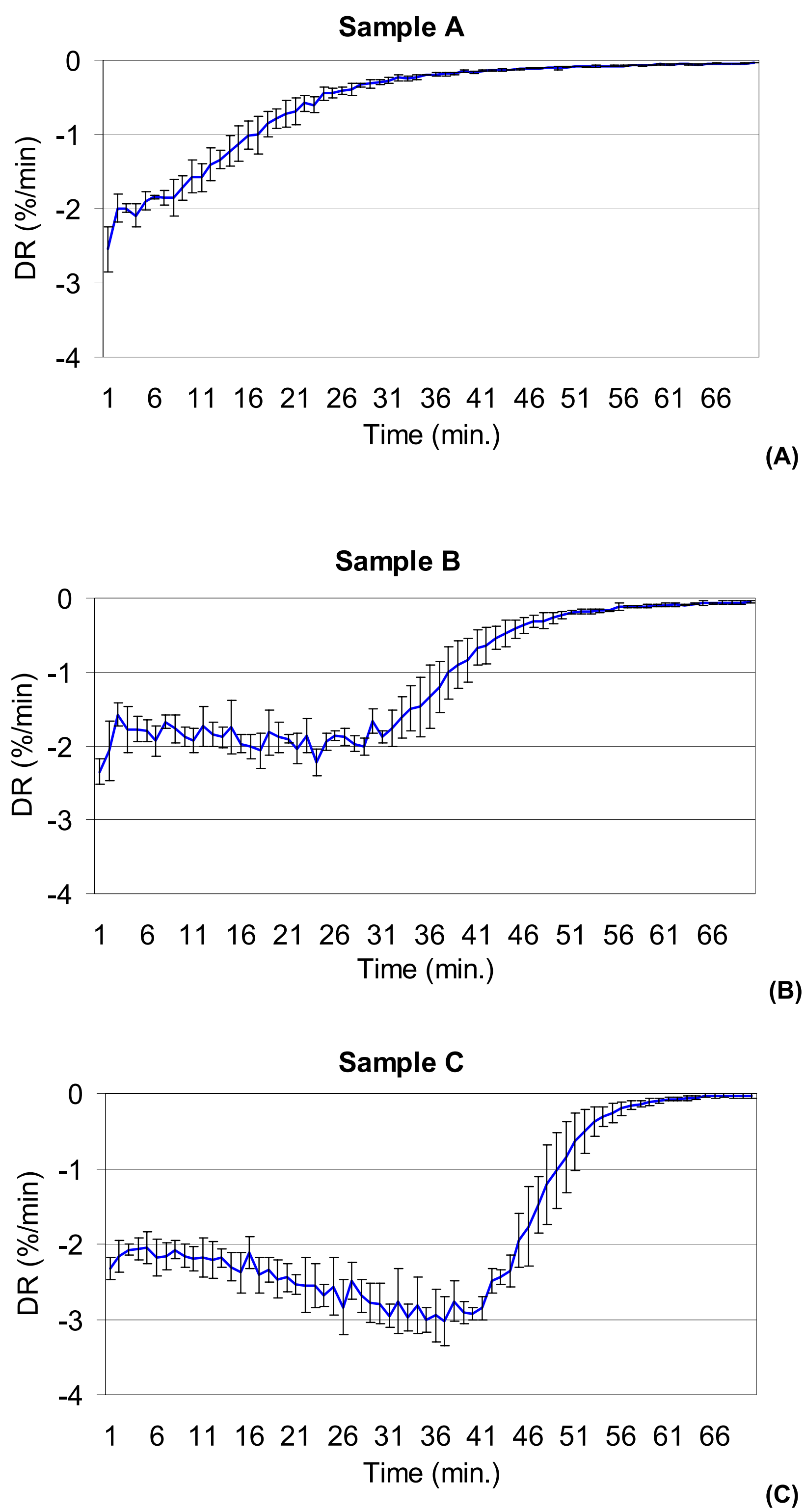


Figure 13.2. Dehydration curves representing dehydration rates (DR) during a period of 70 minutes for samples of three materials: sample A (low EWC), sample B (medium EWC) and sample C (high EWC).

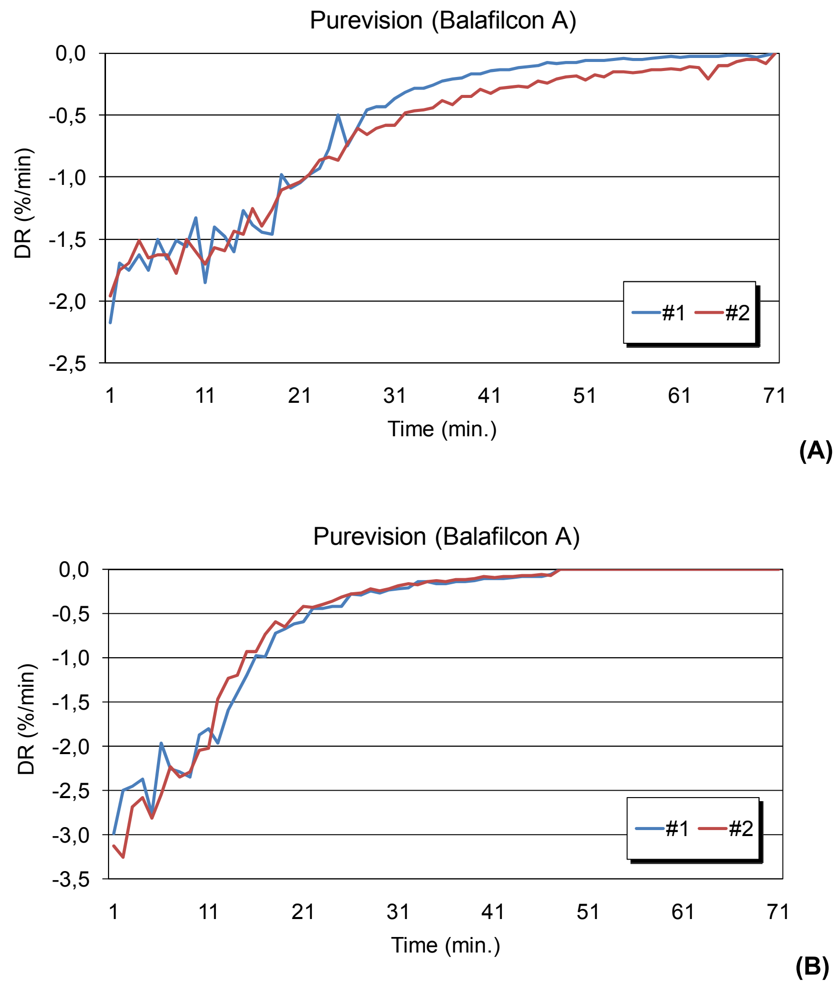


Figure 13.3. Two repeated curves of DR from the same material for a new (A) and a worn CL (B).

13.4. Results

13.4.1. Equilibrium water content

Table 13.2 presents the EWC given directly by the refractometer for the worn lenses and control new lenses made of the same materials.

There is a slight drop in the EWC for worn lenses compared to new samples of the same materials, with the exception of lotrafilcon A material that experienced a slight but statistically significant increase in EWC. On the other hand, galyfilcon A material showed a marked decrease in the EWC of worn lenses, while comfilcon A material, with a similar nominal EWC also showed a statistically significant decrease but significantly lower in quantitative terms. For better visualization of trends, *figure 13.4* displays the corrected values of EWC for unworn and worn CLs. The variability of results expressed by the SD, increased in the group of worn lenses compared with the SD for the same number of new samples in the unworn group. For those materials that experienced a more uniform and moderate decrease in EWC, this values were 2.59 % for balafilcon A, 2.15 % for lotrafilcon B and 2.11 % for comfilcon A.

Table 13.2. Values of EWC measured with manual refractometry for worn and unworn reference samples of the contact lens materials used in this study. Corrected values are underlined

Contact Lens	Unworn Samples (Measured/ Corrected)	Worn Samples (Measured/ Corrected)	Statistical Significance (Corrected)
Air Optix Night & Day *(lotrafilcon A)*	47.00 ± 0.20/ <u>24.55</u> ± 0.43	47.55 ± 0.16/ <u>25.74</u> ± 0.36	0.009‡
Purevision *(balafilcon A)*	53.33 ± 0.58/ <u>38.19</u> ± 1.24	52.13 ± 1.13/ <u>35.60</u> ± 2.43	0.035‡
Air Optix *(lotrafilcon B)*	50.00 ± 0.20/ <u>31.01</u> ± 0.43	49.00 ± 0.22/ <u>28.86</u> ± 0.47	0.002‡
Acuvue Advance (galyfilcon A)	57.13 ± 0.12/ <u>46.37</u> ± 0.25	52.70 ± 0.71/ <u>36.82</u> ± 1.52	<0.001‡
Biofinity (comfilcon A)	57.73 ± 0.12/ <u>47.66</u> ± 0.25	56.76 ± 0.44/ <u>45.55</u> ± 0.95	<0.001‡

† Independent samples T-test; ‡ Mann-Whitney
The corrected values underlined correspond to the data used to calculate statistical significance

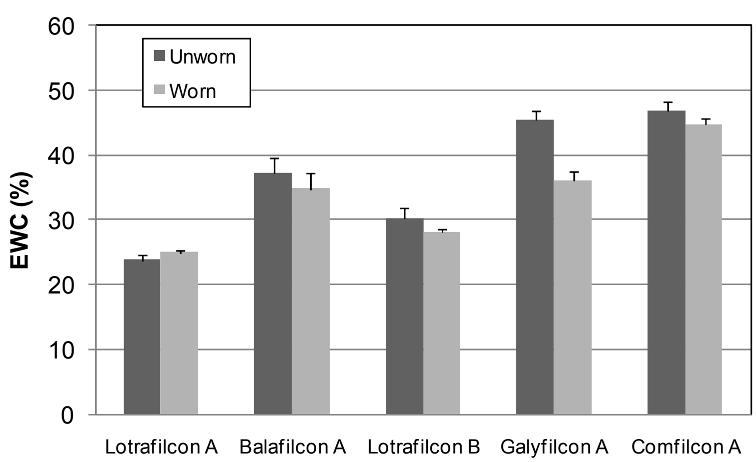


Figure 13.4. Corrected values of EWC measured with manual refractometry for worn and unworn reference samples.

13.4.2. Dehydration curves

Qualitative comparisons of dehydration rate (DR) curves between unworn and worn samples of the same materials show a general trend towards higher initial DR for worn samples that is maintained for a shorter time during the first minutes of the dehydration process and also a shorter phase I (*figures 13.5A to 13.5E*). One exception to this trend is seen for lotrafilcon A material. Such changes in the profile of phase I cannot be observed because the absence of this phase is a characteristic of this material (*figure 13.5A*) as previously reported.[4,14] However the same trend towards a more negative initial DR value is also present.

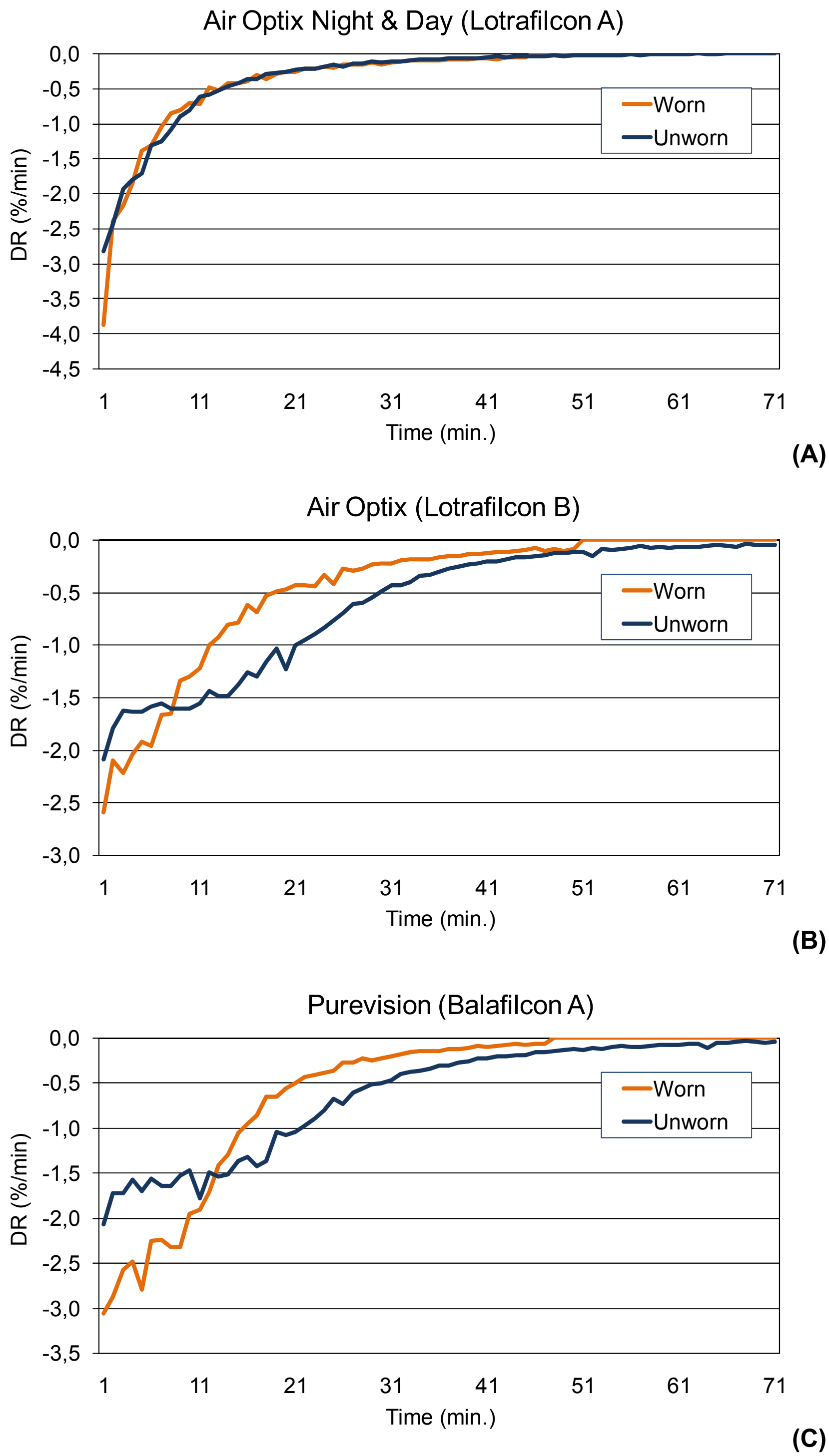
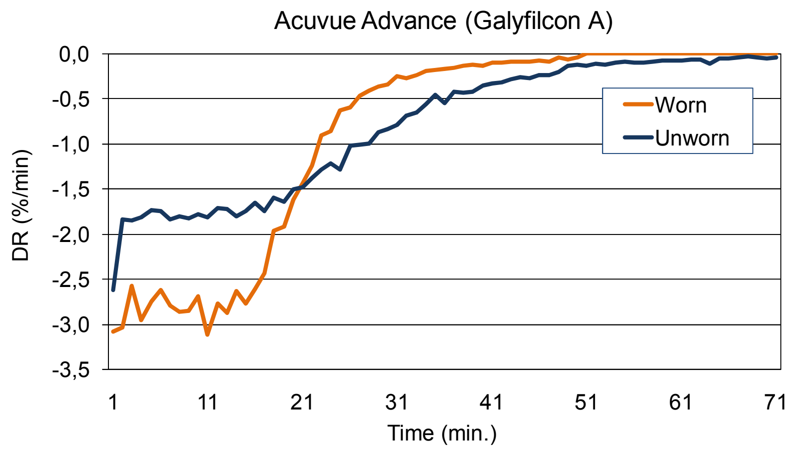
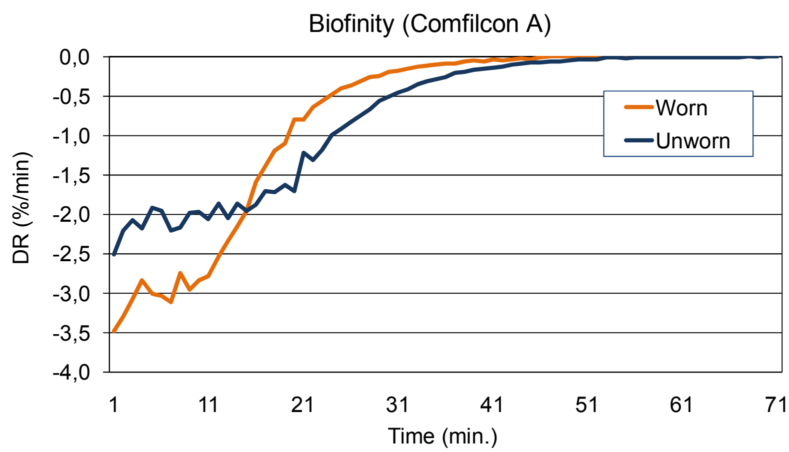


Figure 13.5. Examples of profiles of dehydration rates for worn and the corresponding unworn samples for lotrafilcon A (A), lotrafilcon B (B) and balafilcon A (C).



(D)



(E)

Figure 13.5 *(cont.)* Examples of profiles of dehydration rates for worn and the corresponding unworn samples of galyfilcon A (D) and comfilcon A (E).

The difference in initial dehydration rate is about 1%, being more negative in worn samples than in unworn samples of the same material. Due to the higher dehydration during phase I, phase II of the dehydration rate is characterized by lower values of DR in worn samples than in the unworn reference samples creating a "gap" between both curves at this level. These qualitative facts are quantified in the following parts of the results.

Tables 13.3 to *13.7* present the values of the five quantitative dehydration parameters for unworn and worn samples of the materials along with statistical significant of the differences. As expected, the qualitative characteristics previously described are confirmed statistically in quantitative terms. With just a few exceptions, all differences between unworn and worn samples were statistically significant. These exceptions include the value of initial dehydration for galyfilcon A material (p = 0.062), value of average dehydration during the first five minutes for lotrafilcon A (p = 0.123) and water retention index for lotrafilcon A (p = 0.096). For the remaining parameters, statistically significant differences were observed

(p < 0.05). Initial dehydration rate ($DR_{1'}$) and average dehydration rate ($AvDR_{5'}$) were significantly increased in worn lenses. The average increase in $DR_{1'}$ was 0.9 % per min. from 2.4 ± 0.4 to 3.3 ± 0.3 % per min. for unworn and worn sample, while the average difference for $AvDR_{5'}$ was of 0.7 %, changing from 2.0 ± 0.2 to 2.7 ± 0.4 % per min (*tables 13.3 and 13.4*, respectively). These results are also graphically presented in *figures 13.6* and *13.7*.

Duration of phase I decreased significantly in worn lenses for all materials that presented this phase in the DR curve (*table 13.5* and *figure 13.8*). It seems that the drop in this parameter after the lenses had been worn is very similar among materials, although more significant for lotrafilcon B. Conversely, the changes in CD seem to follow a random trend once the lenses had been worn, decreasing for some samples, remaining unchanged for one material and increasing for another one (*table 13.6* and *figure 13.9*). Water retention index parameter also decreases significantly with lens wear from an average value of 51.9 ± 5.9 % to 38.0 ± 5.1 % (*table 13.7* and *figure 13.10*). Except for lotrafilcon A, all materials presented a similar drop of about 1/3 in their ability to resist dehydration during the first 5 minutes exposed to dehydration according to the value of WRI_2.

Table 13.3. Statistical comparison between worn and unworn reference samples for the values of initial dehydration rate during the 1st minute ($DR_{1'}$)

Contact Lens ***(Material)***	**Unworn Samples (n=10)**	**Worn Samples (n=10)**	**Statistical Significance**
Air Optix Night & Day *(lotrafilcon A)*	2.84 ± 0.18	3.76 ± 0.23	0.002‡
Purevision *(balafilcon A)*	2.12 ± 0.12	3.01 ± 0.25	<0.001†
Air Optix *(lotrafilcon B)*	1.86 ± 0.21	3.02 ± 0.52	<0.001†
Acuvue Advance *(galyfilcon A)*	2.76 ± 0.51	3.10 ± 0.15	0.062†
Biofinity *(comfilcon A)*	2.56 ± 0.11	3.55 ± 0.16	<0.001†

† Independent samples T-test; ‡ Mann-Whitney

Table 13.4. Statistical comparison between worn and unworn reference samples for the values of average dehydration rate during the first 5 minutes (Av $DR_{5'}$)

Contact Lens ***(Material)***	**Unworn Samples (n=10)**	**Worn Samples (n=10)**	**Statistical Significance**
Air Optix Night & Day *(lotrafilcon A)*	2.07 ± 0.17	2.23 ± 0.12	0.123‡
Purevision *(balafilcon A)*	1.73 ± 0.11	2.63 ± 0.13	<0.001†
Air Optix *(lotrafilcon B)*	1.76 ± 0.15	2.51 ± 0.31	<0.001†
Acuvue Advance *(galyfilcon A)*	2.03 ± 0.39	2.86 ± 0.10	<0.001†
Biofinity *(comfilcon A)*	2.28 ± 0.19	3.16 ± 0.15	<0.001†

† Independent samples T-test; ‡ Mann-Whitney

Table 13.5. Statistical comparison between worn and unworn reference materials for duration of phase I (T_{PH-I})

Contact Lens ***(Material)***	**Unworn Samples (n=10)**	**Worn Samples (n=10)**	**Statistical Significance**
Air Optix Night & Day *(lotrafilcon A)*	-	-	-
Purevision *(balafilcon A)*	18.00 ± 2.31	10.11±0.99	<0.001†
Air Optix *(lotrafilcon B)*	17.7 ± 2.27	5.70 ± 0.67	<0.001‡
Acuvue Advance *(galyfilcon A)*	24.3 ± 2.50	15.70 ± 1.83	<0.001†
Biofinity *(comfilcon A)*	16.70 ± 2.98	9.60 ± 0.70	0.002‡

† Independent samples T-test; ‡ Mann-Whitney

Table 13.6. Statistical comparison between worn and unworn reference materials for values of cumulative dehydration at the end of phase I (CD_{TPH-I})

Contact Lens *(Material)*	Unworn Samples (n=10)	Worn Samples (n=10)	Statistical Significance
Air Optix Night & Day *(lotrafilcon A)*	-	-	-
Purevision *(balafilcon A)*	24.43 ± 1.06	23.31 ± 1.21	0.060†
Air Optix *(lotrafilcon B)*	24.63 ± 1.88	14.99 ± 1.37	<0.001†
Acuvue Advance *(galyfilcon A)*	32.89 ± 1.58	36.32 ± 1.90	<0.001‡
Biofinity *(comfilcon A)*	31.38 ± 4.12	26.41 ± 0.95	0.004†

† Independent samples T-test; ‡ Mann-Whitney

Table 13.7. Statistical comparison between worn and unworn reference materials for values of water retention index obtained from the CD at the end of first 5 minutes (WRI_2)

Contact Lens *(Material)*	Unworn Samples (n=10)	Worn Samples (n=10)	Statistical Significance
Air Optix Night & Day *(lotrafilcon A)*	48.70 ± 3.76	45.00 ± 2.44	0.096†
Purevision *(balafilcon A)*	58.21 ± 4.01	38.04 ± 1.82	<0.001†
Air Optix *(lotrafilcon B)*	57.25 ± 4.91	40.42 ± 4.90	<0.001†
Acuvue Advance *(galyfilcon A)*	51.02 ± 10.09	34.98 ± 1.20	0.001†
Biofinity *(comfilcon A)*	44.18 ± 3.71	31.76 ± 5.42	<0.001†

† Independent samples T-test; ‡ Mann-Whitney

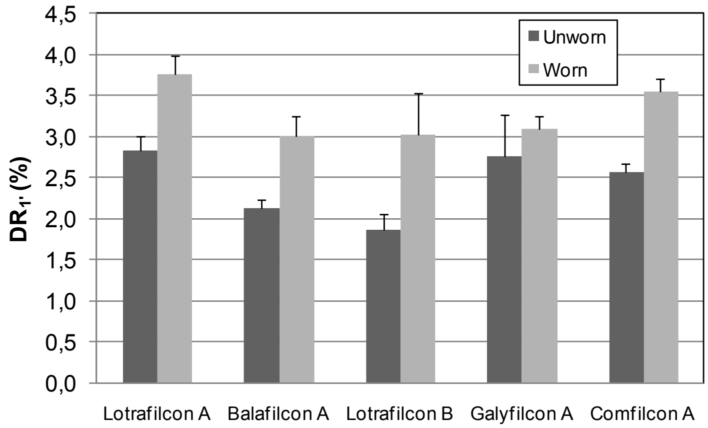


Figure 13.6. Values of initial dehydration rate during the 1st minute ($DR_{1'}$) for worn and unworn samples.

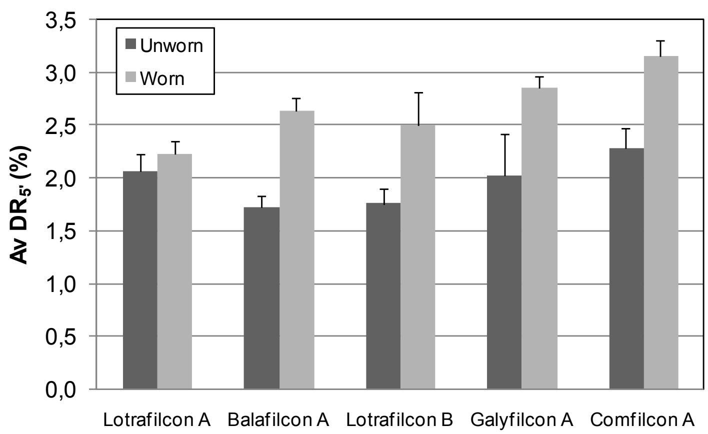


Figure 13.7. Values of average initial dehydration rate during the first 5 minutes (Av $DR_{5'}$) for worn and unworn samples.

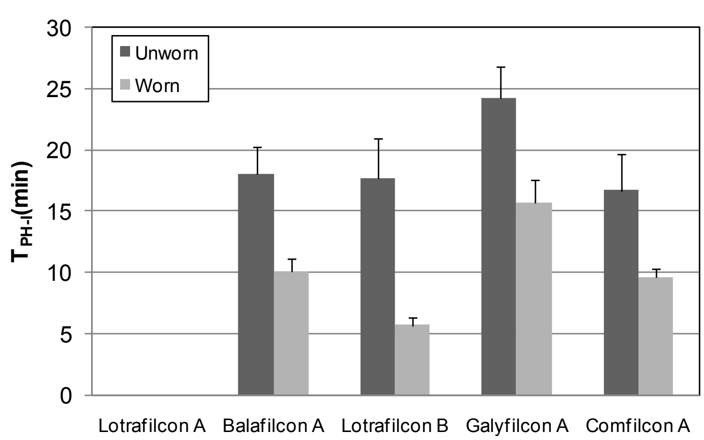


Figure 13.8. Duration of phase I (T_{PH-I}) in the DR curves for worn and unworn samples.

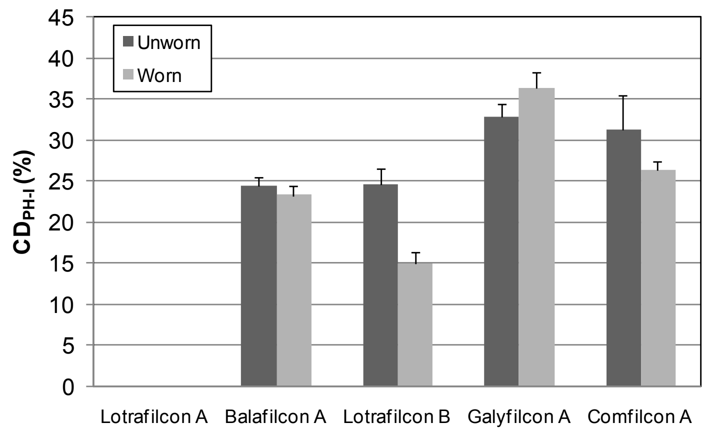


Figure 13.9. Cumulative dehydration at the end of phase I (CD_{TPH-I}) for worn and unworn samples.

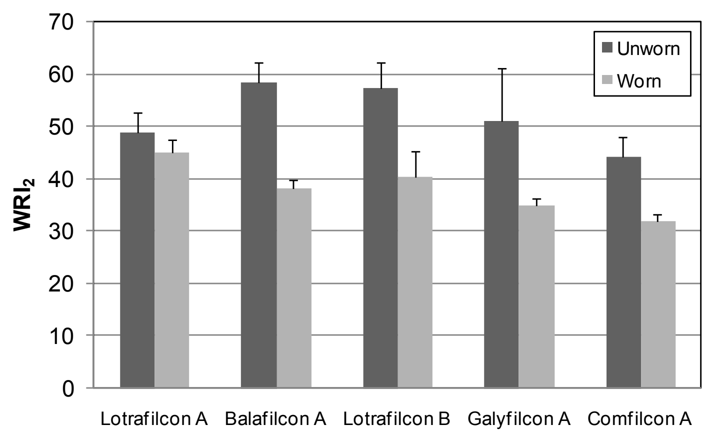


Figure 13.10. Water retention index values obtained from the CD at the end of first 5 minutes (WRI_2) for worn and unworn samples.

13.5. Discussion

The values of EWC measured after the lenses had been worn decreased significantly for most of the materials evaluated. It should be highlighted the small SD of results and the close agreement between EWC of unworn lenses with those values given by the manufacturers once the measured values were corrected using equation 13.1. This is in agreement with our previous experiences measuring EWC and RI with manual and automated refractometry, respectively.[11,13] The higher degree of dehydration in galyfilcon A material cannot be considered as a definitive fact until further work analyzing more samples will be conducted.

However, beyond the values of EWC obtained with the refractometer, the main outcomes of this study are the objective, repeatable and measurable differences in the dehydration pattern of worn Si-Hi lenses compared with unworn samples of the same materials. These changes are statistically significant for most of the parameters of short term dehydration.

Despite many other parameters can be derived from the methodology of data processing used in this work,[4] we have concentrated on the evaluation of the initial dehydration phase. These parameters have potential influence on the *in vivo* dehydration process of CLs. The shorter phase I could be explained with a more rapid elimination of the superficial layers of water due to rapid initial dehydration.

Phase I profile was one of the main qualitative aspects characterizing the in vitro dehydration of materials, showing a high correlation with the EWC of the material in a previous study.[4] Also, this parameter reflects the behavior of the CL regarding to retention of hydration in the short term. If there could be some link between the behavior of the CL under *in vitro* and *in vivo* conditions, this phase of the in vitro dehydration will be certainly the more important.

CL intolerance related to dryness symptoms and discomfort are more common among CL wearers (see chapter 2).[15] This is considered a major limitation for CL market grow-up in the present days as many drop-outs in the CL wear population are due to discomfort-related problems.[16,17]

A study from Morgan *et al.*[9] showed that dehydration of CLs begins soon after the lenses are placed on the eye as the lens has to equilibrate its hydration on a new environment. This dehydration continues during the day and is also evidenced after 1 month of lens wear as a decrease on the ability of the lens to fully re-hydrate to reach its initial nominal EWC.[9] The same study showed an average dehydration value after one month of wear of 2 to 2.5% drop compared to the initial EWC of the lenses, with the lens made of etafilcon A presenting a higher dehydration.[9] Our results for balafilcon A, lotrafilcon B and comfilcon A are in total agreement with these values.

In the present study, we have demonstrated that the *in vitro* dehydration process of different Si-Hi materials is seriously altered after 1 month of wear (15 days for galyfilcon A material). The higher initial dehydration suggests a decrease in the ability of the external CL surface to keep the hydration. This also accelerates the average initial dehydration rate. In a previous study, we have observed that in high EWC the average dehydration rate increases after the lens have lost its more external liquid layer,[4] which is also observed in *figure 13.2C*.

The changes in the quantitative parameters investigated in this work affect particularly the initial dehydration parameters and this is relevant information from the clinical point of view as the in vitro dehydration during the first instants after the lens is exposed to dehydration will probably have some relationship with the *in vivo* behavior. Although some studies have failed to correlate the dehydration of contact lens materials with subjective symptoms of discomfort and dryness,[18,19] the relationship between our *in vitro* dehydration parameters and subjective tolerance of SCLs is yet to be confirmed.

The changes in the initial dehydration parameters will be probably linked to polymeric changes occurring at the most external surface because of re-arrangement of hydrophilic and hydrophobic parts of the molecules, and this could have negative effects on other clinically relevant aspects related to CL deterioration as deposit formation. In fact, both mechanisms could be related as several authors consider that the dehydration of the outer CL surface leads to an external rotation of the hydrophobic parts of the polymer, thus inducing more dehydration and offering more locations for hydrophobic interactions what could increase the incidence of lipid depositions, otherwise more common in Si-Hi materials.

Changes in surface hydration and perhaps other changes in the surface of the CL with time of lens wear are a logical consequence of deposit formation. However, wettability of CL surfaces of first generation Si-Hi did not change significantly after being worn.[20] Moreover, in the short-term, some tear components adhered to the CL surface could even improve wettability of Si-Hi materials.[7,8] In a study comparing two CLs, differences in the wetting angle were reduced after both lenses were worn indicating some normalization effect induced by tear components.[7] However, results from other authors suggest a dynamic behavior with an improvement in this parameter immediately after the lens was placed on the eye,[6] and a reduction for longer periods of wear.[5] In our opinion, this is the more likely mechanism explaining the relations between organic tear deposit formation and CL wettability. From the results of the present study, although an improvement in lens surface wettability could be expected after lens insertion in the short-term, the long term effects of wear seem to be related with a loss in the material ability to maintain the interaction of the external material surface and water molecules. In a previous work, we have observed that after the first amount of water is evaporated from the surface of high EWC SCLs, the dehydration rate increases until the end of phase I. The observation of higher initial dehydration rate derived from this study for all lenses could be related with the absence of a stable superficial water layer, probably due to deposit formation with fewer places for water to bind at the CL surface. Extrapolating this data to the clinical point of view, we could expect that in patients with poorer tear stability, the dehydration rate will increase once the lens has become contaminated after several days or weeks of wear. Thus, the controversy of high vs low EWC lenses for patients with tear deficiency could be solved, at least in patients whose deficiency is due to poor tear stability. In these cases, the rapid lost of the superficial tear film over the lens will rapidly increase the dehydration rate of high EWC lenses. This process could be exacerbated by the higher presence of deposits in high EWC lenses. So for these patients, high EWC lenses should be avoided, which is in agreement with the recommendations of Tomlinson and Caroline.[21] This effect of higher dehydration will be more evident with high EWC SCL and certain environmental conditions. This hypothesis is supported by the studies of Maruyama *et al.*[22] who showed that poor tear stability will be present with such a combination of high EWC and low temperature/dry environmental conditions. New approaches to improve Si-Hi lens wettability and reduce deposit formation could be of help to maintain the lens capacity to remain hydrated for longer periods. Surface treatments other than the plasma treatments presently used with Si-Hi materials are obtaining promising results.[8] The use of surfactants also improved the wettability of a conventional hydrogel CL, increasing the comfort.[23]

In summary, we have observed changes in the *in vitro* dehydration process of Si-Hi CL materials even without a significant change in the EWC of the materials after being worn for 1 month. Further steps in this line of research will consider the effect of different CL care solutions and simulated environmental conditions on the quantitative parameters of dehydration, particularly in the short term (phase I). It will be also interesting to understand how much time of wear will be needed to induce definitive changes in the ability of the CL material to maintain its hydration, or to evaluate if any care solution as MPS, hydrogen peroxide, enzymatic cleaning, surfactants, or combinations of them could be effective to resume the properties of the material regarding water retention, what could be reflected in the normalization of the DR curve, becoming more similar to the curve that characterize unworn samples of the same material. If any of this situations has a potential effect on the dehydration process of the lens, it should be demonstrated in statistical terms using the *in vitro* dehydration parameters. The following step will be considering the potential extrapolation of any beneficial/worsening effects to the clinical field.

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Chapter 14

General Overview of Results, Conclusions and Future Work

14.1. General Discussion

The contact lens (CL) market is changing rapidly, with the incorporation of new materials every year. Some of these materials as it was the case of silicone hydrogels (Si-Hi) use radically different approaches to meet the higher levels of biocompatibility with the ocular surface in terms of oxygenation and hydrophilic surface structure.[1-4] However, other problems arise with the use of such materials, at least with the first generation Si-Hi materials. It was the large amount of research conducted with these materials in the present decade that has made possible that in less than 5 years the industry had reacted with the creation of improved materials without discarding the benefits of this technology, that represents more than 20% of new fits and refits in several countries worldwide.[5,6]

Despite the evolutions in CL material engineering, CL wearers still complain of discomfort, particularly at the end of the day and in certain environmental conditions,[7-11] and this is believed to cause numerous drop-outs each year that are not compensated by the new wearers,[12-14] making that the CL market is considered as stagnant or recessive by many people. This happens despite the high levels of safety and efficacy of current contact lenses (CLs) and the relatively low incidence of adverse reactions and serious complications.[15-17]

The demands of the patients in terms of all day comfort and prolonged wearing time are high and the difference between a tolerant (asymptomatic) and an intolerant (symptomatic) patient wearing CLs is not still fully understood from the perspective of ocular surface physiology[18,19] and its relationship with the CL material.[20]

All these facts motivated that CL research had moved towards "smaller scales" searching for a better characterization of CL material properties, ocular surface structure and physiology and interaction with the CL materials, bacterial interaction with the ocular surface and CLs, the behavior of water inside and outside the polymeric meshwork, deposits formation and other forms of material deterioration. The present Thesis has tried to be a contribution in this direction towards the closer observation of CL materials and their changes as a consequence of wear.

In the present work we have measured objectively several changes in the CL properties that could potentially affect the clinical performance of these materials after two to four weeks of wear, even when compliance with the care systems is warranted. These changes can be summarized in the following aspects:

1) Increase in surface roughness was observed in almost all lenses being analyzed, even after very short periods of wear, however the quantitative change of roughness parameters is different for different materials.
2) Beyond the topographic appearance of the CL surface and the qualitative and quantitative changes associate to lens wear, the present work has also revealed that the mechanical response of the CL surface to the nanoindentation with AFM, changes significantly in some lenses. Although a uniform trend could not be established, there is a general trend towards increase in the elastic modulus of the surface in worn lenses.
3) Worn lenses displayed a lower EWC as measured with refractometry than new samples of the same materials, suggesting that the deterioration of the polymer is associated with a lower ability of the CL to remain hydrated at its surface, and probably within the polymeric meshwork as well.
4) Finally, the quantitative parameters of dehydration under *in vitro* conditions showed that all lenses analyzed in this work partially loss the ability to remain hydrated after being worn by patients when compared with new samples of the same materials. This fact affects primarily the indicators of initial water retention within the first minutes of the dehydration process.

The increase in surface roughness is certainly related with deposit build up. If the biochemical characterization of deposits on CLs has claimed much attention within the scientific community,[21-24] being possible to characterize the relationships between material properties and the formation of certain deposit entities,[22,23,25-29] the impact of these elements on the CL surface has not been equally studied in a systematic manner. The work of Bathia, Goldberg *et al.*[30,31] is to be highlighted as they reported images of conventional hydrogel SCL observed with AFM, and described the changes with wear from a qualitative point of view. However, since their pioneer work, few publications have considered the systematic observation of the surface topography of unworn and worn CLs, particularly regarding new Si-Hi materials. The qualitative and quantitative results presented in this work will certainly contribute to improve the knowledge of surface changes occurring in CL's as a consequence of deposit formation and perhaps have implications in the understanding of the relationship between the CL and the ocular surface.

The changes observed in the elastic modulus are not so simple to justify. The first logical explanation to justify an increase in the rigidity of the material is the lower hydration of the CL, which could be more accentuated at the surface. Despite this is an obvious explanation, this reason cannot justify why some lenses present a higher increase in modulus than did other lenses. Of particular relevance is the fact that galyfilcon A was the material presenting a more evident drop in EWC (chapter 13), but did not show an increase in the modulus of the CL surface on nanoindentation with AFM (chapter 12). Changes at the CL surface are supported by the fact that this is the part of the CL most directly exposed to air. Opdahl et al demonstrated using AFM that CL materials dehydrated at a higher rate in low relative humidity environments, while the polymer could still remain hydrated.[32]

Other explanation for the higher rigidity of the surface of the materials after being worn could rely on the formation of plaques of deposits, particularly of denaturized proteins. The potential association between higher denaturized proteins in Si-Hi CL,[27] along with a higher modulus of this material, could help to explain the higher incidence of CLGPC in Si-Hi CL wearers.[33] Maldonado-Codina *et al.*[34] found different patterns of incidence of CLGPC between two Si-Hi CLs with different mechanical and surface properties. This suggests that mechanical interaction has an important role in CLGPC related with Si-Hi[35] and this effect could be worse if CL increase their modulus with wear. However, at present, we do not know which influence could have lipids or protein (in normal state or denaturized) in the mechanical behavior of the CL surface. The potential effects of modulus on other aspects of the histological structure and physiological function of the cornea[36] is to be further investigated.

The dehydration of CL materials is a natural process, and occurs immediately even in new lenses in order to re-equilibrate with the ocular environment after removal from the storage case. However, it can be exacerbated under certain environmental conditions,[9,37] although not all authors agree with this fact,[10] and in the presence of tear deficiency.[38] High EWC CLs suffer from more dehydration,[9] and are still considered a risk factor for contact lens-related dry eye.[39] The results of this work clearly show that all lenses present poorer indicators of water retention in the short term after being worn for the period of 15 days to 1 month. This effect could explain why some patients have to replace their lenses before the period recommended by the practitioner. Considering that the short term dehydration rate increases naturally with the EWC of the material or when the superficial layer of water is removed from medium and high EWC materials, patients wearing these lenses can be at higher risk of suffering from CL intolerance when the lenses had been worn for several days or weeks. Moreover, those patients with poorer tear quality and poor stability should not be fitted with high EWC lenses, even if they have a satisfactory tear secretion, because the instability of the superficial tear film over the lens would result in a more rapid dehydration of the CL, potentially driven to epithelial desiccation and corneal staining. Our results support present theories of pre-lens tear film thinning used to explain at least in part the contact lens-related dry eye[39,40] attributing a higher potential of dehydration to high EWC SCL.

Virtually, we can link all our findings in a circle of CL deterioration in which each element serves as a feedback mechanism for the remaining elements, with effects on the integrity of the ocular surface. A poorer hydration of the CL surface will induce a more rapid dehydration of the bulk of the CL, and this dehydration will help to bind deposits to the lens surface and into the porous structure of the gel; all these mechanisms will result in a more rigid, irregular and dry surface with an exacerbated mechanical interaction with the ocular surface. This interaction occurs at the anterior side of the lens with the palpebral conjunctiva leading to higher incidence of CLGPC, and at the posterior surface leading to higher incidence of mechanical trauma to the corneal and conjunctival epithelium (keratitis, arcuate lesions, conjuntival indentation), dehydration and solid debris formation behind the CL (mucin balls). Finally, these effects will stimulate the inflammatory responses and affect corneal structures at a deeper level (infiltrative keratitis, changes in keratocyte density). This could be particularly relevant in high EWC and patients with higher potential of deposit formation. For these patients, such lenses should be avoided once that all concurrent events will lead to higher dehydration and contamination, potentially driving to contact lens-related dry eye and contact lens intolerance, which make a significant part of patients to consider their lenses as an inappropriate way of correction and later to contact lens drop-out.[41]

Perhaps the best way to break the chain relays on a better hydration of the CL surface that will prevent more rapid dehydration, deposit consolidation on the lens surface resulting in a smoother CL surface. New formulations are necessary to improve the physiologic tolerance of CL biomaterials, particularly in those aspects related to the polymer ability to reach and maintain the nominal EWC after being worn.

14.2. Conclusions

The work developed and presented in this Thesis integrates several potential techniques to be included in a routine for the objective evaluation and characterization of CL biomaterials in their original state and after deterioration with wear. With this work we have achieved a more exhaustive knowledge of physic-chemical behavior of biomaterials used for CL manufacture and how some of their properties can change as a result of wear. The main outcomes of this work can be summarized as follow:

- Silicone hydrogel already represent a very important part of the CL market despite their limited availability in terms of brands and designs when compared with conventional hydrophilic and RGP lenses;

- Discomfort an contact lens-related dry eye symptoms are relatively frequent in soft contact lens wearers, particularly in females. There are some symptoms that are more prevalent among the SCL wearers as scratchiness;

- The association between Si-Hi contact lens wear and exposure to potentially aggressive environments as air conditioning rooms or prolonged time of video display terminal will be a common scenario in the following decades in contact lens practice;

- We have characterized several important physic-chemical properties of some of the biomaterials most frequently used in, and their changes as a consequence of wear under daily wear conditions, the most common schedule in current CL practice;

- The classical relationships between EWC and refractive index used for conventional hydrogels based on HEMA (Brix scale) are no longer valid for silicone hydrogel materials. However, they seem to follow a predictable mathematical relationship, so this could be implemented in new refractometers;

- Atomic force microscopy is an effective and high resolution tool to characterize the topographical and surface mechanical properties of soft contact lenses in the hydrated state;

- At a nanometric scale, the surface topography of SCLs is distorted with an overall increase in surface roughness parameters even after very short periods of time. In initially smoother surfaces, deposits increase significantly the roughness, while in other more irregular surfaces, lens wear increase roughness at a lower extent;

- The changes in the mechanical behavior of the CLs when measured with nanoindentation techniques could have clinical impact on the relationship between the CL surface and the ocular surface, particularly at the level of most superficial corneal and conjunctival cells;

- The ability of the CL material to remain fully hydrated decreases with time of wear. According to our results, as a general rule, the EWC of the CL partially decreases overtime and the nominal EWC (value before lens had been worn) is not totally reached in the end of the life-time of the lens. The dehydration curves also demonstrate that significant changes in the speed of dehydration are expected, with higher initial dehydration rates and a lower values of water retention index;

- The deterioration of polymeric properties related with hydration maintenance could affect particularly those patients exposed to prolonged work with computers and video display terminals. The first reason is that more people is nowadays exposed to these environmental aggressions, and the second one is that CL wear still induce significant changes in the relationship between the material and hydration agents even when care and replacement schedules are respected.

14.3. Future Work

From the discussion of the contents of this work and the main outcomes and conclusions quoted above new questions have raised that should be addressed in the future using the knowledge acquired during the preparation of the present Thesis. They primarily arise from the application of the routines of examination presented here. Examples of areas with potential interest for the industry and clinicians are the following ones:

- Extend the present characterization routine to other materials not assayed in this project with major relevance in current CL practice;

- Systematic evaluation of new materials that would be launched to the market in the following years and comparison with other already available at the moment;

- Clinical project involving subjective responses from the patients and objective and subjective clinical variables that could reflect the impact of differences in the material's properties observed objectively using the experimental routines used in this work;

- The association between Si-Hi contact lens wear and exposure to potentially aggressive environments as air conditioning rooms or prolonged time of video display terminal will be a common scenario in the following decades in contact lens practice and the impact of such combination must be investigated;

- As new silicone hydrogel materials will be deliver to the market even in an extended EWC range, it should be possible to develop a new model to accurately predict the EWC of the material as a function of its refractive index;

- will be possible to Further investigations on the surface topography, dehydration process and mechanical parameters with different wearing times or in materials submitted to artificial ageing processes under *in vitro* and *in vivo* conditions;

- The nanometric topography of the inner and outer CL surfaces and the changes associated with CL wear should be analyzed separately in order to evaluate the potential of the CL surface interaction with both the corneal and bulbar conjunctiva (posterior lens and edge) and tarsal conjunctiva (anterior CL surface);

- To evaluate the dehydration process of different CL materials with different care solutions and artificial tears in order to determine which combination can be more suitable to maintain the hydration of the CL for longer periods of time. These experiments could also be carried out with solutions simulating the natural composition of the tears (proteins, lipids, ions,...);

- Correlate the behavior of CLs materials on *in vitro* dehydration experiments with parameters of free, bound and intermediate water proportions obtained with thermo-gravimetric methods;

- Analyze the actual on-eye dehydration of CLs with refractometry and gravimetric methods in order to differentiate between surface dehydration and bulk dehydration;

- Evaluate the in vitro dehydration process of CLs under different environmental conditions and try to correlate it with the subjective response of patients under similar conditions.

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"Science is about searching for the truth
in order to explain why things happen"
Anonymous

"A Ciência está sempre em falta. Nunca
soluciona um problema sem criar outros dez"
George Bernard Shaw

"O fim de qualquer exploração é chegar ao
ponto de partida e conhecer o lugar pela
primeira vez"
Thomas S. Eliot

"Nunca se descobriria nada se ficássemos
satisfeitos com o que já se descobriu"
Séneca