OCULAR RESPONSE TO SILICONE-HYDROGEL CONTACT LENSES

JACINTO SANTODOMINGO RUBIDO

Doctor of Philosophy

NEUROSCIENCES RESEARCH INSTITUTE
ASTON UNIVERSITY

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Summary
The thesis investigates the ocular response to silicone-hydrogel (SiH) contact lens wear, a relatively new contact lens material that has a higher modulus of rigidity and different surface coating than used in conventional hydrogel materials. The properties of SiH materials differ significantly from conventional hydrogels and, using subjective and objective means of assessment, the thesis examines how these properties affect refraction and biometry, ocular physiology, tear film characteristics, symptomatology, adverse events and complications. A range of standard and newly designed investigative techniques were employed, the latter involving novel imaging techniques, for the objective assessment of physiological changes which occur with contact lens wear. The study is the first to combine these techniques with biochemical analyses of the tear film composition.

Forty-seven subjects were fitted with SiH lenses and randomly allocated to one of the two materials currently on the market (Lotrafilcon A or Balafilcon A) on an either daily or continuous wear basis. An additional control group of 14 age-matched non-contact lens wearers were monitored over the same period. Measurements were taken before and 1, 3, 6, 12 and 18 months after initial fitting.

Refraction and biometry- Myopia increased significantly in subjects wearing Lotrafilcon A lenses on a daily wear basis and was accompanied by a correlated increase in axial length. However, no significant relationship was found between change in refractive error and the amount of near work undertaken, or in initial axial length/corneal curvature ratio. Possible reasons for the increase in myopia include a directly induced physical/physiological contact lens effect, a higher rate of progression for the lower level of myopia evident in the group, and finally that compromised immunology due to contact lens wear may trigger ocular growth in the posterior segment. Contact lenses may also induce more myopia by virtue of generating a different peripheral image shell compared to spectacles.
Ocular physiology- An increase in bulbar, limbal and palpebral hyperaemia was observed in most of the contact lens groups and could be attributed to mechanical effects induced by the contact lenses. An increase in corneal staining was also observed in all contact lens groups and could again be attributed to mechanical effects and, in addition, to epithelial microtrauma induced by mucin balls. The relationship between subjective and objective measures was also investigated.
Tear film characteristics- Clinical measures of tear film characteristics showed little difference between materials and regimes of wear, whereas biochemical results appeared to be more sensitive in detecting subtle changes in tear film composition. An increase in the positive incidence of protein specific markers such as kininogen and IgE was found with contact lens wear and in certain adverse events. Lipid deposition profiles were higher with Balafilcon A lenses and could be attributed to the higher hydrophobicity of the lens surface compared to Lotrafilcon A lenses.
Symptomatology- Dryness was the most commonly reported symptom. However, generally symptoms were mild and the high subjective acceptance judgements reported by all contact lens groups suggest that overall the clinical performance of SiH lenses is very high.
Adverse events and complications- Mechanically induced events, such as contact lens papillary conjunctivitis and superior epithelial arcuate lesions were found and are likely to occur as a result of the slightly stiffer nature of SiH materials compared to conventional hydrogel lenses together with poor lens wettability. Inflammatory conditions such as contact lens peripheral ulcers were also found possibly as a result of bacteria infiltration through a compromised epithelium. Other complications such as scleral indentation and increased meibomian gland dysfunction with SiH have not been previously reported and may be related to mechanical moulding. A case of drug-induced bilateral transient myopia with the sulphonamide sulfasalazine was also identified. Events and complications were more commonly found with continuous wear of contact lenses, especially with Lotrafilcon A lenses.

The findings reported in this thesis will enable contact lens practitioners and manufacturers to understand further the optical, physiological and biochemical nature of the ocular response to SiH contact lenses and hence facilitate the development of this important generation of contact lens material.

Keywords: Daily wear, continuous wear, Lotrafilcon A, Balafilcon A.

This thesis is dedicated to my Mum, *María José Rubido Crespo*, and Dad, *Jacinto Santodomingo Araujo*, who have done so much for me that words can not justify

-The key to success is the ability to go from one failure to another with no loss of enthusiasm-

-Sir Wisdom Churchill (1874-1965)-

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

OCULAR RESPONSE TO SILICONE HYDROGEL CONTACT LENSES

GENERAL INTRODUCTION

Patients with different degrees of refractive errors have continued to seek an alternative to spectacles for the correction of their visual needs over the last decade. Daily wear of contact lenses is a common and convenient alternative for many patients. Contact lenses offer in many cases several functional advantages over other means of refractive correction such as visual, cosmetic, occupational, medical and psychological aspects of ocular status. Although, contact lenses do not offer the convenience of refractive surgery, most surgical techniques are to date irreversible, relatively expensive and not free of complications. If ametropic patients had access to a safe, cost-effective, convenient extended wear contact lens which provides vision comparable to spectacles, then this would certainly be considered a viable option by many. Whereas, a large number of studies in the field of contact lenses have been carried out throughout the years, many of the effects of contact lenses on anterior segment physiology and function are not fully understood. As the contact lens industry develops, new contact lens materials and designs are launched onto the market and on occasion induce different effects on the eye than those previously reported. Research on the use of silicone-hydrogel contact lenses for continuous wear has been extensive over the past few years. The material is very different from conventional hydrogels in terms of, for example, the high modulus of elasticity and surface coating (Tighe, 2000).

The aim of this thesis is to investigate the refractive, biometric, ocular physiology, clinical/biological tear film, symptomatology and ocular health effects induced by silicone-hydrogel contact lenses in young adult neophyte contact lens wearers. The thesis addresses limitations found in previous studies by using more precise devices and by implementing alternative study designs. Although not an integral part of this PhD thesis, an additional collaborative work has been done with the Biomaterials Research Unit at Aston University who analysed tear samples collected throughout the study. In this regard the research environment and facilities at Aston University are especially conducive to inter-disciplinary work between optometric (Ophthalmic and Physiological Optics Research

Group) and biochemical (Biomaterials Research Group) research. The work reported represents the first randomised clinical trial to examine the biometric and biochemical consequences of the silicone-hydrogel Balafilcon A (*PureVision*, Baush & Lomb) and fluoro-silicone hydrogel Lotrafilcon A (*Focus Night & Day*, CibaVision) continuous wear contact lenses when worn on both a daily and continuous wear basis. These high-Dk continuous wear lenses became commercially available in the UK market in 1999. However, the ocular effects induced by these lenses are not fully understood. Although, the use of silicone-hydrogel lenses in routine contact lens practice is increasing, they are unlikely to become a lens of first choice until practitioners feel more comfortable with the characteristics of the lens materials and appropriate patient selection. In order to achieve this, further research needs to be done to clarify the ocular effects induced by these lenses.

Refractive effects

The first reports in the 1970s on refractive changes associated with soft contact lenses suggested that lens wear induced significant increases in myopia (Harris *et al.*, 1975; Grosvenor, 1975; Barnett and Rengstorff, 1977). The reasons put forward invariably centred around physiological and mechanical changes in the cornea. Improvements in lens materials and designs, which resulted in increased oxygen transmission through the contact lenses, are believed to have eliminated the physiological basis for increased myopia reported in soft contact lens wearers. However, very little work has been published on the refractive changes associated with silicone-hydrogel contact lens wear. It is not well known whether silicone-hydrogel contact lens wear induce changes in ocular refraction. In order to determine whether silicone-hydrogel contact lens wear induce changes in ocular refraction, a controlled study investigating changes in ocular refraction and biometry is of particular value.

Biometric effects

Measurements of eye dimensions such as axial length, anterior chamber depth, corneal curvature and corneal thickness are of great value in assessing accurately and precisely the true changes occurring with contact lens wear. It is well documented that an increase in posterior vitreous chamber depth is the principal structural correlate of myopia (Bullimore *et al.*, 1992; Goss *et al.*, 1997; Grosvenor and Scott, 1991; Wildsoet, 1998). A number of studies have shown that the axial length/corneal curvature ratio can be utilised as a predictor of the onset and development of myopia (Goss and Jackson, 1995; Grosvenor and

Scott, 1993, 1994). Most of the previous studies on hydrogel contact lenses have used relative imprecise techniques for assessing changes in ocular dimensions (e.g. A-scan ultrasonography and keratometers) (Dumbleton *et al.*, 1999; Fulk *et al.*, 2003). Work needs to be done, with accurate and precise devices to further understand the biometric changes occurring with silicone hydrogels.

Ocular physiology effects

Contact lens patients can present with a variety of contact lens induced complications of the anterior ocular structures. Grading accurately the severity of the most clinically relevant conditions and signs is of great value for both the patient and the practitioner. Ocular health will be monitored clinically and graded both subjective and objectively.

Clinical and biochemical tear film effects

The pre-ocular tear film is a complex physically heterogeneous fluid composed of three main layers: the thin, superficial lipid layer, the thick, aqueous, central layer and the thin, deep, mucin layer. In recent years, the pre-corneal tear film has been a subject of intense study due to its importance in the preservation of the normal optical properties of the most important refractory system of the eye, the cornea (Michaud and Guisson, 2002). The clinical assessment of tears is likely to play an important role in the screening of potential contact lens wearers. Pre-ocular tear film parameters must be maintained within moderately narrow limits to allow the normal function of the different tasks of the lacrimal system. Dysfunction of the surrounding corneal and conjunctival structures can arise from deficiencies in the quantity or quality of any of the vital tear film components. Several clinical tests and techniques have been developed to assess both quantity (e.g. Schirmer test, phenol red thread test and the tear meniscus height) (Port and Asaria, 1990; Glasson *et al.*, 2003) and quality (e.g. *Tearscope* plus and non-invasive tear break up time) (Guillon and Guillon, 1993) of tears. Some of these tests will be employed and evaluated in studies reported in this thesis.

The three layers of the pre-ocular tear film are composed of proteins, lipids, carbohydrates and electrolytes which form a stable and structured anti-microbial system providing protection for the eye. The tear film profile can be analysed using different analytical techniques (e.g. immunodiffusion assays, fluorescent antibody tagging, spectrophotofluorimetry and ultra-violet spectroscopy). Biochemical analysis of the tear

film profile leads to a greater understanding of soft contact lenses, arising from the interaction of tears with ophthalmic biomaterials such as contact lenses. This type of analysis requires the use of highly sensitive analytical techniques in conjunction with carefully controlled clinical trials and parallel *in vitro* studies. Whereas, laboratory-based studies are ideal for providing comparative data between both contact lens materials and care products, *in vivo* clinical studies are crucial to further understanding of these results in the real world.

The high modulus of elasticity and surface coating of the current generation silicone-hydrogel lenses result in significantly different tear tribology. This thesis aims to further investigate the clinical and biological tear film effects taking place with two different silicone hydrogel contact lenses when worn both on a daily and a continuous wear basis.

Symptomatology effects

The aetiologies and mechanisms of the subjective responses reported by contact lens wearers are not well understood, some of the most commonly reported include, for example, discomfort, dryness, burning, itching, blurred vision, excess tearing, photophobia and lens handling problems. Grading these symptoms is of particular relevance for a further understanding on the effects of contact lenses on the eye. The nature of these subjective responses will be investigated in terms of grading systems and related to clinical and/or biomechanical work.

Ocular health effects

A relatively large number of ocular adverse events and complications have been reported with both extended and continuous wear of soft contact lenses. These adverse events and complications are likely to occur as a result of hypoxia: as the cornea is gradually deprived of oxygen, it will become compromised and prone to infections. With the introduction of the new generation of high-Dk silicone hydrogel contact lenses, which provide oxygen transmissibilities similar to those found in an eye not wearing contact lenses, many of the contact lens-related complications have been significantly reduced. The incidence and significance of these complications will be discussed in this thesis.

Research issues

It is well known that contact lens wear induces different effects on ocular physiology and function. The mechanisms responsible for the effects remain obscure, particularly with the

new generation of silicone-hydrogel contact lenses. By running a longitudinal study in which young adult neophyte contact lens wearers will be fitted with silicone-hydrogel contact lenses and monitored over an 18-month period, this thesis aims to investigate further the nature of these changes. The aims prompt consideration of various research issues, which are addressed by a series of research questions:

i) Do silicone-hydrogel contact lenses induce increases in myopia? What is the structural correlate for the increase in myopia? Is this the same as other soft contact lenses?

ii) Do silicone-hydrogel contact lenses affect anterior and posterior ocular dimensions?

iii) What type of ocular complications are seen with silicone-hydrogel contact lenses? What is the incidence and significance of these complications? Are these complications different from daily wear *vs.* continuous wear? Are these complications different from soft other contact lens materials?

iv) How does ocular health change with silicone-hydrogel wear? Is it different from other soft contact lens materials? Is it different from daily wear *vs.* continuous wear? How do we compare subjective *vs.* objective means of ocular health grading?

v) What clinical and biological tear film changes take place with silicone-hydrogel contact lenses? Are these changes different from daily wear *vs.* continuous wear? Are the changes different from other contact lens materials?

vi) What symptoms are expected with these contact lenses? Are they different from other soft contact lenses? Are they different from daily wear *vs.* continuous wear?

Previous literature has considered to greater and lesser extents the above issues and Chapter 1 will review the effects previously reported with soft contact lens wear. The chapter will be subdivided into six main areas: refractive, biometric, continuous wear, clinical and biological tear film, ocular health and symptomatology effects.

Methods of measurement

Chapter 2 describes the methodology and methods of statistical analysis behind the study in other to address the above research questions. To assess the true changes in refractive state with contact lens wear, accurate and repeatable measurements of refractive error are essential. The study will measure refractive error objectively using the open-view infrared

Shin-Nippon SRW-5001 autorefractor, which has been previously found to be highly reliable (Davies *et al.*, 2003).

To identify changes in ocular dimensions, such as corneal thickness, axial length, anterior chamber depth and corneal shape factors, the following measures will be taken throughout the study:

Axial length, anterior chamber depth and axial length/corneal curvature ratio measurements will be carried with the *IOLMaster* (Zeiss Instruments, Carl Zeiss Jena GmbH, Germany), a relatively new method of measurement which incorporates partial coherence interferometry.

A corneal topographer (*EyeSys 2000*, EyeSys Instruments, Houston, TX, USA) instead of a keratometer will be employed, which will provide a further insight of the anterior corneal shape changes occurring during contact lens wear.

The tear film covering the anterior ocular surface within the palpebral fissure is believed to play an important role during contact lens wear. However, its characteristics and function are not fully understood and clinical tests for assessing tear quality and quantity, such as the non-invasive tear break up time, the tear meniscus height and the *Tearscope* plus (*Keeler Instruments Ltd.*, Windsor, UK), will be used to monitor tear changes occurring during contact lens wear. Additionally, laboratory-based assessment of the biological aspects of the tears and contact lenses will be carried out in collaboration with the Biomaterial Research Unit at Aston University.

Ocular health will be monitored, graded and recorded photographically using a slit-lamp and a video-camera system. Efron grading scales will be employed for subjective grading purposes. A novel way of objectively grading different ocular health conditions will also be analysed and compared to subjective methods. The symptomatology of contact lens wear will be examined throughout the study in all subjects using specially designed subjective questionnaires.

A range of data presentation and analysis methods will be used in Chapters 3, 4, 5, 6 and 7 to assess the significance of the results. It is envisaged that the conclusions and suggestions for future work offered in Chapter 8 will advance our knowledge and understanding of the ocular effects of contact lens wear.

REFRACTIVE EFFECTS

1.1 Initial observations

The first reports in the 1970s on refractive changes associated with soft contact lenses suggested that wearing lenses induced significant increases in myopia (of the order of 0.30 D) (Harris *et al.*, 1975; Grosvenor, 1975; Barnett and Rengstorff, 1977) (see Table 1.1). In 1990, Andreo reported retrospective data on teenage children. No significant difference, after 1 year, in the rate of myopia progression was found when a group of daily wearers of soft contact lenses was compared to an age-matched group of spectacle lens wearers (Andreo, 1990). McGlone and Farkas (1991) reported a small but significant myopic shift of 0.25 D in soft contact lens wearers after a 2-year period of lens wear. Pence (1992) reported an increase of 0.13 D in myopia per year in soft contact lens wearers compared to a group wearing spectacles. A later report in myopia progression performed with a large sample (n=175) of adolescent wearers of soft contact lenses and spectacles (Horner *et al.*, 1999) over a period of 3 years showed no clinical or statistical significant difference in the spherical equivalent progression of myopia between the groups. Recently, Bullimore *et al.* (2002) in a retrospective study found significant myopia progression with soft contact lenses (at least –1.00 D over 5 years) in approximately 20% of the young myopic adults in their twenties and in approximately 10% of the adults in their thirties. They failed to find an association of myopia progression with near work, education, family history, or mode of refractive correction.

There is no clear agreement between researchers on whether soft contact lens wear induces shifts towards myopia. On the other hand, myopia progression rates between –0.05 and –0.20 D per year have been found to occur normally in young adult non-contact lens wearers (Grosvenor, 1977; Goss *et al.*, 1985; Kinge and Midelfart, 1999).

The shift towards myopia in the studies discussed earlier justifies the need for further longitudinal rather than cross-sectional investigation in this field.

1.2.Effects of oxygen transmissibility

Rengstorff and Nilson (1985) studied recovery data in long-term (average of 5.4 years) extended soft lens wearers. Nineteen monocular extended wear subjects were followed for a week after lens removal. They demonstrated no significant reduction in myopia in eyes that had worn the lenses compared to the contralateral eye that had not worn contact lenses.

McGlone and Farkas (1991) reported that a significantly greater increase in myopia occurred in a group wearing low water content lenses in a daily schedule (0.29 D) than in a group wearing medium water content lenses on an extended wear schedule (0.15 D). The effect of extended wear of low and medium water content lenses on myopia progression was evaluated in a subsequent follow-up report on 7000 cases reviewed retrospectively by McGlone and Farkas (1992). They found that when the groups were matched for age and initial refractive error, low water content lenses worn on an extended wear basis produce a greater increase in myopia than medium water content lenses. There was no significant interaction between water content and wearing schedule. Conversely, Horner *et al.* (1999) did not shown an increase in myopia progression over a 3-year period in adolescent wearers of soft contact lenses of low water content and Dk (8.9) compared to a group wearing spectacles. More recently, Fulk *et al.* (2003) assessed the 1-year effect of changing from glasses to soft contact lenses on myopia progression in adolescents. They showed a significant increase in myopia of 0.74 D in 19 children who switched from glasses to daily wear of conventional soft contact lenses compared with 0.25 D for children remaining in glasses. This increase was accompanied with an increase in axial length and corneal steepening.

MacDonald *et al.* (1995) showed a small but significant increase in myopia with extended wear of low-Dk (25) hydrogel lenses, but there was no change with extended wear lenses of high-Dk (90). Dumbleton *et al.* (1999) showed that 9-months extended wear of Lotrafilcon A lenses of high-Dk (140) induces no change in the spherical myopic correction, whereas a slight increase in myopia was found for the group wearing Etafilcon low-Dk (28) lenses. Sweeney and co-workers (2000) found in long-term wearers of daily soft contact lenses who were refitted with silicone hydrogel contact lenses a reduction in myopia in the order of –0.25 D after 12-months of wear. Fonn *et al.* (2002) compared the ocular effects of a high Dk Balafilcon A silicone hydrogel lens *vs.* a low-Dk HEMA lens. Twenty-four subjects who were adapted to daily wear of soft lenses wore a high-Dk lens in one eye and a low-Dk HEMA lens in the other eye for four months on an extended wear basis. They found a significant increase in myopia in the eyes wearing low-Dk HEMA lens (mean = 0.50 D) compared to an insignificant myopic increase of 0.06 D in the eyes wearing the high Dk Balafilcon A lens.

1.3 Possible explanations

The influences of hydrogel lens wear on corneal curvature are well documented (Grosvenor, 1975; Hovding, 1983). Corneal changes induced by these lenses produce an initial flattening followed by gradual steepening with longer periods of lens wear. The term "myopic creep" has been used to refer to the need for increased minus power in subjects wearing daily wear or extended wear soft contact lenses which suggested that physiological changes in the cornea may be the cause of the increased myopia (Caroline and Campbell, 1991; Edmonds, 1993).

Rengstorff (1979) suggested that both mechanical moulding of the cornea to match the back surface of the lens together with lens-induced oedema might be the causes for the corneal steepening. Several of the studies reviewed earlier suggested that hypoxia may play a major role in any topographical shifts induced by soft contact lens wear. According to Terry *et al.* (1993) contact lens-induced refractive changes exceeding - 0.50 D in spherical refraction and - 0.75 D of astigmatism represent a genuine myopic change.

Improvements in materials and lens designs, which result in increased oxygen transmission through the contact lenses, are likely to offset some of the physiological causes for increased myopia in soft contact lens wearers. Some studies have shown that higher oxygen transmission resulted in less corneal swelling (Papas *et al.*, 1997; Keay *et al.*, 2000; Fonn *et al.*, 2002). It is envisaged that the small increases in myopia related to corneal swelling will become insignificant as materials continue to improve. Clearly, research is required to elucidate further whether soft contact lens wear could in itself induce increases in myopia.

1.4 Aims of the thesis

Most of the previous studies cited above are limited by small sample size, poor controls, and the length of time that the subjects were observed. However, the reasons put forward for the increase or decrease in myopia with contact lens wear were attributed to changes in corneal and axial length induced by the contact lens, and hence specific attention has been drawn to these parameters in this thesis.

Many reports have been published on refractive changes associated with hydrogel soft contact lenses; however, very little work has been done with silicone-hydrogel contact lenses. Previous reports on myopia progression with silicone-hydrogel contact lenses have been carried out over relatively short periods of time (MacDonald *et al.*, 1995; Dumbleton

et al., 1999; Fonn *et al.*, 2002). The results found in these studies are therefore more likely to show reversible corneal physiological increases in myopia rather than permanent biometric changes. To date, no work has been reported that has assessed the rate of increase in myopia over more than 12-months and incorporated concomitant accurate and precise biometric measures; the latter being essential to identify the structural correlates of myopia. Silicone-hydrogel contact lenses have a higher modulus of rigidity compared to hydrogel contact lenses (Tighe, 2000). The question of whether silicone-hydrogel contact lenses induce changes in myopia and ocular biometry in a different manner than other soft contact lenses needs to be further examined. The work presented in this thesis aims to provide greater understanding on the refractive changes occurring in silicone hydrogel contact lenses by fitting new young adult contact lens wearers and monitoring ocular changes over an 18-month period. Accurate and precise measures of refractive error will be taken at regular intervals in a masked, randomised clinical trial, together with measures of axial length, anterior chamber depth, corneal topography and corneal thickness.

Study	Number of Subjects	Length of the study	Increase in myopia progression (spherical equivalent)
Harris *et al.* (1975)	5	9 months	0.35 D
Grosvenor (1975)	10	12 months	0.25 D
Barnett & Rengstoff (1977)	40	3 months	0.50 D
Rengstoff & Nilsson (1985)	19	5.4 years	< 0.37 D$^{\bullet}$
Andreo (1990)	56	1year	0.20 D$^{\bullet}$
McGlone & Farkas (1991)	-	2 years	0.25 D
Pence (1992)	-	-	0.13 D
Horner *et al.* (1999)	175	3 years	< 0.25 D$^{\bullet}$
MacDonald *et al.* (1995)	24	4 months	-^{1} and -$^{\bullet 2}$
Dumbleton *et al.* (1999)	62	9 months	0.30 D^{1} and 0.00 D$^{\bullet 2}$
Sweeney *et al.* (2000)	-	12 months	0.25 D^{-}
Bullimore *et al.* (2002)	291	5 years	0.44 D
Fonn *et al.* (2002)	24	4-months	0.50 D^{1} and 0.06 D$^{\bullet 2}$

Table 1.1. Summary of the results found in previous studies on the effect of soft contact lenses upon myopia progression. $^{-}$ Not specified in the study; $^{\bullet}$ Not statistically significant;, ^{1} Refers to lenses of low-Dk; ^{2} Refers to lenses of high-Dk.

BIOMETRIC EFFECTS

1.5 Introduction

Previous studies have shown that measurements of eye dimensions such as axial length, anterior chamber depth and corneal curvature and peripheral asphericity are of great value in quantifying structural changes occurring with contact lens wear, as highlighted below.

1.6 Axial length and anterior chamber depth changes

Many previous studies aiming to assess the refractive changes with contact lens wear have failed to measure axial length. It is well documented that an increase in posterior vitreous chamber depth is the principal structural correlate of myopia (Bullimore *et al.*, 1992; Goss *et al.*, 1997; Grosvenor and Scott, 1991; Wildsoet, 1998). Traditionally, axial length has been measured with A-scan ultrasonography which has a resolution of the order of 0.12 to 0.20 mm (Boerrigter *et al.*, 1985; Butcher and O'Brien, 1991). Due to the resolution of A-scan ultrasonography, changes in refraction of the order of 0.25 to 0.50 D will be undetected by this technique. More, recently, a new optical laser interferometer (*IOLMaster*), based on the principle of partial coherence interferometry, has been developed which produces higher resolution measures of axial length compared to ultrasonic methods. The manufacturer claims a resolution of the order of 0.01 mm, which will therefore detect changes in refraction as small as 0.03 D, if they are axial in nature. In addition, the thesis will also utilise the fact that this instrument uses image analysis to also provide high-resolution (i.e. 0.01 mm) measures of anterior chamber depth. Haigis *et al.* (2000) have found the *IOLMaster* to be highly accurate and repeatable. This finding has been corroborated and reported by the author and colleagues in normal subjects (Santodomingo-Rubido *et al.*, 2002). Haigis *et al.* (2000) found that no optical measurements could be obtained in 12 % of the eyes assessed. Among the reasons were severe tear film problems, keratopathy, corneal scarring, mature cataract and lid and fundus abnormalities. Similarly, Hitzenberger *et al.* (1993) using a similar optical laser interferometer found that the precision of the instrument was not influenced by the cataract grade except for mature cataracts.

1.7 Corneal topography changes

The cornea has also been found to play an important role in emmetropia and myopia (Grosvenor and Goss, 1998). Most of the early studies on the effects of contact lenses on corneal curvature have used keratometers as the principal measurement device. It has been shown that appropriately calibrated conventional keratometers provide readings extremely close to the sagittal radius of curvature (Bennett and Rabbetts, 1991). Whereas the keratometer is a valid instrument for measuring corneal refractive power for an eye that never has worn a contact lens, it fails to measure the portion of the cornea that might be crucial for determining the refractive error of an eye that has worn contact lenses (i.e. near the apex). It is well known that conventional keratometers only measure corneal curvature in an approximately 3 mm mean diameter measuring cap centred about the apex of the cornea. Keratometers assume uniformity of the central area of the cornea where measurements are taken. In order to determine the extent to which changes in keratometer findings differ in contact lenses wearers (with reference to changes in apical corneal refracting power), a controlled study making use of corneal mapping (in addition to routine keratometry) would be of particular value. Corneal topography examination is used routinely in refractive surgery (Ambrosio *et al.*, 2003), in the detection, diagnosis, monitoring and treatment of corneal pathologies and surgery (e.g. keratoconus) (Siganos *et al.*, 2003), in assessing the effects induced by contact lens wear and to design the contact lens back surface geometry to achieve an optimum fit (Douthwaite, 1991; Szczotka, 1995). The *EyeSys* corneal topographer is one of the most commonly used videokeratometers in recent years. It has been validated and is widely accepted clinically (Dave *et al.*, 1998a, b; Vámosi *et al.*, 1998). In addition to central keratometry, the videokeratometer provides an eccentricity value which indicates the rate of corneal flattening over a corneal diameter of approximately 9.2 mm (Nieves and Applegate, 1992).

The *EyeSys* corneal topographer is useful in monitoring corneal changes due to its good repeatability although its accuracy displaying absolute values when measuring aspherical surfaces has been criticised (Douthwaite, 1995; Dave *et al.*, 1998a, b). Similar results have been found with other videokeratoscopes (i.e. *TMS-1*, Tomey Instruments, Phoneix, USA) (Douthwaite and Mantilla, 1996). It has been found that when measuring normal human corneas with the *EyeSys* videokeratoscope, corneal tilting of the order of 1° to 6° normally occurs in the temporal direction. Tilts of around 5° are likely to induce small measurements errors in this instrument and may be responsible for the apparent nasal/temporal asymmetry seen in videokeratoscope images of human corneas (Douthwaite

and Pardhan, 1998; Douthwaite *et. al.*, 1996). The *EyeSys* corneal topographer will be employed in this study. The axial length/corneal curvature ratio is considered to be a useful predictor of the onset and development of myopia (Goss and Jackson, 1995; Grosvenor and Scott, 1993, 1994). It was found that the axial length/corneal radius ratio was significantly greater in the became-myopic group than in the remained-emmetropic group. The general conclusion advanced was that greater corneal powers and greater axial length/corneal curvature ratios are risk factors for youth onset myopia and both can easily be assessed with the *IOLMaster.*

1.8 Corneal thickness changes

Contact lenses can have an effect upon all major corneal structures- the epithelium, stroma and endothelium. The most superficial layer, the epithelium is likely to be the first one to react. As indicated in the review by Bergmanson (2001), when assessing changes in corneal ultrastructure it is appropriate to consider the three major structures of the cornea separately.

Corneal epithelium

Corneal epithelial thinning may occur as a result of inhibited epithelial mitosis due to the presence of a contact lens. Additionally, the shearing force exerted on the eye by the lids is affected by contact lens wear, reducing the rate of cells removed from the epithelium surface. It has been also proposed that the physical weight and tension of the upper eyelid may compress the mouldable epithelium into a more flattened form. Increased tear osmolarity found in reflex tears of contact lens wearers (Gilbard *et al.*, 1986; Martin, 1987) due to chronic exposure to a hyperosmotic tear film has also been reported to be capable of inducing generalised corneal thinning (Gilbard *et al.*, 1978), similar to that occurring during adaptation to rigid lenses.

Corneal epithelial oedema may occur as a result of traumatic loss of surface epithelial cells allowing fluid to move in. Abrasion and staining is commonly seen in contact lens wearers and refers to loss of epithelial cells.

Corneal stroma

Several studies have suggested that the major cells of the stroma, the keratocytes, may be affected by contact lens wear and therefore induce stromal thickness changes. Loss of keratocytes may induce corneal thinning, whereas stromal oedema is characterized by pooling of fluid around keratocytes.

Corneal endothelium

The aetiology of endothelial changes with contact lens wear remains obscure. Most studies have concentrated on studying endothelial polymegethism by means of specular reflection (Esgin and Erda, 2002). Whereas the image obtained is two-dimensional, research employing three-dimensional specular reflection techniques is likely to reveal different interpretations of the clinical picture. Indeed, lateral observations of the endothelial cells suggest that cells rearranged their three-dimensional configuration in response to a change in their environment, but do not shrink or became bloated (Bergmanson, 1992). If this is the case, polymegethism may not in fact threaten the cell and thus be of no concern to the clinician.

Changes in corneal thickness with contact lens wear

Several studies have been carried out to assess whether contact lens wear induces either corneal thinning or thickening. However, contradictory results have been found. Corneal thickness has been reported to increase after initial wearing of contact lenses (i.e. from a few days to a few months) and corneal thinning has been observed with prolonged wearing times (i.e. several months to years) for a variety of contact lens types (Bonanno and Polse, 1985; Holden *et al.*, 1985; Iskeleli *et al.*, 1996). Long-term contact lens wear appears to decrease thickness across the whole of the cornea together with increased corneal curvature and surface irregularity. Additionally, central corneal thickness has been found to be lower in subjects wearing hard contact lenses that in those wearing soft contact lenses (Lui and Pflugfelder, 2000). Conversely, Myrowitz *et al.* (2002) recently concluded that long-term soft contact lens wear did not significantly change corneal thickness compared to non-contact lens wearers. The mechanisms responsible for corneal thickness changes remain unclear.

Possible explanations

Possible explanations offered include chronic oedema and biochemical changes in the corneal stroma (Holden *et al.*, 1985; Vreugdenhil *et al.*, 1990). Large inter-subject variability may also account for the differences found between studies. It has been proposed that epithelial and endothelial metabolic rates are more important than stromal thickness in determination of oxygen demand (Myrowitz *et al.*, 2002). An initial increase in corneal thickness with contact lens wear is likely to occur as a result of hypoxia. However, corneal thickness decreases with long-term contact lens wear as well as with contact lens wear cessation after long-term wear. These latter affects are likely to be due to diminished corneal oedema and reconfiguration of corneal ultrastructure.

An interesting review of multiple studies on the effect of long-term low-Dk contact lens wear on the cells of the cornea has been reported by Bourne (2001). A summary of the results is available in Table 1.2. Bourne (2001) concluded that no detrimental effects have been found on the cells of the cornea from the long-term use of daily wear of contact lenses. Although contact lenses can cause endothelial polymegethism, no functional deficits have been found. Continuous wear lenses may cause changes in all three cell types, but it is not well established whether these effects are detrimental or if they occur with newer lenses of high oxygen transmissibility.

Stapleton *et al.* (2001) evaluated the changes in corneal epithelial cell morphology and physiology following short-term (3-months) wear of high-Dk (on a continuous wear basis) and low-Dk (on an extended wear basis) contact lenses. They found an 8% increase in epithelial cell diameter in extended wearers of low Dk contact lenses, whereas no difference was found in cell size, morphology and viability between high Dk contact lens wearers and the non-contact lens wearers group. Preliminary studies on corneal structure with silicone hydrogel contact lenses have shown much lower corneal swelling than that found with standard hydrogel lenses of low Dk; however, some swelling is still observed (Mueller *et al.*, 2001; Nguyen *et al.*, 2001). A small decrease in posterior keratocyte density following 6-months of CW of silicone-hydrogel lenses accompanied with an unchanged corneal endothelium has been previously reported (Perez-Gomez *et al.*, 2001). Further studies need to be carried out to understand fully the effects of high-Dk silicone-hydrogel contact lenses on corneal physiological structure.

Table 1.2. Effect of long-term contact lens wear on corneal cells (adapted from Bourne, 2001)

In order to understand fully the corneal effects induced by silicone-hydrogel contact lens wear, carefully controlled clinical trials and parallel light and electron microscopy studies need to be performed.

1.9 Comment

Little work has been done to evaluate the biometric effects induced by silicone hydrogel contact lenses. Previous studies (Dumbleton *et al.*, 1999; Fonn *et al.*, 2002) have focused on keratometric changes. To date, no studies have assessed longitudinal changes in axial length, anterior chamber depth and corneal thickness with these lenses. The high modulus of elasticity of the current generation of silicone-hydrogel lenses may induce different ocular biometric changes than those previous reported with both soft and hard contact lenses.

CURRENT ASPECTS OF CONTINUOUS WEAR OF SOFT CONTACT LENSES

1.10 Introduction

Extended wear (EW) of contact lenses generally refers to sleeping over night with the lenses *in situ* for one or more nights per week, commonly extending to seven days (incorporating six nights) of extended wear without removal, as recommended by the Food and Drug Administration in 1989. Continuous wear (CW) regimens generally refer to wearing lenses continuously for 30 days without removal. The lenses may be removed at intervals for care regimes and/or replacement. Continuous wear has the advantage over conventional daily lens wear of minimised need for cleaning and disinfection procedures and a reduced need for lens manipulation/handling.

1.11 Initial observations

Early studies of hydrogel EW lenses for cosmetic use were promising and encouraging, with few complications found (Leibowitz *et al.*, 1973; Binder and Worthen, 1977; Stark and Martin, 1981; Binder, 1983). Due to the successful outcome of these early trials, the use of CW lenses increased rapidly. However, with time a large number of complications were subsequently reported, such as corneal oedema, striae, folds in Descemet's membrane, epithelial and stromal thinning, epithelial microcysts, limbal injection, endothelial polymegethism, papillary conjunctivitis and corneal staining (Bruce and Brennan, 1990; Fleiszig *et al.*, 1992; Sankaridurg *et al.*, 1999; Keay *et al.*, 2000), the most severe being infectious keratitis (Brennan and Coles, 1997; Sankaridurg *et al.*, 1999). However, discomfort, dryness, visual problems and red eye were found to be the principal reasons for discontinuation of lens wear (Brennan and Efron, 1989; Fonn *et al.*, 1995). The higher prevalence of serious contact lens complications found with CW, especially infiltrative infectious keratitis (approximately 5x greater than soft daily wear and 20x greater than RGP wear) (Brennan and Coles, 1997) led to a substantial reduction in the number of wearers and concern among eye specialists. It has been shown that frequent replacement of contact lenses minimises poor vision, discomfort, acute red eye, keratitis and other complications, often as a result of the lower incidence of lens deposits (Hamano *et al.*, 1994; Pritchard *et al.*, 1996). However, disposability does not eliminate completely the risk of infectious keratitis (Maguen *et al.*, 1991; Efron *et al.*, 1991; Cohen *et al.*, 1991).

1.12 Possible explanations for adverse reactions with extended wear lenses

Risk factors responsible for complications associated with hydrogel EW lenses include a lack of or poor compliance, poor hygiene, over-wear, diminution/stagnation of the post-lens tear film (due to reduced tears overnight), tear inadequacies, fluctuations in fit and uncorrected visual anomalies. These complications result principally from contact lens material properties (such as oxygen transmissibility and minimal post-lens tear exchange), but may be exacerbated by non-compliance. Most of the adverse reactions found with EW of hydrogel lenses are likely to occur as a result of hypoxia. As the cornea is gradually deprived of oxygen, it will become compromised and prone to infections (Brennan and Coles, 1997; Efron and Brennan, 1999). The cornea naturally swells overnight by 2.0-4.0% (Mertz, 1980; Holden *et al.*, 1984; La Hood *et al.*, 1988). For a contact lens not to cause additional swelling, the permeability must be $\geq 87 \times 10^{-11}$ cm^2/s ml_{O_2}/ml_{lens} mmHg (barrers) (Holden and Mertz, 1984). Re-evaluation of corneal oxygen needs resulted in a recommendation of $\geq 125 \times 10^{-9}$ barrers (Harvitt and Bonanno, 1999). However, hydrogel soft lenses are limited by the Dk of water, which is approximately 60×10^{-11} barrers. This led manufactures to invest in developing new contact lens materials. The silicone-hydrogel material can achieve much higher Dk, thus supplying higher levels of oxygen to the cornea and therefore alleviating many of the adverse events previously reported. Figure 1.1. shows the relationship between equilibrium water content and the *Dk* of conventional hydrogels and silicone-containing hydrogels. From the graph, it is important to note that there is an upper limit to how much oxygen permeability can be attained simply by increasing the equilibrium water content of conventional hydrogel materials. Whereas, the oxygen permeability of silicone-hydrogel materials at water contents below 50 % do not depend upon water content and will be very dependent upon the precise composition of the non-aqueous part of the structure. It is, therefore, perfectly possible to make a series of silicone-containing hydrogels that have higher or lower permeabilities than those shown.

1.13 The new generation of silicone-hydrogel soft contact lenses

Understanding of contact lens behaviour has established the importance of achieving adequate wettability, mechanical properties and oxygen permeability. The recognition of the outstanding oxygen permeability of silicone rubber (polydimethyl siloxane) has led to attempts to modify this material and indeed its mechanical properties in order to develop a commercially viable and clinically acceptable lens. Silicone rubber has been used with

limited success as a contact lens material in the form of silicone elastomer lenses due to the intractable problem of lens tightening and poor surface wettability (Dow Corning Corporation, 1967). The problem of lens tightening and poor surface wettability has been overcome by combining silicone with hydrogels and by surface-treating the lenses using gas plasma techniques, respectively. The resultant lens has a significantly greater modulus of rigidity compared to conventional hydrogels (i.e. they are stiffer). Such mechanical characteristics mean that the lenses are easy to handle but have also been implicated in the aetiology of a number of clinical complications (Skotnitsky *et al.*, 2002). Whereas, contact lens-related complications due to hypoxia are virtually eliminated with silicone-hydrogel lenses due to their high oxygen transmissibilities; the ideal contact lens material and design in terms of mechanical and wettable properties has yet to be defined. Two generation of silicone-hydrogel contact lenses are currently available on the market since 1999- the Balafilcon A (e.g. *PureVision*, Baush & Lomb) and Lotrafilcon A (e.g. *Focus Night & Day*, CibaVision). The lens properties and characteristics are outlined in Table 1.3.

Figure 1.1. Relationship between *Dk* and equilibrium water content for conventional hydrogels and silicone-containing hydrogels (redrawn from Tighe, 2000).

1.14 Adverse events with silicone-hydrogel contact lenses

Contact lens-related complications due to hypoxia are significantly reduced with silicone-hydrogel contact lenses. Microcysts, the main clinical indicator of corneal oedema, are rarely seen with silicone hydrogel contact lenses (Keay *et al.*, 2000; Covey *et al.*, 2001; Nilsson, 2001; Fonn *et al.*, 2002; Morgan and Efron, 2002). However, preliminary data shows similar rates of inflammatory conditions such as contact lens-induced peripheral ulcers, contact lens-induced acute red eye and infiltrative keratitis with silicone-hydrogel lenses compared to traditional hydrogel lenses (Fonn *et al.*, 2002; Holden, 2002). Other adverse events, due to the higher stiffness of silicone hydrogel compared to hydrogel lenses causing mechanical trauma (i.e. superior epithelial arcuate lesions and local contact lens induced papillary conjunctivitis) may have higher incidence rates (Skotnitsky *et al.*, 2000; Fonn *et al.*, 2002; Holden, 2002).

These complications are almost certainly material-dependent. Although, contact lens-induced papillary conjunctivitis can result from an immunological response to denatured tear film protein deposits that reside on the contact lens surface during wear (Allansmith *et al.*, 1977; Refojo and Holly, 1977; Hart *et al.*, 1989), the type seen with silicone hydrogels has a faster onset and resolves more quickly on lens removal suggesting a mechanical origin (Holden, 2002; Skotnitsky *et al.*, 2002).

Finally, the problem of post-lens tear exchange needs still to be addressed, as an adequate tear exchange is required to supply the nutritional requirements to the cornea. Stagnation of the post-lens tear film can prolong corneal contact of bacteria and debris trapped behind the lens and thus increase the risk of inflammatory conditions such as contact lens-induced peripheral ulcers, contact lens-induced acute red eye and infiltrative keratitis (Brennan and Coles, 1997). Two mechanisms are involved in tear exchange; during open eye, the amount of tear exchange with normal blinking may be sufficient to prevent the required duration of exposure for bacterial invasion into the cornea; and the rapid eye movements during sleep might provide a similar function. However, this tear exchange is restricted when contact lenses are worn. Fleiszig (1996) suggested that a contact time of 2 to 3 hours is adequate for certain strains of *Pseudomonas aeruginosa* to invade the corneal epithelium in tissue culture. In a recent study, similar rates of bacterial colonization were shown between low (Etafilcon A lenses) and high Dk (Lotrafilcon A) (Keay *et al.*, 2001). Coagulase-negative *staphylococci* and *propionibacterium* were the most commonly observed bacterias colonizing silicone-hydrogel contact lenses when worn on a CW basis during asymptomatic lens wear. These non-pathogenic microorganisms are commonly found in

the normal ocular environment (e.g. conjunctiva and lids). Up to two years of continuous wear of silicone-hydrogel lenses does not appear to alter the types and number of bacteria colonizing the eye during wear when the lenses are replaced on a monthly schedule and the patients remain asymptomatic (Keay *et al.*, 2001; Willcox *et al.*, 2002).

In order to overcome the adverse reactions reported with silicone hydrogel lenses, carefully controlled clinical trials and parallel *in vitro* laboratory-based studies need to be carried out to further understand the mechanism responsible for such events. In this regard the research environment and facilities at Aston University are especially conducive to inter-disciplinary work between optometric (i.e. Ophthalmic and Physiological Optics Research Group) and biochemical (i.e. Biomaterials Research Group) research.

Proprietary Name	PureVision	Focus Night & Day
Manufacturer	Bausch & Lomb	CIBA Vision
Material	Balafilcon A	Lotrafilcon A
Back vertex power range (D) (steps)	+0.50 to +6.00 (0.25) DS -0.50 to -6.00 (0.25) DS -6.50 to –9.00 (0.50) DS	+0.25 to +6.00 (0.25) DS -0.25 to –8.00 (0.25) DS -8.50 to –10.00 (0.50)
Back optic zone radius (mm)	8.6	8.6, 8.4
Total diameter (mm)	14.0	13.8
Centre thickness (@ -3.00 D) mm	0.09	0.08
Dk	99	140
Dk/t (10^{-9}) @ 35°C	110	175
Water content (%)	36	24
Replacement frequency	1/12	1/12
Moulding method of manufacture	Mould	Mould
Design/ Features	Front surface: Tri-curve Back surface: Bi-curve	Back surface: Bi-curve
Surface treatment	Plasma treatment	Plasma coating
"Stiffness" (g/mm2)	110	120
FDA group	III	I

Table 1.3. Properties of the silicone-hydrogel lenses presently on the market worldwide.

1.15 Summary

High-Dk silicone-hydrogel contact lenses have significantly reduced most of the hypoxic adverse reactions previously seen with traditional hydrogel soft contact lens materials. However, various inflammatory and mechanical conditions induced by silicone-hydrogel lenses have shown similar or higher rates of incidence compared to hydrogel lenses. The work presented in this thesis aims to provide evidence for a better understanding of the clinical/biological interactions occurring when silicone-hydrogel contact lenses are worn in a daily and a continuous wear basis.

THE TEAR FILM

1. 16 Introduction

The entire anterior ocular surface is covered by a highly specialized and carefully structured moist film called the tear film. An intact tear film is essential to preserve a healthy and functional visual system. The tear film has many functions of which the most important ones are as follows; firstly, it provides a regular and smooth optical surface for what constitutes the strongest refractive component of the eye, the cornea, by eliminating the small irregularities of the corneal epithelium and/or the contact lens; secondly, it lubricates the palpebral and bulbar conjunctival surfaces and washes away debris, irritants and foreign bodies with assistance of the lids; thirdly, since the cornea is avascular, the tear film provides nutrition to the cornea to assist its normal metabolic activity; and finally, the tear film represents the first line of defence against harmful microorganisms achieved primarily by the antibacterial properties of certain of its constituent proteins and enzymes (e.g. lyzozyme, lactoferrin, albumin and immunoglobulins).

A great deal of clinical and biochemical research has been directed toward determining the effects of contact lenses on the tear film. Contact lenses alter the structure, composition, physicochemical properties and dynamic behaviour of the normal tear film (Tomlinson, 1992). The study of the tear film is of key importance in understanding the ocular effects induced by contact lens wear.

1.17 Origin, innervation, structure, composition, function and alterations with contact lens wear

The normal preocular tear film has been classically described as a three-layer structure (Wolf, 1946; Holly and Lemp, 1977): (1) The thin, superficial, lipid layer; (2) the thick, aqueous, central layer; and (3) the thin, deep, mucin layer (Figure 1.2). More recently, it has been proposed that the tear film is more complex that originally believed. A six-layer model has been described which includes additional layers and interfaces (Tiffany, 1988).

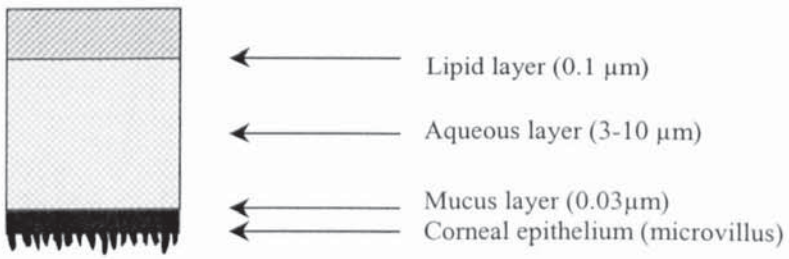


Figure 1.2. Schematic representation of the pre-ocular tear film

1.17.1 The lipid layer

1.17.1.a Origin and innervation

The lipid layer is mainly secreted by the meibomian glands with small contributions from the glands of Zeiss and Moll situated at the lid margins (Bron and Tiffany, 1998). This layer encapsulates the tear film and provides a stable interface between the aqueous layer and air. The blinking action fills and releases meibomian gland secretion from its orifices (Wolff, 1946; Chew *et al.*, 1993; Korb *et al.*, 1994), with forceful blinking significantly increasing the thickness of the lipid layer (Korb *et al.*, 1994). Conversely, incomplete blinking or a decrease in blink rate reduces lipid secretion (Linton *et al.*, 1961). The composition of meibomian lipids in humans varies considerably between individuals (Farris, 1985). After a complete blink, the lipids spread upward from the lower lid margin to the upper lid margin (Lemp and Holly, 1972; Kaercher *et al.*, 1993, 1994; Tiffany, 1995). Innervation of the meibomian glands is not fully understood, but recent work has indicated that the glands, and the vessels associated closely with them, are richly innervated by both sympathetic and parasympathetic nerve fibres (Chung *et al.*, 1996).

1.17.1.b Structure

The lipid layer is a relatively thin, oily layer of approximately 0.1 μm thick, compromising approximately 1-2 % of the total thickness of the tear film (Holly and Lemp, 1977). The existence of the lipid layer has been assumed on optical evidence obtained from the biomicroscopic observation of interference patterns in the tear film (McDonald, 1969; Guillon, 1986; Doane, 1989). The presence of these patterns on aqueous surfaces is commonly due to oil floating on water. Lipid layer structure was first characterized by Hamano (1981), and later by Guillon (1986), based on the appearance of coloured fringe patterns of the specularly reflected lipid layer. It has been suggested that the lipid layer is composed of two structures, an outer, homogeneous and mechanically stable layer, and a heterogeneous inner layer (Forst, 1987a). The reason put forward for this was that the lipid layer is composed of sebaceous and meibomian gland secretions (Nicolaides, 1986). The sebaceous gland secretions provide the exterior lipid layer with hydrophile waxy esters and to a lesser extent polar triacylglyceroles and fatty acids. These components are believed to be responsible for a stable, cohesive lipid layer during blinking (Forst, 1987b). Conversely, the meibomian gland secretion mainly supplies cholesterol esters, with small amounts of

cholesterols and free fatty acids to the inner lipid layer; the latter providing a strong affinity to the aqueous layer of the tear film.

1.17.1.c Composition

The composition of the tear film is achieved when the fluid of the lacrimal gland is combined with the secretions of the accessory glands, the ocular surface epithelium and the meibomian glands (Dartt, 1992).

The composition of non-stimulated tears (basal) has been found to differ significantly from stimulated tears (reflex) (Stuchell *et al.*, 1981; Fullard and Snyder, 1990). It is well established that different types of tears (e.g., basal, stimulated, emotional, open eye, closed eye) have different compositions.

The composition of meibomian lipids in humans varies considerably between individuals (Farris, 1985). All classes of lipids have been found in meibomian secretions: hydrocarbons, wax esters, cholesterol esters, triglycerides, and in lesser amounts, diglycerides, monoglycerides, fatty acids, cholesterol and phospholipids; with the sterol esters accounting for nearly one-third of the mixture (Bright and Tighe, 1993).

1.17.1.d Functions

The main functions of the lipid layer are to: (a) Retard evaporation of the underlying aqueous layer (Mishima and Maurice, 1961a, b; Craig and Tomlinson, 1997); (b) lower the surface tension of the tear film, drawing water into the tear film and thickening the aqueous layer; and (c) lubricate the eye lids (Kanski, 1999). A summary of the functions of the different tear film layers are given in Table 1.5. It has been previously reported that compromised lipid layers increase significantly tear evaporation, whereas thick and homogeneous layers achieve the greatest tear film stability (Craig and Tomlinson, 1997; Guillon *et al.*, 1997). Mishima and Maurice (1961a, b) demonstrated in rabbits that tear film evaporation increases 10 times in the absence of tarsal gland secretion and that tear film evaporation plays an important role in the control of normal corneal thickness.

1.17.1.e Alterations with contact lens wear

When a contact lens is inserted into the eye, it normally settles within the aqueous layer, partitioning this layer into two separate layers, which cover the anterior and posterior surface of the contact lens. The pre-lens tear film layer is made up of an outer lipid layer and a base aqueous layer (Bruce and Brennan, 1988). The post-lens tear film is made up of

a thin aqueous layer and of a compressed mucin phase (Guillon and Maissa, 2000). Very recently, non-invasive interferometric techniques, which have been found to be more accurate than pachymetric methods, have found values of the pre- and post-lens tear film thickness of soft contact lens wearers to be of the order of 3 μm. A thickening of the tear film as a whole was found when contact lenses are worn, probably as a result of reflex tearing (Nichols and King-Smith, 2003; Wang *et al.*, 2003). However, the stability of the pre- and post-lens tear film, even thicker than previously thought, is likely to be compromised in soft contact lens wear.

The smooth surface over which the lids must sweep during a blink to re-establish the tear film is also disrupted by a contact lens (Guillon, 1986). For a stable tear film to be formed on the contact lens surface, the contact lens material is required to be entirely biocompatible with the tear film and its surrounding structures, allowing a continuous tear film (including a complete lipid layer) to be formed on top of the contact lens surface. However, the ability to cover the contact lens with a tear film is restricted by the relatively hydrophobic nature of the contact lens material.

It has been shown that the stability of the tear film is significantly reduced with contact lens wear (Guillon and Guillon, 1993; Guillon, 1998). Thick lipid layers, prior to lens fitting, are likely to show higher tear film stabilities than thin lipid layers (Guillon and Guillon, 1993). This has a direct implication for contact lens wear, as thick lipid layers are more likely to show greater tear film stabilities on top of the contact lens than thin lipid layers, thus increasing the chance of successful contact lens wear. When a contact lens is inserted in the eye, it quickly becomes covered with a layer of mucus, which dramatically improves its wettability (Benjamin *et al.*, 1984). However, with time, deposits are likely to build up rapidly from both tear film and environmental sources, reducing the contact lens surface wettability and therefore its tear film stability (Lowther, 1997).

1.17.2 The aqueous layer

1.17.2.a Origin and innervation

The central aqueous layer is mainly secreted by the lacrimal gland, located in the superior temporal angle of the orbit, with small contributions from the accessory lacrimal glands of Krause and Wolfring. Innervation control of the tear secretion is derived from the trigeminal nerve (cranial nerve V) (principal afferent pathway), the facial nerve (cranial nerve VII) (principal efferent pathway) and the cervical sympathetic nerve fibres (Milder, 1987). The lacrimal gland is responsible for reflex secretion. Reflex secretion may be of peripheral sensory origin through trigeminal nerve stimulation (e.g. cornea, conjunctiva, skin, nose) or of central origin. Neuronal control of lacrimal gland secretion is not well understood. The parasympathetic nerves primarily control electrolyte/water and protein secretion by means of the neurotransmitter, acetylcholine, and biologically active peptide, VIP (vasoactice intestinal peptide) (Dartt, 1992). Stimulation of the cholinergic agonist produces vasodilatation which increases the rate of lacrimal secretion. The sympathetic nervous system mainly innervates the lacrimal gland blood vessels, by means of the neurotransmitter norepinephrine. Other neurotransmitters found in the parasympathetic and sympathetic sensory nerve fibres that are believed to play potential roles in the control of electrolyte, water and protein secretion include Substance P, an enkephalin family of peptides, calcitonin gene-related peptide and neuropeptide Y (Dartt, 1992).

1.17.2.b Structure

The aqueous layer is approximately 7 μm thick, compromising about 98 % of the total tear film thickness. The aqueous layer is anteriorly in contact with the inner lipid layer and posteriorly with the mucus layer. The inner lipid layer is mainly composed of meibomian secretion providing a strong affinity to the aqueous layer of the tear film (Forst, 1987b). The mucin layer increases the wetting properties of the corneal epithelium by converting the hydrophobic epithelium into hydrophilic and thus providing a stable surface on which the aqueous layer can lie.

1.17.2.c Composition

The aqueous layer is composed of proteins, salts, urea, glucose, leucocytes, and tissue debris (Bright and Tighe, 1993). The protein components of tears are found chiefly in the

middle aqueous layer. The concentration of proteinaceous substances in the tear film can vary depending on whether the tears are unstimulated, emotionally stimulated or irritant-induced. More than 60 different proteins have been identified in human tears (Gachon *et al.*, 1979), but only the major tear proteins will be described here. Some of the most important proteins found in this layer are albumin, lactoferrin, lysozyme and immunoglobulins and the kinin family with lysozyme and lactoferrin being the most important in terms of antibacterial properties (Tighe, 1997). Some of these proteins are locally produced tear-specific proteins and they are primarily secreted by the main lacrimal gland and to a lesser extend by the accessory glands of Krause and Wolfring. Other proteins detected in the aqueous layer are derived from plasma/serum and their concentration varies depending on the stability of the blood-tear barrier. This barrier can be affected by many factors including inflammation and eye closure, but in the normal uncompromised eye plasma proteins can still be detected (Fullard and Snyder, 1990), with albumin, transferrin and IgG being present at high concentrations. Table 1.4 gives a summary the characteristics of the seven proteins of interest in this thesis.

Lysozyme

Lysozyme was first detected and described as an antibacterial enzyme by Alexander Fleming (1922). In tears it is derived from the lacrimal gland. Around 20-40 % of the total tear protein is made up of lysozyme (Farris, 1985). The average concentration in the open unstimulated eye is estimated at 1.85 mg/ml with values ranging between 0.65-5.55 mg/ml depending on the methods of collection and/or analysis (Bright and Tighe, 1993). One of lysozyme's main functions is to trigger the innate immune response to bacteria and destroy certain classes of bacteria, mainly gram positive, by disrupting the peptidoglycan cell wall. The level of lysozyme concentration in human tears can be used as an indicator of tear dysfunction. For example, in subjects with dry eye associated with Sjögren's syndrome, lysozyme levels are dramatically reduced (Seal *et al.*, 1986).

Lactoferrin

Lactoferrin is an iron binding glycoprotein present in milk and to a lesser extend in other body fluids such as saliva, nasal secretions, bile, tears and other biological fluids associated with epithelial surfaces (Farris, 1985). In tears, it is mainly derived from the main and accessory lacrimal glands and its concentration is reduced with reduced tear flow, such as that seen in aqueous deficiency dry eyes (Seal *et al.*, 1986). The average concentration of

lactoferrin in the open eye of unstimulated tears is 2.1 mg/ml with values ranging between 0.81-3.4 mg/ml depending on collection and analysis techniques (Bright and Tighe, 1993). Lactoferrin is assumed to play an important role in the defense of the eye against bacterial invasion by up taking iron, the essential mineral nutrient for bacteria, and thus inhibiting bacterial growth and colonization (Broekhuyse, 1974). Its action is therefore classified as bacteristatic rather than bactericidal. It has been also suggested that lactoferrin may be involved in aiding lysozyme to kill gram negative bacteria, by disrupting the outer membrane of the bacteria and exposing the peptidoglycan for lysis (Ellison III and Giehl, 1991).

Albumin

Albumin is one of the four main proteins found in tears. Prealbumin in tears is specifically produced by the lacrimal gland (Bonavida *et al.*, 1969), whereas serum albumin is derived though leakage from the bloodstream (Franklin, 1989). In the normal open eye the mean concentration of albumin has been estimated at 1.3 mg/ml (Bright and Tighe, 1993). Albumin concentration in human tears rises markedly with conjunctival stimulation (Sapse *et al.*, 1969).

The specific function of albumin in human tears remains largely unresolved. It has been proposed that tear albumin may serve as a carrier for hydrophobic compounds of the tear film. Also it has been shown that tear albumin is capable of binding and transporting a large number of lipid molecules, such as fatty acids, fatty alcohols, phospholipids, glycolipids and cholesterol. It has been suggested that by transporting certain lipids in aqueous tears albumin may prevent hydrophobic molecules from directly contaminating the mucous layer when thinned and thus contribute to tear film stability (Glasgow *et al.*, 1995). It has further been suggested that albumin may aid in the even distribution of lipids in the tear film, although its physiological role may be more complex than simply binding or transporting lipids. The role of serum albumin in tears is uncertain, but its presence is indicative of the permeability in the blood-tear barrier: inflammation, for example, affects the blood-tear barrier and results in serum leakage.

Immunoglobulins

Immunoglobulins are glycoproteins synthesized by plasma cells with antibody activity. The antibody activity of immunoglobulins involves the specific combination with a substance (antigen) in order to elicit their formation. Immunoglobulins form the humoral

arm of the immune response providing exceptional specificity in a world of vast diversity. In humans, there are five main classes of antibody, immunoglobulins IgG, IgA, IgM, IgE and IgD. They are similar in general molecular structure, but they have different amino acid sequences which confer different biological functions, with each class assuming an individual role in the defence of the host against foreign or potentially harmful bodies. Individual immunoglobulins are antigen-specific. IgM is known as the first line of defence against foreign harmful bodies and provides the main humoral immune response during the host's first encounter with a particular antigen. The encounter between IgM and the foreign antigen stimulates an increase in IgG and IgA. IgE and IgD are present in the body in much lower levels. The biological function of IgD is poorly understood, whereas IgE is known to play an important role in allergic responses by triggering the release of inflammatory mediators from mast cells. IgG is the predominant antibody of serum, present with a concentration five times higher than IgA. The concentration of the immunoglobulins, IgE, IgM and IgG is significantly higher in the presence of ocular inflammation (McClellan *et al.*, 1973). IgA, the predominant immunoglobulin of the tears, is the main protective antibody of the mucosal and secretory immune system, including the external surface of the eye. Activation of IgA induces a furnishing of the conjunctiva with an immunologic coating (Heremans, 1968). Despite the avascularity of the cornea, it possesses the highest concentration of immunoglobulins of all ocular tissues (Allansmith *et al.*, 1973), with IgA and IgG being the most predominant. IgM, a large molecule, cannot diffuse into the corneal stroma and is concentrated in the limbus.

Other proteins: the kinin family

The kinin family is a group of proteins/glycoproteins which has been recently linked to a variety of inflammatory episodes, such as those found with contact lens wear. The role of the kinin system is the generation of the inflammatory response. The kinin cascade is triggered by contact with a variety of negatively charged surfaces and progresses to produce bradykinin as the end product. The consequences of kinin activation include an increase in vascular permeability, vasodilatation, pain, smooth muscle contraction and an ability to stimulate arachidonic acid metabolism (Stites and Terr, 1991). High molecular weight kininogen, a key protein in the mediation of inflammation, has been implicated in a variety of disorders and allergic responses at other mucosal body tissues (Mann and Tighe, 2000).

	Average conc. in tears (mg/ml)	*Tear/ Plasma derived*	*Function*
Albumin	0.1*	Plasma	Transportation of free fatty acids, stabilizing the osmotic pressure
Lactoferrin	1.4*	Tear	Inhibitor of bacterial growth, possible anti-inflammatory properties
IgA	0.3*	Plasma/Tear	Primary antibody of the mucosal surfaces
IgG	0.13*	Plasma	Predominant antibody in serum immunoregulation
Kininogen	n/a	Plasma	Peptide mediator produced in an inflammatory episode
Kallikrein	n/a	Plasma	Cleaves kininogen to release bradykinin – a vasoactive peptide
IgE	0.014	Plasma	Triggers the release of pharmacological mediators from mast cells during allergic response

Table 1.4. Characteristics of the 7 proteins of interest in this thesis. *The concentrations have been extensively analysed in the Biomaterials Research Unit adopting a defined set of criteria. Fresh unpooled samples from the non-stimulated normal eye were measured by immunodiffusion techniques.

1.17.2.d Functions

The main functions of the aqueous layer are: (a) to supply atmospheric oxygen to the avascular corneal epithelium; (b) to provide antibacterial properties to the tears; (c) to support the immune response; (d) to serve as a vehicle for the influx of healing agents during injury (e.g. polymorphonucleocytes or fibronectin); (e) to abolish any tiny irregularities of the anterior corneal surface; (f) to wash away debris, irritants and foreign bodies; (g) to maintain epithelial integrity; (h) to provide a generalized wetting action by lowering surface tension, and thus allowing the tear film to spread effectively over the cornea and conjunctival surfaces (Kanski, 1999; Craig, 2002).

1.17.2.e Alterations with contact lens wear

Contact lens wear is known to alter tear film composition and therefore its functions and properties (Tomlinson, 1992). During adaptation to contact lens wear, there is an increase in vascular response and tear flow (increased reflex secretion) from the lacrimal gland. This is believed to be due to mechanical irritation/ stimulation induced by the insertion of a foreign body (a contact lens) into the eye. The increased vascular response will affect the integrity of the blood/tear barrier inducing leaking of proteins derived from serum into the tear film. The increased vascular response and tear flow induce changes in the concentration of electrolytes, proteins and glucose levels. The implications of altered tear film components with contact lens wear are not well understood.

1.17.3 The mucin layer

1.17.3.a Origin and innervation

The deep mucin layer is primarily secreted by specialized conjunctival globet cells with contributions from the crypts of Henle in the fornices. Secondary sources of mucin secretion into the tear film are from the non-globet epithelial cells of the conjunctiva (Dilly, 1986). The mechanism of mucin secretion is not fully understood, but is believed to be driven by neuronal control (Dartt, 1992).

Globet cells are not directed innervated (Kessing, 1968). However, it is believed that the conjunctival stroma and the stratified squamous cells of the epithelium are innervated, allowing the diffusion of neurotransmitters to the globet cells (Ruskell, 1985). It has been suggested that neurotransmitter ligand binding to cell surface receptors causes the mucin granule membranes to fuse with the apical globet cell membrane and release mucin onto the ocular surface (Dartt, 1994).

1.17.3.b Structure

There is uncertainty over the precise thickness of the mucin layer. Early research revealed values of 0.02-0.04 μm (Holly, 1973). Research on guinea pigs suggested values of 0.8-1.0 μm (Nichols *et al.*, 1985). However, more recently Prydal *et al.* (1992) reported a mean total tear film thickness of 34-45 μm, and they proposed that the film seems to be composed substantially of mucus, not of aqueous fluid as previously thought.

1.17.3.c Functions

The mucin layer is known to increase the wetting properties of the corneal epithelium, allowing the aqueous tears to spread over the cornea and thus ensure adequate tear film stability (Lin and Brenner, 1986; Dartt, 1994). Traditionally, the corneal epithelium was believed to be hydrophobic in nature and it was suggested that the mucin layer plays a main role in overcoming hydrophobicity which is essential for maintaining tear film stability (Lemp *et al.*, 1970; Holly and Lemp, 1971; Holly, 1973). Later work by Tiffany (1990a, b) has shown that the corneal epithelium is relatively hydrophilic and capable of supporting the tear film without the aid of mucus. However, when areas of non-wetting develop in the corneal surface, such as in cases of surface damage, the mucus may play an essential role in overcoming the temporary hydrophobicity (Tiffany, 1994). It has been proposed that the microvilli of the corneal surface must act to increase corneal epithelium

wettability by geometrically increasing the effective surface area (Danielli *et al.*, 1958). An adequate supply of mucus to the tear film is required to maintain adequate hydration and lubrication of the cornea and conjunctiva (Kaura and Tiffany, 1986; Rohen and Lütjen-Drecoll, 1992).

The mucin layer provides protection to the epithelial surfaces. Mucus threads cover foreign bodies with a slippery coating and thus protect the cornea and conjunctiva from abrasion.

1.17.3.d Composition

The main composition of this layer comprises salts, free proteins and glycoproteins together with a balance of water (Bright and Tighe, 1993).

1.17.3.e Alterations with contact lens wear

Changes in mucus production and composition have been reported with contact lenses wear (Greiner and Allansmith, 1981; Versura *et al.*, 1987). The implications for successful contact lens wear are not well known; however, these changes may result in a higher rate of contact lens deposition and, consequently may be partially responsible for the reduction in tear film stability observed in contact lens wearers.

Lipid layer	Retard evaporation of the underlying aqueous layer
	Lower the surface tension of the tear film, drawing water into the tear film and thickening the aqueous layer
	Lubricate the eye lids
Aqueous layer	Supply atmospheric oxygen to the avascular corneal epithelium
	Provide antibacterial properties to the tears
	Abolish any tiny irregularities of the anterior corneal surface
	Wash away debris, irritants and foreign bodies
	Supports the immune response
	Serves as a vehicle for the influx of healing agents during injury (e.g. polymorphonucleocytes or fibronectin
Mucin layer	Converts the hydrophobic corneal epithelium into a wettable hydrophilic surface, allowing the aqueous tears to spread over the cornea by creating a low interfacial tension between the cornea and the tear film
	Maintenance of the corneal epithelium

Table 1.5. Summary of tear film functions

Table 1.6. Composition of the major tear components and their concentrations in the tear film (mg/ml) in normal healthy unstimulated tears. Data obtained from a survey of over 100 published reports (adapted from Bright and Tighe, 1993).

1.18 Mechanisms for tear film formation and rupture

The fact that the tear film is composed of several layers, together with the interactions between these layers at the air-lipid and mucin-corneal epithelium interfaces, suggests that the mechanisms of tear film formation and rupture are heterogeneous. Agreement in the mechanisms of tear film formation has been found between researchers; however, the exact mechanisms of tear film rupture remain unclear. Several theories have been proposed and are summarized below (Holly, 1973, 1978; Holly and Lemp, 1971, 1977; Lin and Brenner, 1982; Sharma and Ruckenstein, 1985).

Formation

Involuntary periodic blinking has a primary role in maintaining the structural integrity of the tear film as the blinking process distributes a smooth, stable and thin tear film across the corneal surface, between the eyelids and over the ocular globe. Blinking distributes in the superficial lipid layer the meibomian lipids present at the lid edges. Subsequently, mucin layer formation occurs as a result of mucus spreading secreted by the conjunctival globet cells and crypts of Henle on the corneal epithelium. Removal of lipid contaminants from the corneal epithelium is also evident with blinking (Holly, 1973). Mucin layer formation increases wettability of the corneal epithelium allowing a stable aqueous layer to overlie it. The thickness of the tear film is maximum just after a blink and decays to a minimum over time until it ruptures.

Rupture

Following a blink, tear film thickness in the normal eye decreases as a result of evaporation, drainage and filtration across the cornea by about 50 % in 15 to 60 seconds. At this point the film ruptures almost immediately (Norn, 1969).

The main function of the lipid layer is to retard evaporation. However, 5-20 minutes of continuous evaporation are needed to eliminate the tear film under normal conditions (Mishima and Maurice, 1961a, b). About 7 % of the aqueous layer evaporates in 1 minute under normal circumstances (Holly, 1981). On the other hand, clinical observation shows that when the eyes are held open for a long period of time the tear film breaks in less than a minute, leading to dry spot formation (Lemp *et al.*, 1970; Holly, 1973).

Several theories have been proposed to explain the mechanisms of tear film rupture. Holly (1973) proposed that tear film rupture occurred due to disruption of the mucin layer as a

result of contamination from lipid which had migrated from the lipid layer. Migration of lipids to the mucin layer were believed to overwhelm the hydrophilic capacity of the mucus layer, thus creating localized areas of high hydrophobicity on the corneal epithelium. These non-wettable areas increase until the aqueous layer comes in contact with the corneal epithelium and substantial tear film break-up takes place. The widely accepted theory of Holly has been challenged by Sharma and Ruckenstein (1985). They proposed that the presence of lipids is not necessary for tear film rupture as it is observed even in the event of complete obstruction of the meibomian gland openings (Holly and Lemp, 1977). Sharma and Ruckenstein (1985) elaborated a theory based on the previous work of Lin and Brenner (1982) in which they proposed that the entire tear film breaks as a result of van der Waal dispersion forces acting on the aqueous layer. This theory can be summarized in three stages. The blinking process distributes a smooth tear film onto the corneal epithelium. At this point the tear film is stable, but is gradually thinning as a result of evaporation and drainage leading to localized areas of reduced tear film thickness. Dispersion forces act on the mucin layer at points where this is initially thinner destabilizing this layer. If this process is not reversed by the blinking process, the growing interfacial perturbations cause layer rupture within 15 to 50 seconds in a normal eye. The final stage of the process occurs when the aqueous film comes into contact with the exposed hydrophobic epithelium at various sites where the mucus layer is ruptured, resulting in lipid contamination of the cornea and the formation of increasingly large areas of non-wetting. This later theory proposed by Sharma and Ruckenstein (1985) correlates with the work of Tiffany and colleagues (1989) who found a negative correlation between tear surface tension and tear film break-up.

A different theory for tear film rupture has been proposed by Liotet *et al.* (1987) who suggested that the surfacting agent of the corneal epithelium is glycocalyx and not mucus. Therefore, the even spread of the tear film is a function of the cells of the corneal epithelium and not simply a result of mucus spreading onto it. According to this theory, epithelial cell integrity is essential for tear film stability. The development of dry spot formation on the cornea results from failure of the corneal epithelial cells to synthesize glycocalyx leading to lack of specific sites of fixation for mucus proteins. Such a failure could occur from physical trauma or nutritional deprivation resulting from contact lens wear. It is of interest in view of this theory that work by Lemp *et al.* (1971) showed a positive correlation between the tear break-up time and the population of globet cells. An

alternative hypothesis to the incompleteness or absence of mucus leading to dryness during contact lens wear has been offered by Vesura *et al.* (1987), who suggested that contact lens wear could alter the normal mucus production leading to a reduced tear film stability.

1.19 Tear film thickness

Measurement of tear film thickness has been carried out by many researchers (Ehlers, 1965; Mishima, 1965; Benedetto *et al.*, 1975; Guillon, 1986; Prydal *et al.*, 1992; Danjo *et al.*, 1994; Creech *et al.*, 1998; King-Smith *et al.*, 2000). However, there is uncertainty over the precise total tear film thickness and that of the individual layers. Since the early work of Mishima (1965) in rabbit eyes, estimation of the tear film thickness varies greatly in the literature from 3 μm (King-Smith *et al.*, 2000) to 45 μm (Prydal *et al.*, 1992), with no consensus about the correct value. Table 1.7 shows the published values of tear film thickness in human eyes.

Early measurements of tear film thickness in humans and animals used invasive methods, such as fluorometric methods (Mishima, 1965; Benedetto *et al.*, 1975), touching the cornea with a wettable paper (Ehlers, 1965), or placing a glass fibre against the cornea (Mishima, 1965). The invasive nature of these methods is likely to disrupt the normal tear film characteristics and increase reflex lacrimation. The controversy in tear film thickness has risen in the last decade with the development of new non-invasive interferometric methods which reported values in the range of 3-12 μm (Danjo *et al.*, 1994; Fogt *et al.*, 1998; King-Smith *et al.*, 2000). Very recently, pre- and postlens tear film thickness has been measured *in vivo* by interferometry. Wang *et al.* (2003) using optical coherence tomography reported a precorneal tear film of 3.3 μm. This value was reported to increase significantly to 4.7 μm after removal of soft contact lenses and was attributed to reflex tearing. They reported a pre- and post-lens tear film thickness of 3.6 μm and 4.6 μm, respectively with conventional hydrogels and silicone hydrogel contact lenses. Nichols and King-Smith (2003) using a novel inteferometric technique reported a pre- and post-lens tear film thickness of 2.31 and 2.34 μm respectively with conventional hydrogel contact lenses. No significant differences in the pre- and post-tear film thickness have been found between *Acuvue* and Lotrafilcon and between *Acuvue* and Balafilcon lenses (Nichols and King-Smith, 2001; Wang *et al.*, 2003). However, these findings should be interpreted with caution as the thickness of the tear film is likely to change with movement, wearing times, ambient humidity, palpebral aperture size, corneal curvature, ethnicity, contact lens material and corneal thickness (Nichols and King-Smith, 2003).

Interference methods work by producing interference between the light beam reflected by the different layers of the tear film, giving rise to coloured fringes. The coloured fringes observed in the tear film correspond to the superficial lipid layer (Guillon, 1986; Doane, 1989). Careful analysis of these fringes, particularly those of maxima and minima intensity (bright and dark bands), permits measurement of the tear film thickness.

A review of the literature can be summarized as follows:

- Tear film thickness is likely to be in the range of 3-10 μm, varying greatly between individuals.
- The different values reported are likely to be due to the different techniques employed.
- The search for an indisputable value of the precorneal, pre-lens and post-lens tear film thickness continues.

Ehlers (1965)	Invasive: absorbing the tear film onto a piece of paper	7μm
Mishima (1965)	Invasive: glass filament technique Invasive: fluorometric method	7.5 μm 6.5μm
Benedetto *et al.* (1975)	Invasive: fluorometry	4 μm
Guillon (1986)	Non-invasive: interferometry	4.4 μm
Prydal *et al.* (1992)	Non-invasive: interferometry	34–45 μm
Danjo *et al.* (1994)	Non-invasive: interferometry	10.3–12 μm
Creech *et al.* (1998)	Invasive: fluoremetry	6-12 μm
King-Smith *et al.* (2000)	Non-invasive: interferometry	3 μm
Wang *et al.* (2003)	Non-invasive: interferometry	3.3 μm

Table 1.7. Published values of tear film thickness in human eyes.

1.20 Clinical and biochemical aspects of the tear film

In recent years, the precorneal tear film has been subject to intense study due to its importance in the preservation of the normal optical properties of the largest refractory component of the eye, the cornea. The assessment of tears has been found to be extremely important in the screening of potential contact lens wearers. Preocular tear film parameters must be maintained within moderately narrow limits to facilitate the various functions of the lacrimal system. Dysfunction of the surrounding corneal and conjunctival structures

can arise from deficiencies in the quality or quantity of any of the vital tear film components. Several tests and techniques have been developed to assess both quantity and quality of tears.

1.20.1 Clinical aspects

Clinical assessment of the tear film is of special interest in understanding *in vivo* interactions of contact lenses with ocular tissues and fluids. Since Schirmer developed in 1903 his tear production test, several tests and techniques have been described for the clinical assessment of the tear film (Guillon, 2002), such as surface interference phenomena, tear meniscus height, tear break-up time and the phenol red thread test. Of special interest in this thesis are those techniques which assess surface interference phenomena, tear film stability and tear volume due to their non-invasive nature.

Surface interference phenomena

It is well established that the lipid layer plays a major role in providing tear film stability. Observation, assessment and categorization of this layer may provide further insight into the interaction of contact lenses with the tear film and ocular anexa. Surface phenomena have been proposed for the observation of the lipid layer of the tear film since the introduction of slit-lamp biomicroscopes. Interference phenomena methods work by producing interference between the light beam reflected by the different layers of the tear film, giving rise to coloured fringes. The coloured fringes observed in the tear film correspond to the superficial lipid layer (Guillon, 1986; Doane, 1989).

Guillon (1986) used interference methods to study the lipid layer of non-wearers and contact lens wearers, and his observations led to the development of the *Keeler Tearscope plus*. This instrument allows *in vivo* lipid layer visualisation and categorisation of the preocular, pre-soft and pre-RGP contact lens tear film lipid patterns. The utility of this instrument has been further analysed and improved by Guillon and Guillon (1993). Perrigin *et al.* (2000) investigated inter- and intra-subject consistency of responses with the *Keeler Tearscope plus* when assessing the lipid layer. They found large variation in both between and within groups of inexperienced observers. The agreement between observers declined as the number of observers increased. The *Keeler Tearscope plus* is the only commercially available instrument for the observation, assessment and categorization of the lipid layer. Lipid layer assessment is presented in this study to investigate the effects induced by contact lenses. Assessment of the lipid layer has been carried out in all the

subjects prior to and during contact lens wear as well as in a group of non-contact lens wearers.

Tear break up time

Tear break-up time has been widely accepted as a measure of tear film stability since it was first introduced by Norn (1969) and is defined as the interval in seconds between the last blink and the appearance of the first black dry spot or streak in the fluorescein-stained tear film (Norn, 1969; Lemp and Hamill, 1973). Tear break-up time measurements therefore require instillation of fluorescein into the eye for the observation of tear film break-up. It has been shown that topical instillation of fluorescein in the eye decreases tear film stability (Mengher *et al.*, 1985a, b; Patel *et al.*, 1985). As a result of the invasive nature of the fluorescein tear break-up time several non-invasive techniques for measuring tear break-up time have been developed. It has been suggested that non-invasive tests are superior to invasive methods but give higher values of tear break-up time. All these non-invasive techniques are optical in nature and most are based on the original idea of Lamble *et al.* (1976), who suggested that observation of a grid projected onto the corneal surface may provide a non-invasive indication of tear film stability. Non-invasive tear break-up time (NITBUT) techniques include the Mengher method (Mengher *et al.*, 1985a, b), the non-invasive tear assessment instrument (Cho, 1993), the *HIR/ CAL grid* (Hirji *et al.*, 1989), the *Loveridge grid* (Loveridge, 1993), and the *Keeler Tearscope plus* (Guillon, 1986). The use of the *Keeler Tearscope plus* for the measurement of tear film stability is widely accepted clinically and it has been found to be the most repeatable technique when compared to other techniques (Elliot *et al.*, 1998). It is well known that contact lens wear affects precorneal tear film stability (Faber *et al.*, 1991) and therefore tear stability measurements with the *Keeler Tearscope plus* are presented in this thesis.

Tear volume

The tear meniscus or tear prism, which is formed between the lid surface and the bulbar conjunctiva, is present along the superior and inferior lid margins. It holds 75 to 90 % of the total volume of the tear film. Careful examination of the lower lid tear meniscus height (TMH) may provide a simple but clinically useful indication of tear volume. Traditionally, normal TMH values were believed to vary between 0.2 and 0.5 mm (Lamberts *et al.*, 1979; Port and Asaria, 1990; Guillon *et al.*, 1997). However, recent studies using image analysis techniques have found much lower values (of the order of 0.2 mm) of TMH that those

previously reported (Kwong and Cho, 2001; Doughty *et al.*, 2001, 2002). Assuming a normal TMH to be around 0.2 mm, very sensitive techniques will need to be employed to detect subtle changes in meniscus dimensions. Other quantitative assessments of the tear film meniscus include determination of the radius of curvature, height, width, volume and cross-sectional area using high magnification slit lamp photography and image analysis techniques (Mainstone *et al.*, 1996; Yokoi *et al.*, 1999).

It is not clear whether contact lens wear affects tear volume and thus TMH measurements will be included in this thesis.

1.20.2 Biochemical aspects

The use of polymers for contact lenses represents an example of the biomedical application of synthetic materials. When contact lenses are inserted into the eye they present specific problems associated with their compatibility, strength and permeability. The general biomedical principle of designing a contact lens material is to provide a balance of properties appropriate to the ocular environment. In terms of polymer design, three essential features of the ocular environment need to be considered: the cornea, the eyelid and the tears. The cornea is avascular and the need to ensure oxygen transport to the corneal surface governs the permeability requirement of the contact lens material. The eyelid dictates the range of acceptable mechanical properties, with comfort and retention of visual stability during the blink cycle dominating acceptable upper and lower limits of contact lens elasticity. The interaction of a contact lens with tears is an important example of interaction of a biomaterial with a complex biological environment.

Although the design of successful contact lens materials requires attention to mechanical properties (which are controlled by polymer structure and cross-link density as well as water content), probably the most persistent issue of the last two decades is biocompatibility. The eye, therefore, presents a unique opportunity for *in vivo* studies of biocompatibility provided that the detailed nature and composition of the tear film are suffiently understood. It is well known that contact lens deposits can adversely affect successful contact lens wear. Furthermore, contact lens deposits have been implicated as the causative mechanism behind inflammatory reactions such as giant papillary conjunctivitis and acute red eye syndrome (Grant *et al.*, 1987; Grant *et al.*, 1989). These deposits consist primarily of proteins and lipids from tears, with extraneous substances such us facials cosmetics and skin lipids also potentially implicated (Jones *et al.*, 1997).

Biochemical analysis of tear film components

Several techniques have been described for the analysis of tear film components. The techniques used to identify and quantify the different protein components present in normal human tears include electrophoresis, immunochemistry and enzymatic assays. By far the most widely used analytical techniques are based on electrophoresis (Mann *et al.*, 2002; Mann and Tighe, 2002). Electrophoresis involves an antigen and its respective antibody being driven towards each other in an electrical field. It is a very sensitive and rapid detection method. The basic set-up requires the diffusion of the antigen and the antibody into a gel, which is afterwards examined by electrophoresis. After electrophoresis the precipitation lines allow visualisation of the proteins present in the sample. Specific proteins were investigated in this thesis for their assumed potential to regulate and/or assist in identifying the extent or nature of the host immune response. These are albumin, lactoferrin, IgA, IgE, IgG, Kininogen and Kallikrein. Lipid analysis techniques are commonly based on fluorescence methods which are non-destructive techniques that rely on the fluorescence of lipoidal species following excitation by UV light (Abbott *et al.*, 1991). The technique is based on the intrinsic fluorescence produced by the conjugated double bonds that are present in the majority of lipids found in the tears.

Invasive methods of tear collection, such as the Schirmer filter strip, stimulate the conjunctiva, inducing serum leakage, resulting in a higher concentration of serum proteins than that found in non-stimulated tears. A similar increase in serum proteins is found in the tears of patients with inflammatory diseases (Mann *et al.*, 2002; Mann and Tighe, 2002). Less invasive methods of tear collection, such as the glass microcapillary, have shown higher concentrations of proteins derived from the lacrimal gland (Milder, 1987).

1.21 Aims of this thesis

The aim of this thesis is to further understand and correlate the clinical and biochemical implications of changes in tear film components with contact lens wear. This has been carried out in collaboration with the Biomaterials Research Unit at Aston University where analysis of a variety of proteins and lipids extracted from tear samples and contact lenses collected throughout the study was conducted.

OCULAR PHYSIOLOGY

1.22 Introduction

Contact lens patients can present with a variety of contact lens-induced complications affecting anterior ocular structures. These complications are normally exacerbated when lenses are worn on an extended wear basis (Holden, 1989). Changes in vascular response and corneal integrity are commonly associated with contact lens-induced complications.

Changes in vascular response with contact lens wear

Contact lens wear is well known to induce changes in the hyperaemic state of the bulbar and limbal conjunctiva (McMonnies *et al.*, 1982; Holden, 1989). Some degree of hyperaemia is considered to be a normal consequence of lens wear (Efron, 1987). Whereas, in most instances an increase in ocular redness may represent simply a cosmetic problem, of greater concern is the evidence suggesting that limbal hyperaemia is a necessary precursor to corneal neovascularisation (Collin, 1973). Ocular inflammation, allergy, corneal hypoxia, mechanically-induced effects, surface deposits and other forms of lens degradation which normally occur with contact lens wear are likely to affect the vascular appearance of the bulbar, limbal and palpebral conjunctiva as well as tear film characteristics.

Changes in the palpebral conjunctiva with contact lens wear

Changes in the palpebral conjunctiva have been proposed as a major complication of contact lens wear. These changes include increased redness and roughness of the conjunctiva and are considered primarily to be a consequence of allergic stimuli and mechanical irritation (Allansmith *et al.*, 1977; Efron, 2000).

Changes in corneal integrity with contact lens wear

Corneal integrity and especially epithelial integrity is essential for maintaining a healthy cornea that is free of infection and inflammation. Fluorescein has been widely used for many years to assess corneal integrity and it is commonly accepted that fluorescein staining represents compromised corneal epithelium. Common causes of staining in clinical practice include contact lens wear, keratopathies and complications of systemic disease. However, staining can occur without any obvious case. It has been found that up to 79% of healthy non-contact wearers can present with some degree of staining (Dundas

et al., 2000). Since contact lens wear is likely to compromise the state of the bulbar, limbal and palpebral conjunctiva as well as the epithelial integrity, close monitoring is essential in order to prevent serious contact-lens complications. Furthermore, quantitative assessment of ocular physiology and tear film changes during lens wear has potential implications for the further understanding of the biocompatibility of contact lenses and solutions, as well as ophthalmic medications (Villumsen and Alm, 1989; Owen *et al.*, 1996).

Effect of silicone hydrogel contact lenses on ocular physiology

Clinical trials with the new generation of silicone-hydrogel contact lenses have shown that hypoxic-related complications are virtually eliminated due to their high oxygen permeability (Papas *et al.*, 1997; Keay *et al.*, 2000). As a result of the increased rate of oxygen permeability, several studies have found a decreased vascular response with silicone-hydrogel lenses compared with conventional soft contact lenses (Papas *et al.*, 1997; Dumbleton *et al.*, 2001; Brennan *et al.*, 2002). However, additional problems have been identified; mechanically-induced adverse reactions such as superior epithelial arcuate lesions and localized contact lens-induced papillary conjunctivitis have been previously reported with these new lenses (Holden *et al.*, 2001; Skotnitsky *et al.*, 2000, 2002). Other inflammatory conditions such as corneal infiltrates and contact lens-induced peripheral ulcers do not appear to have diminished with silicone hydrogel materials compared to conventional hydrogels (Holden, 2002; Brennan *et al.*, 2002; Fonn *et al.*, 2002). Protein deposits, lens ageing, mechanical effects and bacterial contamination, as well as problems with lens design and biocompatibility of contact lens materials with ocular tissues and fluids, have all been implicated in the development of these adverse reactions. Other studies have reported decreased levels of ocular health in extended wear of conventional hydrogel lenses when compared to high-Dk silicone hydrogel contact lenses (Brennan *et al.*, 2002; Dumbleton *et al.*, 1999). However, most of these studies have compared 7 days of extended wear with a conventional hydrogel lens *vs.* 30 days of continuous wear with a single high-Dk silicone hydrogel contact lens. These previous studies have assessed in pre-adapted contact lens wearers a limited number of parameters over a short period of time. To date, little is known about the long-term effects on ocular physiology and tear film characteristics of the two silicone hydrogel contact lens currently available commercially (Lotrafilcon A and Balafilcon A) when worn by neophytes on both a daily and continuous wear basis.

1.23 Clinical monitoring of ocular physiology

Grading scales for assessing the severity of ophthalmic conditions are increasingly popular with practitioners as part of their clinical decision-making and record keeping. Grading accurately the severity of the most clinically relevant conditions and signs is of undoubted value for both the patient and practitioner. Development of grading tools for assessing the severity of ocular complications of contact lens wear has been of particular interest in recent times.

Subjective grading

In the past, contact lens-related complications have been graded with reference to qualitative textual categories (i.e. mild, severe, etc.). However, this approach presents several problems in the absence of any form of standardisation; that is, what appears to be "mild" to one practitioner may be "severe" to another. More recently, full colour, illustrative contact lens grading scales have been developed (Annunziato *et al.*, circa 1992; Andersen *et al.*, 1996; CCLRU, 1997; Efron, 1998). This type of grading provides the contact lens practitioner with a visual reference to grade the severity of a particular condition with the help of a graded series of reference photographs, paintings or drawings. These illustrative contact lens grading scales have been validated by Efron *et al.* (2001) who found them all to be valid and useful in gauging the severity and monitoring the progression of ocular complications of contact lens wear. However, due to the differences in the design of these illustrative grading scales, the author opted to use the same Efron grading system throughout. It is well accepted that grading ocular complications by interpolation or extrapolation to the nearest 0.1 grade scale unit tends to optimise grading sensitivity (Bailey *et al.*, 1991). A difference or change in grade of approximately 1.0 (range 0.5 to 1.2 units) has been proposed to be both clinically and statistically significant when using these grading scales (Efron, 1998; Efron *et al.*, 2001; Mackinven *et al.*, 2001). The combined influence of knowledge, training and experience as determinants of grading reliability has been found to have a minimal effect when assessing the severity of contact lens complications (Efron *et al.*, 2003a, b).

Objective grading

Several objective techniques have been developed for the quantitative assessment of ocular physiology (Villumsen and Alm, 1989; Guillon and Shah, 1996; Owen *et al.*, 1996; Papas, 2000; Wolffsohn and Purslow, 2003). These techniques involve digital imaging in conjunction with computerised image analysis, which allow objective, clinically valid and repeatable quantification of ocular features, offering the possibility of improved diagnosis and monitoring of changes in ocular physiology (Wolffsohn and Purslow, 2003). Objective techniques are inherently less variable than subjective grading. Whereas, subjective grading scales might be useful in routine clinical practice, they are unlikely to be sensitive enough to detect subtle changes required for robust clinical research studies.

1.24 Aim of this thesis

The aim of this thesis is to monitor ocular health in silicone-hydrogel contact lens wearers with both subjective and objective means of assessment and to relate the results to associated and concurrent biochemical and symptomatological work. Additionally, special attention has been given to the grading and monitoring of more serious adverse reactions such as, for example, contact lens-induced peripheral ulcers. The aetiology, clinical signs and symptoms, incidence rates and treatment are further evaluated. Subjective grading is carried out using Efron grading scales (Efron, 1998). Additionally, photographs of bulbar conjunctiva, tarsal plate and corneal staining have been taken throughout the study for objective assessment and comparison with subjective grading. It is envisaged that these pictures, together with those of the corneal section and tear meniscus, could be employed to standardize a new objective image analysis technique and to develop a new grading scale. The new objective image analysis consists of dedicated computer software written by the author's associate supervisor Dr J.S. Wolffsohn for the assessment of the most common ocular physiology changes seen with contact lens wear (Wolffsohn and Purslow, 2003).

SYMPTOMATOLOGY

1.25 Introduction

Knowledge of symptoms, visual quality and ocular comfort is clearly essential in managing patients' ocular history. The aetiologies and mechanisms of subjective responses reported by contact lens wearers are not well understood. Subjective assessment of symptoms is as relevant as the clinical management of the contact lens patient due to the lack of association between ocular signs and symptoms (McMonnies, 1986; Schein *et al.*, 1997a; McCarty *et al.*, 1998). It has been suggested that this lack of association may be partly due to the lack of understanding of symptoms and how they relate to clinical test results (Nichols *et al.*, 1999). It has been also proposed that the lack of association may be due to the limited standardization of diagnostic tests and symptomatology questionnaires (Lemp, 1995). Moreover, the clinical significance of abnormal clinical test results in the absence of symptoms has been questioned (Schein *et al.*, 1997b). Contact lens-related symptomatolgy may partly arise from contact lens care systems. Multipurpose solutions have gained a great deal of popularity in the last few years, due to their convenience and low cost. Currently, two multipurpose systems are commonly in use with silicone-hydrogel materials: a polyaminopropyl biguanide-based system (*ReNu MultiPlus*, Bausch & Lomb) and a polyquad-based system (*Opti-Free Express*, Alcon Laboratories). Jones *et al.* (2002) found significantly higher levels of corneal staining in subjects using the polyaminopropyl biguanide-based system compared to polyquad-based system. However, significant symptoms were not correlated with the degree of staining, with no differences in lens comfort or overall preference being reported between the multipurpose systems. Grading accurately subjective responses to contact lens wear will aid in identifying risk factors for adverse events and further understanding the effects of contact lenses on the eye. Knowledge of these risk factors may allow clinicians to offset any potential for discomfort, compromised ocular health and ultimately failure of contact lens wear.

1.26 Common symptoms

Some of the more commonly reported symptoms to contact lens wear include dryness, discomfort, burning, itching, blurred vision, excess tearing, photophobia, lens handling problems and others. Contradictory results on reported symptoms with contact lens wear have been reported in the literature. Sweeney *et al.* (2000) found that only 20% of soft and silicone-hydrogel contact lens wearers reported no symptoms, whereas Nilsson (2001) reported that about 80% of a group of continuous and extended wear subjects wearing silicone-hydrogel lenses did not report any symptoms or express complaints. Dryness and discomfort are by far the most frequently reported symptoms in contact lens wearers compared to non-contact lens wearers (Begley *et al.*, 2001). It is envisaged that contact lens-related symptomatolgy may be partly related to alterations caused to the tear film. However, post-lens tear film morphology has been shown to be unrelated to commonly reported contact lens-related symptoms (Little and Bruce, 1994).

Dryness

Some studies have reported as many as 50-75 % of contact lens wearers always experience dryness (Brennan and Efron, 1989; Doughty *et al.*, 1997; Moss *et al.*, 2000). Nichols *et al.* (2002) found that self-diagnosis of dry eye and symptoms of dryness whilst wearing contact lenses were significant predictors of contact lens-related dry eye. Silicone-hydrogel lenses have been reported to be preferable in terms of dryness than traditional hydrogel lenses (Brennan *et al.*, 2002). Lubricating eyedrops have been used successfully in alleviating end-of-day dryness or dryness upon waking in continuous wear of silicone-hydrogel contact lenses (Iruzubieta *et al.*, 2001).

Comfort

Comfort is one of the main reasons for patient unhappiness and dropout from contact lens wear (Vajdic *et al.*, 1999; Young *et al.*, 2002). Terry *et al.* (1993) proposed that a successful contact lens wearer must consistently experience an overall comfort equivalent to a rating of 60 or better both immediately on insertion and throughout the period of wear (1 = pain induced by the contact lens; 100 = the lens cannot be felt at all). Nichols *et al.* (2000) found equally successful both daily disposable and disposable extended wear contact lens modalities in terms of comfort. Nilsson (2001) carried out a 1-year study on 504 subjects wearing Balafilcon A silicone-hydrogel contact lenses on either an extended or continuous wear basis and found a subjective judgment of comfort of 91 and 92,

respectively, in a scale from 0 (worst) to 100 (best). No significant difference was found in symptoms/complaints between the two groups. Iruzubieta *et al.* (2001) in a study of 85 subjects who were dispensed Lotrafilcon A fluorosilicone-hydrogel continuous wear contact lenses, reported an overall comfort of 9.1 for a 6-month period, where 0 indicates unacceptable and 10 excellent comfort. Siegel and Spilkin (2000) found subjective comfort to be significantly better with *PureVision* lenses than with *Focus Night & Day* lenses, both worn on a 7-day extended schedule for 1 month. Dumbleton *et al.* (2002) reported that 24% of subjects previously fitted with 8.6 mm base curve Lotrafilcon A lenses required an 8.4 mm base curve in order to alleviate subjective discomfort. Furthermore, they proposed the use of the 8.4 mm base curve lenses for corneal curvatures 45.50 D or when the comfort (15 minutes after insertion) was approximately 8 while wearing the 8.6 mm base curve lenses (1 = poor comfort, 10 = excellent comfort). As a result of dryness most of these studies have reported reduced comfort towards the end of the day and on awakening. Nichols *et al.* (2000) and Iruzubieta *et al.* (2001) found a significant number of patients reporting increased levels of ocular discomfort and irritation in the morning while in the extended wear modality compared to the daily disposable modality. Higher levels of comfort have been reported with silicone-hydrogel materials compared to traditional hydrogel materials (Sweeney *et al.*, 2000; Brennan *et al.*, 2002). The level of comfort with Balafilcon A and Lotrafilcon A silicone-hydrogel lenses when worn either on a daily or continuous wear basis is presented in this thesis and compared to non-contact lens wearers.

Vision

Vision should always be maintained at a high level if successful contact lens wear is the expected outcome. Terry *et al.* (1993) proposed that vision should be maintained at least to a rating of 60, with no significant blur, visual fluctuation, haloes or flare, where 100 is considered "perfect" vision or at least comparable with the best corrected spectacle performance. Nichols *et al.* (2000) and Fonn *et al.* (2002) reported no difference in high and low contrast visual acuity and vision between daily disposable and extended wear of contact lenses. Nilsson (2001) reported a visual acuity of 20/20 or better in approximately 85% of their subjects wearing Balafilcon A lenses in either an extended or continuous wear basis. Iruzubieta *et al.* (2001) reported an overall satisfaction of vision of 9.4 in a group of continuous wear subjects wearing silicone-hydrogel lenses. Sweeney *et al.* (2000) reported that both silicone-hydrogel and daily-soft contact lenses gave excellent overall vision throughout the day and problems were only encountered in specific individuals where lens

deposits and distorted lenses (warped) were the reasons put forward. The level of visual performance achieved in all subjects groups is presented in this thesis and cases of poor vision analysed.

Patient satisfaction

Sweeney and co-workers (2000) in a study of 74 patients wearing silicone-hydrogel lenses on a continuous wear basis for 12 months or longer reported that 93 % of patients rated their lens system as excellent. The main reason for their satisfaction was its convenience. Other factors such as minimal care and maintenance or lens handling (88 %), being able to see in the morning (7 %) and excellent comfort (5 %) were also responsible for the high level of satisfaction reported. Ten per cent of patients reported being unaware of wearing lenses. Siegel and Spilkin (2000) found overall satisfaction to be significantly better for Balafilcon A than Lotrafilcon A materials, when both were worn on an extended wear schedule for 1-month. Long *et al.* (2000) in a six months study with high-Dk Lotrafilcon A soft contact lens reported that 82% of patients were very satisfied. A recent publication by Iruzubieta *et al.* (2001) on practical experience with Lotrafilcon A fluorosilicone-hydrogel extended wear lenses in Spain reported an overall satisfaction of 98 % with patients expressing that they were very satisfied (84 %) or somewhat satisfied (15 %) at the six month aftercare visit. A way to assess the success or otherwise of continuous wear of contact lenses is to record whether patients are complying with the proposed wear schedule; that is, how often the patients have to break the 30-night day circle, either to rub, rinse and immediately re-inset their lenses or to remove them for longer periods, possibly involving an overnight break. Contact lens removal is a way of dealing with minor episodes of discomfort, dryness or surface deposits that may occur and should be recorded. Sweeney and co-workers (2000) reported that 79 % of silicone-hydrogel patients were compliant with their 30-days prescribed wear schedule with no unscheduled overnight removals, and over 90 % of patients removed their lenses only once or twice for an overnight break during the 30-night period.

1.27 Subjective grading of symptoms in contact lens wearers

Subjective assessment of symptoms with contact lens wear plays an important role in detecting contact lens-related complications and ensuring successful contact lens wear. Several questionnaires have been developed to grade these subjective responses (Du Toit *et al.*, 2002; Nichols *et al.*, 2002). Grading symptoms accurately can be difficult due to the subjectivity of the methods of assessment and the diurnal changes in their frequency and severity (Begley *et al.*, 2001). Additionally, comparison between studies is a problem due to the lack of standardization of questionnaires. A fully validated questionnaire would lead to a wider understanding of the demographics and risk factors induced by contact lens wear. The contact lens dry eye questionnaire (CLDEQ) has been found to be accurate in discriminating contact lens-related dry eye, especially when compared to McMonnies questionnaire (Nichols *et al.*, 2002). Whereas McMonnies' survey focuses on risk factors associated with dry eye, the CLDEQ focuses on the severity, frequency and impact of a large variety of symptoms commonly found in contact lens wearers. A similar version of the CLDEQ, the dry eye questionnaire (DEQ) is also available for detecting non-contact lens wearers with dry eye. Du Toit *et al.* (2002) compared three different scales for rating contact lens handling: visual analogue scale, visual analogue scale with demarcations and descriptors and likert (refers to qualitative textual categories) rating scale. They found visual analogue scales to be the most accurate of the three systems analysed and they proposed that this system provide a simple and repeatable tool for measuring subjective responses. The search continues for an indisputable and universally accepted questionnaire that accurately grades different contact lens-related symptoms.

1.28 Aim of this thesis

The aim of this thesis is to analyse the subjective responses experienced in all the subject groups by means of visual analogue scales and the CLDEQ and relate these symptoms to clinical and biochemical work. Comparisons between contact lens materials, regimes of wear and care systems are also presented.

CHAPTER 2
INSTRUMENTATION AND APPARATUS

2.1 Introduction

Chapter 2 outlines and summarises the instrumentation, apparatus and techniques employed in the experimental work. Details of commercially available devices are included and modification and validation described. Novel techniques specifically designed during the course of this thesis are also described together with dedicated digital image analysis tools.

2.2 Refractive and biometric

2.2.1 The Shin-Nippon NVision-K 5001 open view infrared autorefractor

The Shin-Nippon NVision-K 5001 autorefractor (Shin-Nippon Commerce, Inc., Japan) is a relatively new device for the objective measurement of refractive error and keratometry. Automated refraction has been demonstrated to be more repeatable than subjective refraction and therefore more appropriate for studies of refractive error (Bullimore *et al.*, 1988). Figure 2.1 shows the Shin-Nippon NVision-K 5001 open view infrared autorefractor. The open field design makes the device particularly useful in refractive research. This instrument has been validated clinically in our research laboratories by research fellow Leon Davies and colleagues (Davies *et al.*, 2003). The instrument was found to produce valid and repeatable refraction and keratometric measurements in normal subjects and therefore is suitable for research studies. All refractive measurements were taken with this device for this thesis.

The refractive measurement procedure can be summarized as follows:

Subjects were positioned on the instrument chin rest and instructed to view a distance target. The instrument was directly aligned with the visual axis of the eye under examination. Depression of the measurement button on the instrument's joystick projects a 2.3 mm diameter 3-segment ring target of infrared light into the eye, which is reflected by the retina. The size of the reflected ring image is analysed digitally and compared to the size of the initial ring target in order to calculate refractive error. Five measurements were taken, averaged and the mean spherical equivalent calculated (MSE). The same procedure was repeated on the subject's other eye.

Davies *et al.* (2003) found refractive error as measured by the Shin-Nippon NVision-K 5001 autorefractor to be not statistically different ($p = 0.67$) to subjective refraction (difference, 0.14 ± 0.35D). They also found good repeatability as assessed by the difference of six repeated readings taken on each subject in one session (mean difference for the mean spherical component, 0.09 D) and by the difference in prescription found at different sessions (95% of second visit prescription findings were approximately within ± 0.50 D of the measurement found at the initial visit).

Figure 2.1. Shin-Nippon NVision-K 5001 autorefractor.

2.2.2 Zeiss *IOLMaster*: Description and clinical evaluation

The Zeiss *IOLMaster* is a device which uses partial coherence interferometry to measure axial length (Hitzenberger, 1991; Haigis *et al.*, 2000). In addition, measures of anterior chamber depth and corneal curvature can be obtained with this instrument by means of image analysis. Whereas its principal application is the computation of intraocular lens power required for patients undergoing cataract surgery, the relatively high order of dioptric resolution for axial length (± 0.03 D) is especially valuable for studies of myopia. Traditionally, the standard reference method for axial length measurements has been A-scan ultrasonography. Ultrasound requires contact with the cornea, thus requiring the use of a topical anaesthetic. The *IOLMaster* is a non-contact device which eliminates the risk of corneal abrasion and reduction in the length of the eye by applanation. Previous laboratory studies have shown good agreement between partial coherence interferometry

and ultrasound methods of measurement (Hitzenberger, 1991; Hitzenberger *et al.*, 1993; Haigis *et al.*, 2000).

Axial length measurements were performed in low room light conditions with the subjects positioned on the instrument chin rest in order to maintain relatively large pupil diameters. They were instructed to view an internal fixation target. The monitor was used to align the right eye followed by the left. Subjects were asked to perform a complete blink just before measurements were taken in order to spread an optically smooth tear film over the cornea. Three measurements were taken in each eye and a mean was calculated.

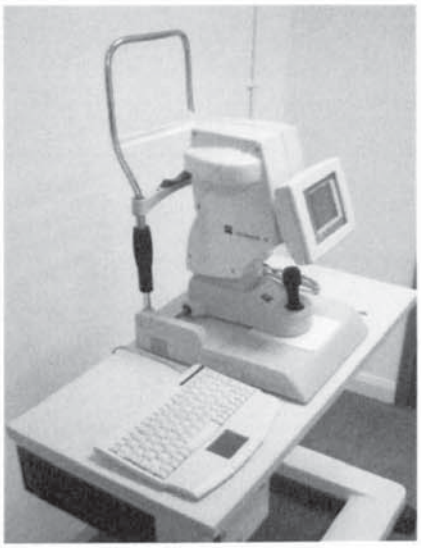


Figure 2.2. Zeiss *IOLMaster*

Anterior chamber depth measurements were taken with subjects positioned in the same manner as for axial length measurements. The instrument camera was aligned so that a slit beam formed an optical section and the internal software measures the distance between the anterior corneal pole and the anterior crystalline lens. A single-shot measurement automatically generates the mean of five consecutive readings, which was used for analysis purposes. The same procedure was repeated on the fellow eye.

Corneal curvature measurements were taken with subjects positioned in the same manner as for axial length measurements. The *IOLMaster* projects into the cornea six points of light arranged in a 2.3 mm diameter hexagonal pattern, which are reflected from the air/tear interface. The separation of opposite pairs of lights is measured objectively by the instrument's internal software and the toroidal surface curvatures calculated from three fixed meridians. One single measurement of corneal curvature was taken with the *IOLMaster* as this was required for anterior chamber depth calculation. However, corneal curvature measurements taken for biometric investigation in this thesis were obtained from the *EyeSys* Corneal Analysis System (see 2.2.3).

Clinical evaluation of the Zeiss IOLMaster

This work was carried out in collaboration with Dr. E. Mallen. A full account of this work is given in Santodomingo-Rubido *et al.* (2002).

Materials and Methods

Fifty-two subjects (104 eyes) free of ocular pathologies, abnormal binocular vision and previous allergy to the topical anaesthetic benoxinate hydrochloride were enrolled in the study. Measurements of corneal curvature, anterior chamber depth and axial length were performed in all subjects with the *IOLMaster*. The validity of the results obtained with the *IOLMaster* was assessed by comparing the results with those obtained using the *EyeSys 2000* Corneal Analysis System, Javal-Schiotz keratometer (Topcon, Japan), and A-scan ultrasonography (*Storz Omega Compu-Scan Biometric Ruler*, Storz International, St. Louis, USA). The repeatability of the *IOLMaster* was examined by measuring corneal curvature, anterior chamber depth and axial length on the same subjects after a period of 1 to 10 days from the initial measurement. All measurements were carried out in same sequence throughout the study.

Results

Corneal curvature results were analysed by vector analysis (J_0 and J_{45}) to enable the assessment of both radius of curvature and axis orientation of principal corneal meridians. Measurement differences and 95% confidence limits for validity and repeatability between the *IOLMaster*, Javal-Schiötz keratometer and videokeratoscope are shown in Tables 2.1 and 2.2. The mean difference in corneal curvature measured by the *IOLMaster* was in better agreement with the Javal-Schiötz keratometer (mean difference –0.03 mm) than the *EyeSys* videokeratoscope (mean difference 0.06 mm), but more variable (Figure 2.3). The dotted lines on the graphs (Figures 2.3-2.5) indicate the extent to which the *IOLMaster* might over- or under- read compared to the alternative methods examined (i.e. the *IOLMaster* could therefore be expected to read as much as 0.01 mm above or 0.13 mm below the corneal video topographer for mean corneal curvature).

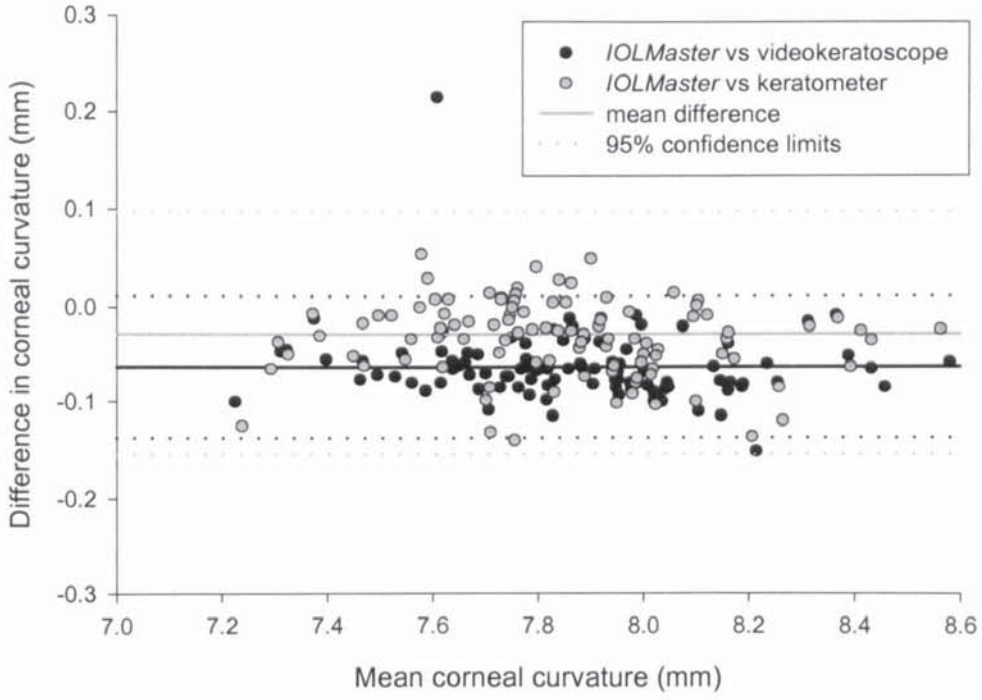


Figure 2.3. Corneal curvature: difference between *IOLMaster* measures and Javal-Schiotz keratometer or *EyeSys* corneal topographer.

Instrument	Function	Mean difference (mm)	95% confidence limits
Javal	Mean k	-0.03	0.13
	J0	0.01	0.11
	J45	0.00	0.06
EyeSys	Mean k	-0.06	0.07
	J0	-0.01	0.08
	J45	-0.03	0.06

Table 2.1. Validity of *IOLMaster* corneal curvature measurements

Function	Mean difference (mm)	95% confidence limits
Mean k	0.00	0.04
J0	0.00	0.05
J45	0.00	0.03

Table 2.2. Repeatability of *IOLMaster* corneal curvature measurements

Anterior chamber depth, as measured with the *IOLMaster*, was significantly shorter (by – 0.06 ± 0.25 mm, $p < 0.02$, paired 2-tailed t-test) than that measured by applanation ultrasound (Figure 2.4). There was no significant mean difference (bias) in the accuracy of the instrument for the whole range of anterior chamber depths evident in this study (i.e. 2.85 to 4.40 mm). The *IOLMaster* could therefore be expected to read as much as 0.43 mm above or 0.54 mm below ultrasound for anterior chamber depth.

Validity and repeatability of anterior chamber depth as measured by *IOLMaster*

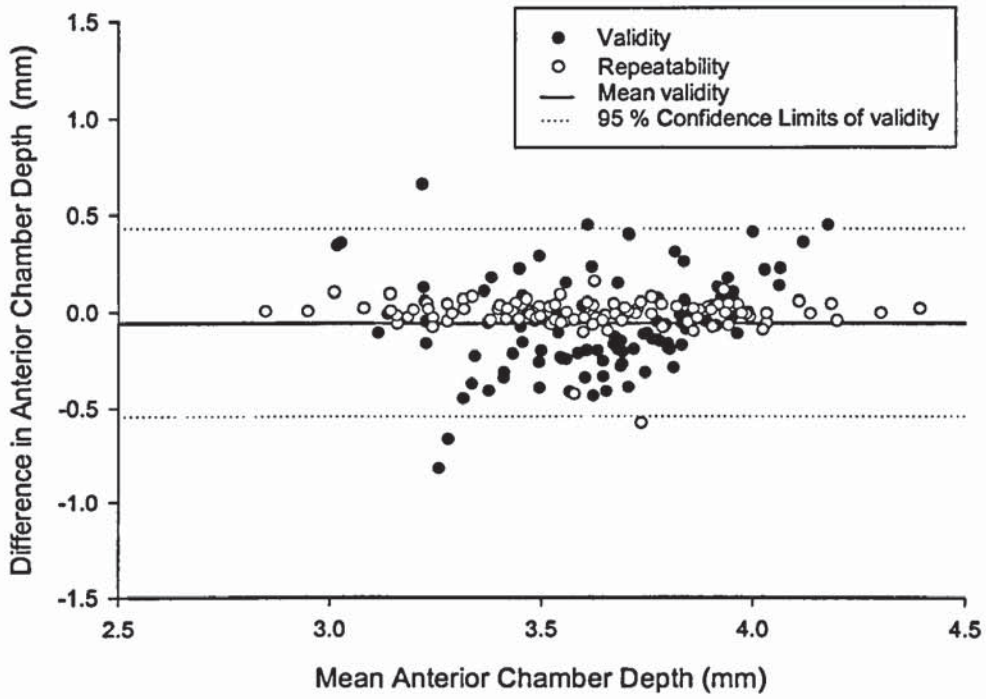


Figure 2.4. Anterior chamber depth: difference between *IOLMaster* and A-Scan ultrasonography; repeatability of *IOLMaster*

Axial length, as measured with the *IOLMaster*, was not statistically different to that measured by applanation ultrasound (difference 0.02 ± 0.32 mm, $p = 0.47$; Figure 2.5). Again, there was no significant bias in the accuracy of the instrument for the whole range of axial lengths evident in this study (i.e. 22.40 to 27.99 mm). The *IOLMaster* could therefore be expected to read as much as 0.65 mm above or 0.61 mm below ultrasound for axial length.

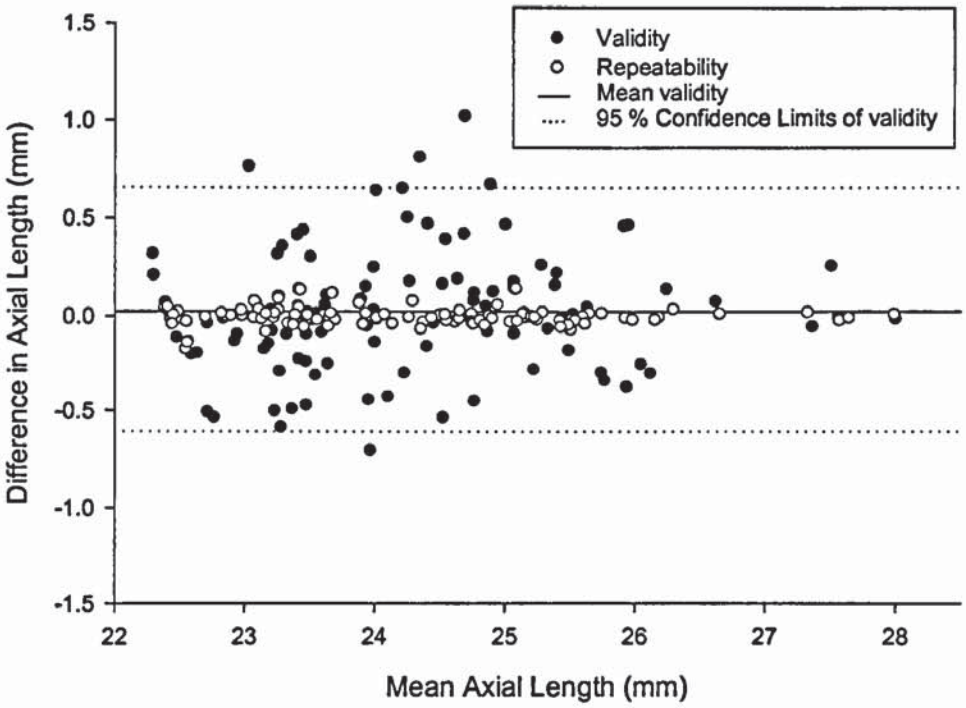


Figure 2.5. Axial length: difference between *IOLMaster* and A-Scan ultrasonography; repeatability of *IOLMaster*.

In conclusion, the *IOLMaster* provides non-contact, successive, repeatable, high-resolution measurements of ocular biometry and thus is suitable for research purposes.

2.2.3 *EyeSys 2000* Corneal Analysis System

Corneal topography has become an essential technique for monitoring corneal changes induced by ocular surgery, corneal disease and the after-effects of contact lens wear. Detailed knowledge of corneal topography provides a method for defining the optical properties of the cornea. The *EyeSys* system is a videokeratoscope based on a Placido disc image analysis technique. This instrument has nine concentric rings of light of known separation and width, which are projected onto the cornea and reflected from the air/tear film interface. The separation of the 18 ring edges is measured objectively, at 1 degree intervals over 360 degrees, over a corneal diameter of 3 mm (Dave *et al.*, 1998b). In addition, an eccentricity value is calculated to indicate the mean rate of corneal flattening using all rings, over a corneal diameter of approximately 9.2 mm (Nieves and Applegate, 1992). The instrument has been validated and is widely accepted clinically (Dave *et al.*,

1998a, b; Vámosi *et al.*, 1998). Corneal topography measurements were performed with the subjects positioned on the instrument chin rest. They were instructed to view an internal fixation target. The monitor together with the joystick was used to align the right eye followed by the left. Subjects were asked to perform a complete blink just before measurements were taken in order to spread an optically smooth tear film over the cornea. One single measurement was taken in each eye which generated a simulated central keratometry reading and the rate of peripheral corneal flattening or steeping with displacement from the corneal apex and thus the degree to which an aspherical surface differs from the spherical form (i.e. p-value, Douthwaite *et al.*, 1999). Each of these values was recorded for biometric investigation purposes.

Figure 2.6. *EyeSys 2000* Corneal Analysis System

2.3 Tear film analysis

2.3.1 Clinical analysis

The Keeler Tearscope plus

The *Keeler Tearscope plus* is a commercially available device which allows *in vivo* lipid layer visualisation and categorisation of the preocular, pre-soft and pre-RGP contact lens tear film lipid patterns by producing interference between the light beams reflected by the different layers of the tear film, giving the appearance of coloured phenomena. The apparatus consists of a hemispherical hand held device with a reflecting inner surface, which is illuminated with cold diffuse light. It has a central hole of approximately 24 x 32 mm in diameter, which allows observation of the tear film lipid pattern by specular reflection. Accessories for this device include several grids that can be inserted into the hemispherical illuminated reflecting system, which together with the stopwatch, allow improved measurement of NITBUT. A clinical handbook is provided with the instrument which illustrates the different lipid layer patterns, together with their prevalence in the population, their mean NITBUT, and clinical implications for each respective pattern.

The *Keeler Tearscope plus* was attached to a slit-lamp biomicroscope (*Topcon SL-7F, Topcon Europe BV*, Capelle a/d Ijssel, The Netherlands). Subjects were positioned on the slit-lamp chin rest and instructed to look centrally in the *Keeler Tearscope plus*. Subjects were instructed to blink normally and the lipid layer pattern was recorded according to Table 2.3 with the slit-lamp set at 10X magnification on the right eye, followed by the left. One single reading of the lipid layer pattern was recorded per eye. NITBUT was performed in the same manner. A grid was inserted into the hemispherical inner surface of the *Tearscope plus*. This grid was projected into the tear film. Subjects were instructed to blink normally and then to refrain from blinking, while the examiner searched carefully for the first discontinuity in the grid reflected from the tear film. The elapsed time between the last blink and the appearance of the first discontinuity was recorded as the NITBUT. In some instances, blinking occurred before any discontinuities in the grid were seen: in these cases the inter-blink period was taken as a measurement of NITBUT. Measurements were truncated at 45 seconds as suggested by Guillon and Guillon (1993). Five readings were taken in each eye and the average as an estimate of NITBUT.

Figure 2.7. *Tearscope plus*

Table 2.3. Pre-ocular tear film lipid patterns
(adapted from Craig and Tomlinson, 1997 and Guillon, 1998).

Tear meniscus height

TMH measurements were performed while subjects observed a target which was located to maintain primary eye gaze. Images of the lower fornix and a portion of the inferior sclera and lower eyelid were brought into focus and quickly recorded. Two images (800x600 pixels) were taken with a camera (*CKY-F58 3-CCD, JVC* Americas Corp., Wayne, USA) attached to a slit lamp under white light and stored in a computer for future analysis. The best of the two images recorded was used for analysis. TMH was measured as the distance between the darker edge of the lower eyelid and the most predominant reflex of the tear strip. A relatively narrow slit beam (0.5 mm) of low intensity was used in order to prevent reflex tearing. TMH was calculated in pixels and converted into millimetres. An average of three readings was recorded. Additionally, at the 12 and 18-month schedule visits, TMH was also measured subjectively with a reticule (*WF10Xmicro, Olympus*, Tokyo) inserted into the eyepiece of the slit lamp for comparison with objective means of assessment. The reticule was calibrated so that actual readings, in 0.03 mm increments, could be made with a 40x ocular.

Tear and contact lens sampling

Tear samples were collected at each of the schedule visits by glass microcapillary and sponge. Glass microcapillary collection was carried out in the right eye by placing a narrow bore microcapillary pipette (*The Binding Site*, Birmingham AD041) on the lateral canthus of the right eye (Figure 2.8). It is a relatively time consuming method but there is little conjunctival irritation, allowing the collection of unstimulated tears rich in lacrimal proteins and with minimal plasma leakage contamination. Sponge collection was performed in the left eye by placing an absorbent triangular sponge (*BD Visispear Eye Sponge, BD Ophthalmic systems*, Sarasota, USA) on the lateral canthus of the left eye. The sponge expands, as the tears are absorbed, the capacity of which can reach in excess of 1ml. The main disadvantage is the requirement for larger volumes of tears as a volume less than approximately 5 µl barely visibly wets the sponge. Other disadvantages are evaporation of the tears moving up the sponge during sampling and variability associated with the need for tears to be extracted from the sponge. Glass microcapillary collection is a better method for detecting proteins whereas the sponge method is better at detecting lipids. All test contact lenses were collected at monthly intervals and inserted and secured in glass vials containing saline. Both tear samples and respective contact lenses were stored in a fridge at a mean temperature of 3 °C for future analysis.

Figure 2.8. Microcapillary tear collection

2.3.2 Biochemical analysis

Tear samples and worn contact lenses were sent to the Biomaterial Research Unit at Aston University for lipid and protein profile evaluation. Tear samples collected by glass microcapillary were analysed directly. Lipids from sponge samples were destructively analysed by *high performance liquid chromatography* (HPLC). Gross lipid and protein deposition profiles of worn contact lenses were analysed non-destructively using *fluorescence spectrophotofluorimetry* and *ultra violet spectroscopy* techniques. *Fluorescence spectrophotofluorimetry* is a novel non-destructive technique developed at the Biomaterials research unit. It is a highly sensitive and reproducible technique that enables analysis of the biological fluorescent components present (Franklin, 1990). Due to the autofluorescent nature of some lipids and proteins it is possible to study their presence on the surface of a contact lens or in the solvent used to extract them from the surface. Non-destructive analysis was followed by application of destructive techniques on worn contact lenses. Destructive techniques rely on extraction of ocular compositions from the sponges and lens surfaces, without chemical change. Application of extraction techniques for analysis of worn contact lenses have the clear disadvantage that material, which is (a) firmly adhered to the lens surface, (b) partitioned into the lens matrix, or (c) chemically changed, cannot be identified and quantified as a deposited tear components in the solution extract.

2.3.2.a Application of non-destructive techniques.

A specially modified *Hitachi F4500 spectrophotofluorimeter* has been developed at the Biomaterials Research Unit.

Surface lipid deposition

Lenses are placed in distilled water in a specially designed cylindrical quartz cell, which allows reproducible orientation of the lens to the incident light beam to be achieved. An incident (excitation) beam wavelength of 360 nm is used and the height of the resultant fluorescence (emission) peak monitored at approximately 440 nm. The height of the emission peak is monitored and provides an estimate of the relative level of deposition.

Baseline fluorescence for the two contact lens materials under investigation in this thesis (Lotrafilcon A and Balafilcon A) were evaluated by examining an unworn new lens as described above. This background trace was then subtracted from the result achieved with each worn lens to assess accurately the degree of deposited material.

Surface protein deposition

Surface protein deposition is evaluated in a similar manner to that for lipids, using non-destructive fluorescence spectrophotofluorimetry. In this case an incident (excitation) beam wavelength of 280 nm is used and the height of the resultant fluorescence (emission) peak is monitored at approximately 340 nm. Baseline fluorescence for each material is subtracted as described above.

Total protein deposition

The measurement of total protein deposition by *ultra violet spectroscopy* was based on an assay measuring protein absorbance on a *Hitachi U2000 spectrophotometer* at 280 nm (Sariri, 1995). The measurement was carried out in matched quartz cells, prior to extraction, providing total deposition measurements pre- and post-extraction, in order to calculate the percentage of protein removed from the lens.

2.3.2.b Application of destructive techniques.

Application of non-destructive *fluorescence spectrophotofluorimetry* and *ultra violet spectroscopy* was followed by extraction of lipids and proteins for their analysis with destructive techniques.

Lipid extraction and analysis

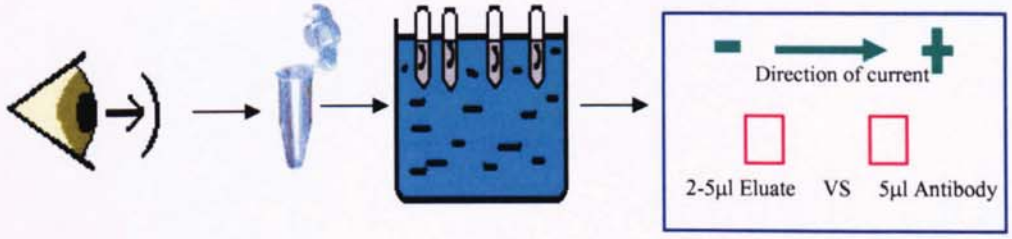
Tear lipids were extracted from contact lenses using methanol, which was then evaporated off by bubbling nitrogen over the surface of the solvent. The resulting lipid extracts were then analysed by *high performance liquid chromatography* (HPLC) (Abbott *et al.*, 1991) after dissolution in the mobile phase.

The HPLC system used is a *Knauer* high pressure liquid chromatograph equipped with a *Rheodyne 7125* injector and a *Lichrosorb* 5µm (250mm X 4mm ID) SI 60 normal phase column used in conjunction with a mobile phase of hexane: propan-2-ol: acetic acid (1000:5:0.5 v/v). The eluent was detected using a *Perkin-Elmer LC-75* ultra violet detector and *Perkin-Elmer* filter fluorescence detector in series. The system is attached to a computer, which is used for data collection and analysis.

The analysis of extracted tear lipids enables the assessment of the tear lipids of wearers together with their variations with time and differences in the profiles of the lipids deposited onto contact lens materials.

Protein extraction and analysis

The optimum lens extraction method for protein removal from lenses, consisted in a solution containing 40 % urea, 1 % sodium dodecyl sulphate (SDS), 1 Mm DL-dithiothritol (DTT) and 100 mM Tris[hydroxymethyl]aminomethane (Tris) (Mann and Tighe, 2002). Each lens to be extracted was heated to 90°C for 3 hours, in a 1 ml eppendorf vial and allowed to cool. 200 µl of solution was adequate and minimized excess dilution (Figure 2.9). Once the proteins were extracted from the contact lens surface, *sodium dodecyl sulphate-polyacrylamine gel electrophoresis* (SDS-PAGE) and *counter immunoelectrophoresis* (CIE) techniques were used for analysis.



1. Removal of contact lens from the eye

2. Placed in eppendorf with a urea/SDS/DTT/ Tris* extraction solution

3. Lenses in extraction solution heated at 90°C for 3hrs

4. Extracted proteins/eluate run by counter immunoelectrophoresis

Figure 2.9. A schematic outlining the laboratory protocol involved in the detection of protein in the eluates of the extracted lenses by CIE. * = urea/sodium dodecyl sulphate /dithiotheriol/tris[hydroxmethyl]aminomethane. Courtesy of Dr Aisling Mann

SDS-PAGE was used for the initial analysis of lens' extract eluates. This standard and routinely used technique was employed to resolve protein mixtures into individual components by molecular weight electrophoresis. A 7.5-20 % gradient gel was used with 5 µl of each sample loaded into each well. Each analyte was pre-treated with a 2-mercaptoethanol (2-ME) containing buffer. The resultant gels post electrophoresis were stained with Coomassie blue stain.

CIE was also employed for analysis of the lenses' extract eluates. The CIE assays were used for analysis of the eluates of the contact lenses under investigation initially tested for protein content by ultra violet *spectroscopy.* Each gel analysed all four of the timed intervals against the antibody specific to each of the proteins under investigation for each subject. A 1.2 % agarose and 3 % PEG in 1 x Tris/Boric acid/Ethylenediamine tetraacetic acid buffer was the semi-solid gel matrix of choice. Five microlitre of the eluted sample was run against each respective antibody, (rabbit anti-human lactoferrin, goat anti-human IgA, goat anti-human IgG, goat anti-human albumin, (Sigma) and goat anti-human high molecular weight Kininogen (light chain). The analytes and the antibodies were loaded into a pre-cut melinex template sheet and allowed to diffuse for 1 hour. The gel was then electrophoresised for 1 hour on a modified *Beckman Paragon* electrophoresis system, Barbital buffer (Fluka) was employed as the tank buffer. The gels were then washed, dried, stained in Coomassie blue and finally de-stained ready for analysis and scanning.

2.4 Ocular physiology

2.4.1 Subjective grading

Subjective grading of bulbar, limbal and palpebral hyperaemia and corneal staining was carried out using the Efron grading scales (Efron, 2000). The Efron system consists of five images which depict different levels of severity of the most commonly seen contact lens-related complications. This type of grading provides a visual reference to grade the severity of contact lens-related conditions with the help of a graded series of technical art representations. The Efron system has been validated by Efron *et al.* (2001). Subjects were positioned in the slit-lamp biomicroscope (details of slit-lamp in 2.2.1) and asked to look nasally for the grading of the temporal bulbar hyperaemia and upwards for assessment of limbal hyperaemia. The upper lid was everted for assessment of palpebral hyperaemia. Corneal staining was graded with the help of fluorescein sodium (*Fluorets, Chauvin Pharmaceuticals Ltd*). Assessment was carried out through the same slit-lamp biomicroscope using diffuse light except for assessment of corneal staining where direct light in conjunction with a cobalt blue filter was employed. The slit-lamp magnification was set at 6X for assessing bulbar and palpebral hyperaemia, 10X for limbal hyperaemia and 16X for corneal staining. Grading was performed by interpolation or extrapolation to the nearest 0.1 grade scale in order to optimise grading sensitivity (Bailey *et al.*, 1991).

2.4.2 Objective grading

Objective grading involved digital imaging in conjunction with computerised image analysis. Two digital images (800x600 pixels) of the temporal bulbar conjunctiva, tarsal plate and corneal staining were recorded with a camera attached to a slit-lamp biomicroscope (as described in 2.3.1) and stored into a computer with the help of specialized software (WinTV, Version 4.6, Hauppauge!®). The images were taken with the slit-lamp magnification set at 6x. Image analysis was performed on the best of the two images of each of the conditions using dedicated computer software (*Labview* and *Vision* software, National Instruments, USA) written by the author's associate supervisor Dr J.S. Wolffsohn (Wolffsohn and Purslow, 2003). An area of 65 x 40 mm^2 was selected when assessing each of the conditions. Special care was taken in avoiding artefacts during image analysis. Typically, artefacts were generated by light reflections and bordering areas (i.e. eyelids and lashes). Three readings were taken on each of the images and a mean was calculated. Bulbar hyperaemia and palpebral hyperaemia were quantified by red extraction

and edge detection techniques. Corneal staining was quantified by green extraction and edge detection techniques. Red and green colour-extraction techniques measure the relative intensity of red or green against the overall intensity of the image, and thus provide an estimation of the overall redness or greenness of the image. For assessment of hyperaemia, edge-detection techniques detect the edges of visible blood vessels to provide an estimate of the number/length of blood vessels. Therefore, an increase in red colouration of the bulbar conjunctiva with a static area of edges detected would indicate vessel filling rather than vessel extension.

2.5 Symptomatology

Several questionnaires have been used in this thesis for rating contact lens management and the amount of time spent performing different near vision tasks.

Subjective symptoms/complaints and judgements questionnaires

Subjective symptoms/complaints (e.g. blurred vision, variable vision, glare, photophobia, lens handling problems, dryness, burning, itching, excess of secretion, excessive tearing, and other problems) were recorded at each visit. Excess of secretion was considered an excess of any fluid substance released on the anterior part of the eye which differs from the normal tears such as mucus secretion. The subjects' subjective judgement of overall visual quality, comfort, convenience, ocular health, eye appearance, quality of life and overall satisfaction was also recorded.

These questionnaires have been based on those used by previous studies on silicone hydrogel contact lenses (Iruzubieta *et al.*, 2001; Nilsson, 2001). The subjects themselves recorded subjective symptoms/complaints at each scheduled visit on a scale of 0 (none) to 10 (unbearable) as these subjective symptoms/complaints were considered negative subjective effects. On the other hand, subjective judgments, which were considered positive subjective effects, were also recorded by the patients themselves at each scheduled visit but this time on a scale of 0 (worst) to 10 (best). Both subjective symptoms/complaints and judgements were graded using visual analogue scales. When using visual analogue scales subjects were asked to mark the position on the line that most adequately described the level at which they had experienced any of the symptoms listed. Certain points on the scale are labelled (far left= no symptom; far right= symptom unbearable) although subjects were not restricted to only using these positions. Subjective symptoms/complaints were considered negative subjective effects and therefore they were graded

Dry eye questionnaires

Two new questionnaires were included at the 12-month scheduled visit: the CLDEQ and DEQ (Nichols *et al.*, 2002). The CLDEQ consists of 59 specific questions, which focus on the severity, frequency and impact of a large variety of contact lens-related symptoms. This questionnaire has nine symptoms subscales: discomfort, dryness, visual changes, soreness and irritation, grittiness and scratchiness, foreign body sensation, burning, photophobia, and itching. Each subscale refers to the frequency of the symptom and, in

order to examine diurnal fluctuations in symptoms, is followed by three questions concerning the intensity of the symptom at different times of day. These time-points include the first two hours after insertion, midday, and the end of the day. The DEQ was employed for detecting non-contact lens wearers with dry eyes.

Previous studies have shown that it is important to assess the distribution of contact lens wearers' symptoms throughout the day (Begley *et al.*, 2000, 2001). The response options pertaining to questions are categorical scales that measure the frequency of each symptom (e.g. never, infrequently, frequently, and constantly) and their intensity (e.g. scales of 1-5 points [1= not at all; 5= very intense]). Contact lens intolerance relative to seven of the nine symptoms was also evaluated by enquiring whether the eyes were affected enough "to stop what you were doing and take out your contact lenses" (e.g. with scoring on a scale of 1-5 points [1= not at all; 5= very intense]).

Near work questionnaire

A near work questionnaire was used for rating the amount of time spent performing different near vision tasks (Bullimore *et al.*, 2002). Subjects were asked how many hours per week had been spent doing each of the following activities: driving, reading and writing, meetings, computers/ VDT, sports, video games, television and crafts. Subjects were asked to grade the response to each question by interpolation or extrapolation to the nearest 0.1 grade scale.

CHAPTER 3

REFRACTIVE AND BIOMETRIC CHANGES WITH SILICONE-HYDROGEL CONTACT LENS WEAR

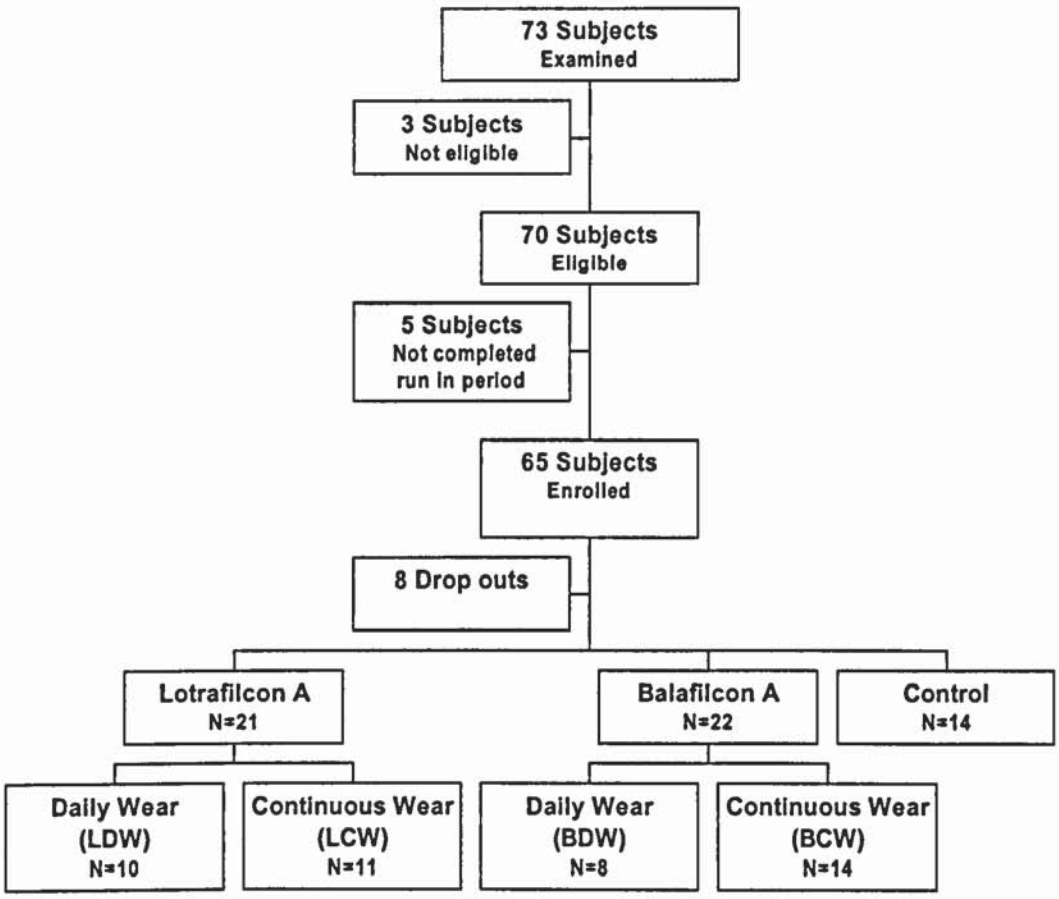
3.1 Introduction

Early studies in the 1970s suggested that soft contact lens wear induced a significant increase in myopia which was associated with general steeping of the cornea (Harris *et al.*, 1975; Grosvenor, 1975; Barnett and Rengstorff, 1977). It was proposed that the oxygen permeability of contact lenses may play an important role in the shifts toward myopia as thick low water content lenses have been found to induce higher levels of myopia (McGlone and Farkas, 1992). This shift has been generally attributed to oedema associated with corneal hypoxia. However, a later study by Horner *et al.* (1999) did not shown an increase in myopia progression over a 3-year period in adolescent wearers of soft contact lenses of low water content (CibaSoft Visitint, 38%) and Dk (8.9) compared to a group wearing spectacles. Two studies reported a small but significant increase in myopia after extended wear of low-Dk hydrogel lenses, but there was no change with high-Dk lenses when worn either on an extended or continuous wear basis (MacDonald *et al.*, 1995; Dumbleton *et al.*, 1999). However, these two later studies were carried out over a short period of time and assessed a limited number of biometric parameters. The characteristics of silicone-hydrogel contact lens materials differ significantly from conventional hydrogel contact lenses (Tighe, 2000). The question of whether silicone-hydrogel contact lenses induce changes in myopia and ocular biometry in a different manner than other soft contact lenses needs to be further examined. The aim of this chapter is to determine the longitudinal changes in refraction and biometry over an 18-month period induced in university students who were first time users of silicone-hydrogel contact lenses.

3.2 Subjects and methods

3.2.1 Subjects

All subjects were students at Aston University. An initial assessment was carried out in all subjects to screen for eligibility. At this stage subjects were given outline information on the nature and purpose of the study, together with the inclusion and exclusion criteria. Copies of the inclusion and exclusion criteria and consent forms supplied to subjects can be found in Appendices 1 and 3. All subjects were normal healthy volunteers recruited under procedures approved by the Declaration of Helsinki and Aston University Human Sciences Ethical Committee (see Appendix 2). Informed consent was obtained from all subjects prior to the commencement of experimental work. Figure 3.1 shows a flow chart of subject recruitment.



Study lenses, care regimes and wearing protocol

Eligible subjects were randomly assigned to wear either Lotrafilcon A (*Focus Night & Day*, CibaVision Corporation, Duluth, GA, USA) or Balafilcon A (*PureVision*, Bausch & Lomb Inc, Rochester, NY, USA) lenses on either a daily or continuous wear basis. Contact

lenses were fitted according to the manufacturer's specifications. Contact lens properties and characteristics are outlined in Table 1.3. All subjects were instructed on insertion, removal and cleaning/ disinfection procedures on the first day and instructions were subsequently reinforced on following visits. Additionally, a group of non-contact lens wearing subjects (the control group) were also recruited and followed over the same study period.

Contact lens subjects were provided with *Opti-Free Express* multipurpose contact lens care system for cleaning, disinfecting and storing purposes (Alcon Laboratories, Inc., TX, USA). Those subjects who showed sensitivity to *Opti-Free Express* were provided with *ReNu MultiPlus* care system (Bausch & Lomb, Inc., Rochester, NY). Subjects who complained of dry eye on awakening and/or at the end of the day were provided with *Opti-Free* lubricant eye drops (Alcon Laboratories, Inc., TX, USA). All subjects wore their lenses on a daily wear basis during the first week with the number of wearing hours being increased progressively throughout the week. At the end of the first week, those subjects in the continuous wear group were introduced into the continuous wear modality. The number of days sleeping in their lenses was progressively increased over the following 2 months until up to 30 days and 29 nights of wear was achieved. However, this level of continuous wear was not achieved by every single subject within each of the continuous wear groups.

It was made clear to all subjects that lenses should be removed if any problems were experienced. Subjects in the daily wear regime were asked to wear their lenses as many hours per day and as many days per week as they could. Lenses and contact lens cases were replaced monthly irrespective of what contact lens material or regime of wear the subjects were allocated. Subjects were instructed on steps to take in the event of an adverse reaction and educated at length to assure adherence to the study protocol; compliance was monitored closely by the author. Subject participation could be discontinued at the author's discretion for the following reasons: adverse reactions (including sight threatening conditions such as corneal ulcers, anterior uveitis, other ocular infections, corneal scarring, or any permanent loss of vision); presence of an infiltrate; persistent grade 3 or 4 finding on the Efron grading scales; lack of motivation; failure to follow up instructions; unacceptable visual acuity and non-attendance for scheduled follow-up visits. Temporary suspension of lens wear of up to 2 weeks was allowed (at the author's discretion) should significant symptoms or slit-lamp findings occur.

Appointments schedules and clinical procedures

Lens assessment and ocular health were evaluated everyday for the first week, and subsequently after 1, 3, 6, 12 and 18-months. Measurements for the evaluation of the ocular response to contact lens wear were performed without lenses in place during the baseline, 1, 3, 6, 12 and 18-month visits. Although these examinations would ideally have been performed early in the morning or at the same time of day, such timetabling was not feasible within the scope of the study as most subjects were unable to attend at the same time to all the follow-up study visits. Figure 3.2 shows a flow chart of the study visits.

3.2.2 Methods

Refractive error monitoring

Objective refraction was recorded on both eyes of all subjects. At each schedule visit, refractive error was measured objectively using the Shin-Nippon SRW-5001 infrared open view autorefractor following the procedure explained in Chapter 2 (section 2.2.1).

Biometric investigation

Measurements of axial length and anterior chamber depth were taken with the *IOLMaster* and corneal curvature and the rate of peripheral corneal flattening with the *EyeSys* instrument at the schedule visits following the procedures explained in Chapter 2. In addition, axial length/corneal curvature (mean of both corneal meridians) ratios of all groups were calculated at baseline.

Subjective questionnaires

Subjects were asked using a subjective questionnaire how much of their time (in hours per week) had been spent doing each of the following activities: driving, reading and writing, meetings, sports, computers/ VDT, video games and crafts (Bullimore *et al.*, 2002). The working distance employed by all the subjects under normal reading conditions was also measured and included in the analysis.

The refractive and biometric data obtained from the experimental groups was normalized against a baseline to eliminate initial differences between groups.

Statistical analysis

Statistical analyses were performed using *StatView* (SAS Institute Inc. 1999, Third Edition). A split-plot two-way analysis of variance was used to assess differences between the different groups over time. Scheffe *post-hoc* comparisons were employed to establish the significance or otherwise of within-factor groups. A 1-way analysis of variance was employed to assess initial differences in axial length/corneal curvature ratios between the different groups. Pearson's product moment correlations were used to assess relationships between refractive and structural changes. The relationship between subjective questionnaires (hours per week enrolled in different activities) and change in refractive error between the baseline and 18-month visit was analysed using multivariate logistic regression and odds ratios with 95% confidence intervals (Bullimore *et al.*, 2002). Data for

the right eye only were used to avoid the confounding effect of using non-independent data from both eyes (Ray and O'Day, 1985). The variance was expressed as standard errors of the mean (SEM) and the level of statistical significance was 5%.

3.3 Results

The subjects' demographics and refractive and biometric state of the right eyes at the start of the study is shown in Table 3.1. The 18-month refractive and biometric changes for all groups can be seen in Table 3.2.

3.3.1 Refraction

Mean spherical equivalent refractive error increased in the myopic direction in all contact lens groups across time ($F= 5.15$; $p= 0.006$). *Post-hoc* comparisons showed that refractive changes increased most between 1- and 6-months ($p= 0.009$) and 1- and 18-months ($p= 0.02$) visits. The LDW group showed the greatest change in myopia progression, with an increase of –0.50 D at the 18-month visit compared to the initial visit, whereas the other groups showed increases of no more than -0.21 D (Figure 3.3). However, differences between groups did not reach statistical significance ($F= 2.17$; $p= 0.09$). No significant difference was found in the interaction between contact lens groups and time ($F= 1.45$; $p= 0.12$). The increase in mean spherical equivalent seen in all contact lens groups was accompanied by an increase in axial length.

Table 3.1. Subjects' demographics and mean refractive (MSE) error and biometric data (± SEM) at the start of the study. Right eye data only.

	All (n= 57)	LDW (n= 10)	LCW (n=11)	BDW (n= 8)	BCW (n=14)	Control (n=14)
Age (years)	20.35 ± 0.21	20.60 ± 0.48	20.54 ± 0.49	20.40 ± 0.68	20.09 ± 0.53	20.24 ± 0.32
M/F	24/33	2/8	7/4	3/5	5/9	7/7
Refraction (D)	-2.35 ± 0.32	-2.18 ± 0.65	-2.68 ± 0.86	-3.22 ± 0.74	-2.43 ± 0.61	-1.62 ± 0.72
Biometry						
AL (mm)	24.47 ± 0.18	23.95 ± 0.32	24.83 ± 0.49	24.57 ± 0.26	24.77 ± 0.34	24.18 ± 0.44
ACD (mm)	3.69 ± 0.03	3.68 ± 0.06	3.67 ± 0.08	3.77 ± 0.08	3.74 ± 0.07	3.63 ± 0.08
KF (mm)	7.87 ± 0.04	7.65 ± 0.11	7.95 ± 0.07	7.82 ± 0.07	7.93 ± 0.09	7.94 ± 0.08
KS (mm)	7.69 ± 0.04	7.51 ± 0.08	7.78 ± 0.06	7.67 ± 0.10	7.78 ± 0.09	7.69 ± 0.08
AL/CC	3.15 ± 0.02	3.16 ± 0.04	3.16 ± 0.06	3.17 ± 0.04	3.16 ± 0.04	3.10 ± 0.05
p-value (units)	0.66 ± 0.01	0.64 ± 0.04	0.67 ± 0.02	0.68 ± 0.04	0.66 ± 0.02	0.63 ± 0.03

M/F: male/female ratio, AL: axial length, ACD: anterior chamber depth, KF: flat meridian, KS: steep meridian, AL/CC: axial length/mean corneal curvature ratios

Table 3.2. Refractive (MSE) and biometric changes after 18-months contact lens wear

	LDW (n= 10)	LCW (n=11)	BDW (n= 8)	BCW (n=14)	Control (n=14)
Refraction (D)	-0.50 ± 0.13	-0.21 ± 0.13	-0.11 ± 0.15	-0.20 ± 0.09	0.00 ± 0.13
Biometry					
AL (mm)	0.14 ± 0.03*	0.06 ± 0.03*	0.07 ± 0.02	0.07 ± 0.02*	0.09 ± 0.03
ACD (mm)	0.02 ± 0.04	0.00 ± 0.01	0.01 ± 0.01	-0.06 ± 0.02*	0.02 ± 0.02*
KF (mm)	0.02 ± 0.01	0.02 ± 0.01*	0.01 ± 0.00	0.01 ± 0.01*	-0.02 ± 0.01
KS (mm)	-0.01 ± 0.02	0.01 ± 0.01	0.00 ± 0.02	0.01 ± 0.01	0.00 ± 0.01*
p-value (units)	-0.03 ± 0.04	0.00 ± 0.03	0.00 ± 0.03	0.01 ± 0.01	0.00 ± 0.02

* Changes in each biometric parameter are significantly correlated with changes in refraction

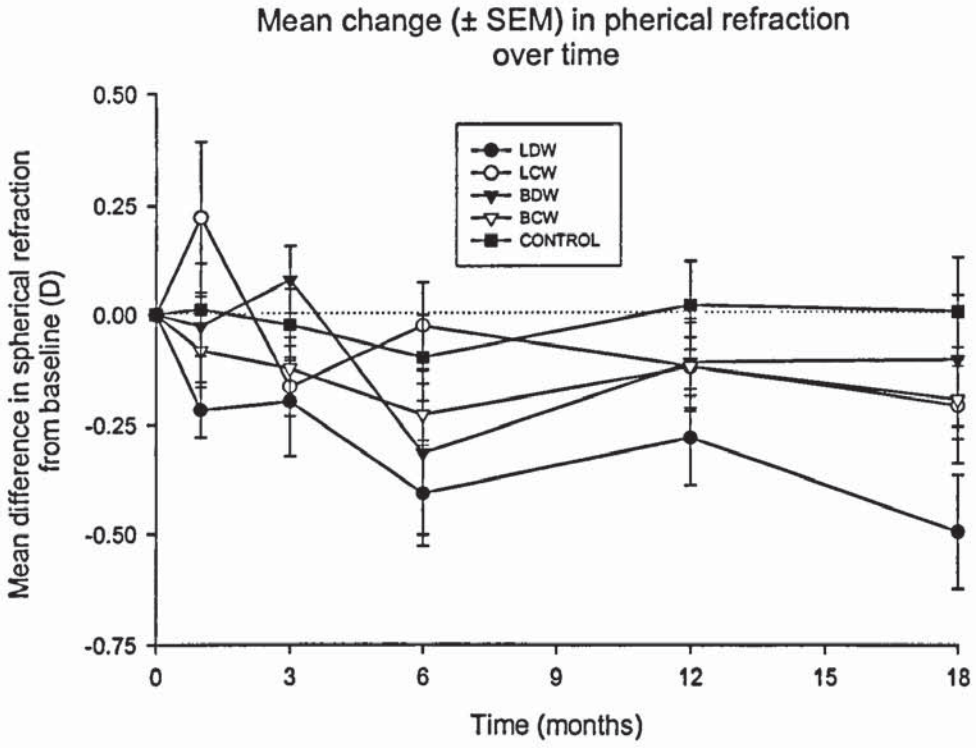


Figure 3.3. Refractive changes for all contact lens groups over time. The errors bars indicate 1 SEM

3.3.2 Biometric changes

Axial length

Axial length increased in all groups over time ($F= 19.29$; $p< 0.0001$). *Post-hoc* comparisons showed that the changes over time reached significance between 1- and 12-months ($p< 0.01$) and between 1, 3, 6, 12- and the 18-month visit (respectively $p< 0.0001$, $p< 0.0001$, $p< 0.0001$, $p< 0.005$). The greatest increase in axial length was seen in the LDW group (0.14 ± 0.03 mm), which also showed the greatest increase in mean spherical equivalent refractive change. A significant correlation between mean change in spherical equivalent and axial length was found in this group across all scheduled visits ($r= -0.53$; $p< 0.0001$). A significant correlation was also found in the LCW ($r= -0.45$; $p< 0.001$) and BCW ($r= -0.37$; $p< 0.05$) groups. No statistically significant differences were found between groups ($F= 1.92$; $p= 0.12$) or in the interaction between contact lens groups and time ($F= 0.78$; $p= 0.71$).

Axial length/corneal curvature ratios

No significant differences between groups were found in the axial length/corneal curvature ratios at the initial visit ($p= 0.76$).

Anterior chamber depth

No significant differences were found over time ($F= 0.71$; $p= 0.59$) nor for the interaction between contact lens group and time ($F= 0.55$; $p= 0.92$). All contact lens groups showed very similar changes with a slight tendency towards increased anterior chamber depth, except group BCW which showed a small decrease. However, differences between groups did not reach statistically significance ($F= 2.30$; $p= 0.07$). A significant correlation was found in the change of refraction *vs.* change in anterior chamber depth for groups BCW ($r= -0.25$; $p< 0.05$) and Control ($r= 0.33$; $p= 0.05$).

Flatter meridian

Lotrafilcon A groups, especially LCW, showed higher levels of corneal flattening than the other experimental groups. However, significant differences between groups did not reach statistical significance ($F= 2.35$; $p= 0.07$). No significant differences were found over time ($F= 0.60$; $p= 0.66$) nor for the interaction between contact lens groups and time ($F= 0.98$;

p= 0.48). The change seen in groups LCW and BCW correlated with the change in refraction across all time visits (r= 0.34; p< 0.05 and r= 0.29; p< 0.05, respectively).

Steeper meridian

The steeper meridian showed similar changes to that found for the flatter meridian, with Lotrafilcon A groups, especially LCW, experiencing higher levels of corneal flattening than the other experimental groups. However, no significant differences were found between groups (F= 0.87; p= 0.49). Changes over time were weakly significant (F= 2.15; p= 0.08). No significant differences were found for the interaction between contact lens groups and time (F= 0.97; p= 0.49). A significant correlation between changes in refraction and the steep meridian was found in the control group only (r= 0.26; p= 0.03).

p-value (rate of peripheral corneal flattening or steeping)

No changes were observed for BCW and control groups, whereas the LDW, LCW and BDW showed changes over time. However, no significant differences were found between groups (F= 0.34; p= 0.85), over time (F= 2.15; p= 0.08) nor for the interaction between contact lens groups and time (F= 1.20; p= 0.27). No significant correlations were found between changes in refraction and p-values for any of the groups across all study visits.

Relationship between near work questionnaires and change in refractive error.

Due to the nature of the statistical analysis employed, the following activities were removed from the analysis: driving, meetings, video games and crafts. The reason for their removal was because the subjects enrolled in this study spent very few to no hours doing these activities and their inclusion affected the statistical outcome. Additionally, due to the small sample sizes of the individual groups, a multivariate logistic regression and odds ratios analysis was performed for all groups combined. No significant relationship between change in refractive error and the subjective questionnaires were found for any of the subjects' groups or for all subject groups combined (p> 0.05).

3.4 Discussion

This study presents data for the refractive and structural changes that took place among university students participating in a randomised contact lens trial. Since subjects were randomised into one of the four contact lens groups, there was no evidence of induced bias due to subject selection to contact lens material and/or regime of wear.

Refraction

An increase in myopia between –0.11 and –0.50 D was found in all contact lens groups, whereas no change was found in the control group (Figure 2.3). The increase in myopia found in this study differs from that reported by other studies in adult low-Dk soft contact lens wearers. In an 11-year longitudinal study, Nizam *et al.* (1996) reported an increase in myopia by 0.30 D in adult non-contact lens wearers myopic eyes, whereas eyes wearing conventional hydrogel lenses (Etafilcon A) on a daily wear basis increased in myopia by 1.12 D during the same period. In another study of 312 adult soft contact lens wearers, myopia progressed by at least –0.50 D over 5 years in 49 % of the subjects (Bullimore *et al.*, 1998). More recently, Bullimore *et al.* (2002) in a retrospective study found significant myopia progression with soft contact lenses (at least –1.00 D over 5 years) in approximately 20% of the young myopic adults in their twenties.

The studies described above have assessed the effects induced by conventional low-Dk soft contact lenses. It has been suggested that the increase in myopia seen in adult wearers of low-Dk lenses is induced by hypoxia (Dumbleton *et al.*, 1999; Fonn *et al.*, 2002). Several studies which compared myopia progression with low-Dk soft *vs.* high-Dk SiH contact lenses reported a significant increase in myopia and hypoxia in wearers of low-Dk lenses, whereas refraction did not change and hypoxic effects were negligible in wearers of high-Dk SiH contact lenses. However, all these previous studies failed to measure structural changes (e.g. axial length) associated with changes in refraction which is essential in identifying the possible causative mechanism for the increase in myopia observed. MacDonald *et al.* (1995) found a significant increase in myopia after extended wear of low-Dk hydrogel lenses, but there was no change with extended wear of high-Dk lenses. Dumbleton *et al.* (1999) reported, over a 9-month period, an increase in myopia of –0.30 D in a group wearing etalfilcon A lenses, whereas no change in myopia was found in the Lotrafilcon A group. More recently, Fonn *et al.* (2002) reported, over a 4-month period, a significant increase in myopia in eyes wearing low-Dk HEMA lenses (-0.50 D) compared to an insignificant increase in myopia in eyes wearing a high-Dk Balafilcon A lenses (-0.06

D). Our results are in direct contrast, in terms of age of the subjects enrolled, with those of Dumbleton *et al.* (1999) and Fonn *et al.* (2002). It is well accepted, that myopia progress at a different fashion depending on the age of the group sample under investigation. We did find an increase in myopia in all our high-Dk SiH groups. However, myopia progression rates between –0.05 and –0.20 D *per* year have been found to occur normally in young adult non-contact lens wearers (Grosvenor, 1977; Goss *et al.*, 1985; Kinge and Midelfart, 1999).

Axial length

The increase in myopic refraction found in this study correlated well with an increase in axial length in the 3 contact lens groups where the myopic shift was higher (LDW, LCW and BCW). It is well documented that an increase in posterior vitreous chamber depth accounts for nearly all of typical myopia progression (Wildsoet, 1998). The precise and well-validated *IOLMaster*, which provides high-resolution measures of the order of 0.01 mm, was used in this study to assess accurately changes in axial length (Haigis *et al.*, 2000; Santodomingo-Rubido *et al.*, 2002). The sample groups assessed in this study were all university students exposed to high educational demands. It well accepted that intensive near work could trigger myopia progression (Rosenfield and Gilmartin, 1998; Kinge *et al.*, 2000).

Effect of near work

No significant relationship between hours spent doing near work and change in refractive error was found in this study. This could be due to the subjective, and hence variable, nature of the results obtained from the questionnaires or to the small group sample sizes. The shift in myopia progression found in our contact lens groups is likely to be a genuine increase in adult onset myopia rather than a contact lens effect (e.g. hypoxia). A follow-up of the subjects without contact lenses being worn over a few days or weeks might provide a better insight of the causative mechanism of myopia progression (i.e. contact lens effect *vs.* genuine increase in adult-onset myopia). However, since the myopic increase was associated with an increase in axial length, the myopic shift is likely to be genuine. Interestingly, no increase in myopia progression was found in our control group, which was likely to be exposed to similar near work demands. Analysis of the control group shows that at least 50% of the subjects are emmetropes and hyperopes. A few high myopes were also present and responsible for the mean myopia recorded at baseline. Emmetropic

and hyperopic subjects were included in the control group due to the impossibility of recruiting enough myopic subjects willing to take part in this experimental group. Additionally, subjects in any of the contact lens groups must have a significant level of refractive error (± 0.50 D) in order to get contact lens correction and thus myopic and hyperopic subjects were only included in these experimental groups. Since myopia is a much more common refractive error than hyperopia, a larger number of myopic subjects were included in the contact lens groups.

Several studies have found that myopia progresses at a slower rate in emmetropes, hyperopes and high myopes (O'Neil and Connon, 1987; McBrien and Adams, 1997; Kinge *et al.*, 1999). Additionally, more low myopes were found in the LDW group than in the other groups. Some studies have found that low myopia progresses at a higher rate than high myopia (Dumbleton *et al.*, 1999). These findings support the view that emmetropia and hyperopia offer some protection against adult myopia progression and may explain the relatively stable refraction found in our control group.

Axial length/corneal curvature ratio

The axial length/corneal curvature ratio, a useful predictor of the onset and development of myopia, of the control group was found to be lower compared to other groups. However, this difference was not statistically significant. Ratios greater than 3 have been associated with a higher increase in myopia progression. It was not clear, from the data obtained in this study, the exact reason for the higher increase in myopia observed in the LDW group. Possible reasons include a directly induced physical/physiological contact lens effect, a higher rate of progression for the lower level of myopia evident in the group, and finally the interesting postulate that compromised immunology due to contact lens wear may trigger ocular growth. There is also the possibility that contact lenses may induce more myopia by virtue of generating a different peripheral image shell compared to spectacles.

Anterior chamber depth

Anterior chamber depth did not change across the study period for all the groups, except for BCW where a small decrease was observed. However, differences between groups did not reach statistical significance. Anterior chamber depth has been found to be larger in myopes than emmetropes and hyperopes. Therefore, one would expect that an increase in myopia would be accompanied with an increase in anterior chamber depth. However, Grosvenor and Scott (1993) only found a weak correlation between the degree of myopia

progression and change in anterior chamber depth. Higher increases in myopic refraction are more likely to be associated with an increase in anterior chamber depth. The small increase in the myopic prescription observed in our subjects is likely to account for the negligible change found in anterior chamber depth.

Keratometry

Keratometric analysis revealed a small but not statistically significant degree of central corneal flattening of both meridians (flatter and steeper) in the Lotrafilcon A groups. The effect was greater in the LCW group. Other studies have also found a degree of central corneal flattening with continuous wear of Lotrafilcon A lenses (Dumbleton *et al.*, 1999; González-Meijome *et al.*, 2003). This is not surprising, since Lotrafilcon A materials have a higher modulus of rigidity compared to Balafilcon A materials (Tighe, 2000). The greater effect seen in the LCW group suggests that overnight lid compression is likely to exacerbate the effects observed. Indirect evidence of the possible mechanical effects induced by SiH lenses arises from the higher rate of superior epithelial arcuate lesions (Holden *et al.*, 2001) and localized contact lens-induced papillary conjunctivitis (Skotnitsky *et al.*, 2002) previously reported. Other mechanical effects observed in our study included indentation ring marks at the lens edge on the bulbar conjunctiva of some of our subjects - most commonly seen in the LCW group.

p-value

The rate of peripheral corneal flattening, assessed with reference to the p-value, did not change significantly for any of the experimental groups. In a cross-sectional study, Carney *et al.* (1997) reported that as the degree of myopia increases, the peripheral cornea flattens, becoming more oblate. In a later longitudinal study by Horner *et al.* (2000), a significant correlation was found between myopia progression and flattening of the peripheral cornea, again becoming more oblate. However, this later study reported an average increase in myopia of 1.46 D. The increases in myopia found in the present study were between –0.11 and –0.50 D, increases probably too small to detect a relationship if present.

	Summary of findings
1	Myopia increased significantly in subjects wearing Lotrafilcon A lenses on a daily wear basis and was accompanied by a correlated increase in axial length. However, no significant relationship was found between change in refractive error and the amount of near work undertaken, or in initial axial length/corneal curvature ratio. Possible reasons for the increase in myopia include a directly induced physical/physiological contact lens effect, a higher rate of progression for the lower level of myopia evident in the group, and finally that compromised immunology due to contact lens wear may trigger ocular growth in the posterior segment. Contact lenses may also induce more myopia by virtue of generating a different peripheral image shell compared to spectacles.
2	Keratometric analysis revealed a small but not statistically significant degree of central corneal flattening in both Lotrafilcon A groups and can be attributed to the higher modulus of rigidity compared to Balafilcon A materials.

CHAPTER 4

OCULAR PHYSIOLOGY CHANGES WITH SILICONE HYDROGEL CONTACT LENS WEAR

4.1 Introduction

Changes in vascular response and corneal integrity are commonly seen in successful contact lens wearers as well as those that exhibit contact lens-induced complications. Whereas in most instances these changes represent no threat to the individual, clinical monitoring of ocular physiology is essential in order to prevent serious ocular complications. Quantitative assessment of ocular physiology during lens wear has potential implications for further understanding the biocompatibility of contact lenses and contact lens care systems, as well as ophthalmic medications (Villumsen and Alm, 1989; Owen *et al.*, 1996).

High-Dk silicone hydrogel lenses have overcome many of the hypoxic problems associated with traditional extended wear (i.e. up to 7 nights) and as a result the popularity of continuous wear (i.e. up to 30 nights) is increasing rapidly. Results from clinical trials indicate that the typical physiological changes associated with oedema from conventional extended wear of low-Dk lenses do not occur with continuous wear silicone hydrogel lenses (Keay *et al.*, 2000; Nilsson, 2001; Fonn *et al.*, 2002). These changes include neovascularization, striae, microcysts and an increase in bulbar and limbal hyperaemia. Most trials have been carried out over short periods of time and have enrolled previously adapted contact lens wearers who had switched from conventional low-Dk materials to high-Dk silicone hydrogel materials. The ocular physiology long-term effects induced by silicone hydrogel materials in neophyte contact lens wearers are not well documented.

The aim of this chapter is to monitor longitudinal changes in ocular physiology over an 18-month period in neophyte silicone-hydrogel contact lens wearers using both subjective and objective means of assessment.

4.2 Subjects and methods

4.2.1 Subjects

The subjects, study lenses, care regimes, wearing protocols and scheduled appointments have been described previously in Chapter 3.

4.2.2 Methods

Ocular physiology was monitored subjectively with Efron grading scales as described in Chapter 2. The four conditions of interest in this chapter were bulbar, limbal and palpebral hyperaemia as well as corneal staining. One single grade was obtained *per* subject and *per* visit. Additionally, bulbar and palpebral hyperaemia were objectively quantified by means of a novel, objective technique (Wolffsohn and Purslow, 2003) also described in Chapter 2. The data obtained from contact lens groups was normalized against a control group to eliminate seasonal changes and against baseline information to eliminate initial differences between groups. Comparison between subjective and objective means of assessment is also discussed in this Chapter.

Statistical analysis

Statistical analyses were performed as detailed in Chapter 3. Pearson's product moment correlations were used to assess the relationship between subjective and objective gradings.

4.3 Results

4.3.1 Subjective grading

Bulbar hyperaemia

A small, but statistically significant, increase in bulbar hyperaemia was found in all contact lens groups across the study visits ($F= 8.26$; $p< 0.0001$). *Post-hoc* comparisons showed that bulbar hyperaemia was lower in the 1st month compared to the 3rd month ($p< 0.01$) and higher at the 3rd month compared to the 6th month ($p< 0.0001$) and 18th month ($p< 0.01$). No significant differences were found between contact lens groups ($F= 0.15$; $p= 0.93$) or for the interaction between contact lens groups and time ($F= 1.14$; $p= 0.33$).

Limbal hyperaemia

Limbal hyperaemia increased significantly over the first six months of lens wear and stabilized at that level thereafter ($F= 3.78$; $p< 0.01$) (Figure 4.1). *Post-hoc* comparisons indicated that limbal hyperaemia was lower at the 1st month visit compared to the 3rd ($p< 0.05$) and 6th month visit ($p< 0.05$). No significant differences were found between groups ($F= 0.59$; $p< 0.63$) or for the interaction between groups and time ($F= 0.75$; $p= 0.70$).

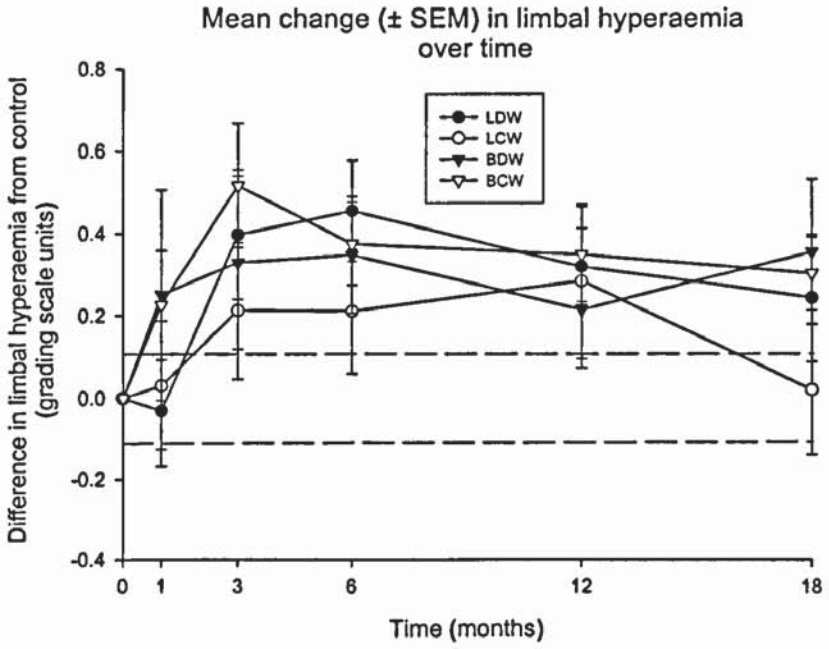


Figure 4.1. Changes in limbal hyperaemia over time. The dashed lines represent 1 SEM for the control group.

Papillary conjunctivitis

An increase in palpebral redness and roughness was found across the 1st three months of lens wear and stabilized at that level thereafter. However, these changes did not reach statistical significance ($F= 2.35$; $p= 0.06$). No significant differences were found between groups ($F= 0.02$; $p= 1.00$) or for the interaction between contact lens groups and time ($F= 1.56$; $p= 0.11$). Ten cases of contact lens papillary conjunctivitis were observed across the study and will be discussed further in Chapter 7.

Corneal staining

Corneal staining was similar for both contact lens materials and regimes of wear (F= 0.57; p= 0.64) (Figure 4.2). However, a significant increase in corneal staining was found between visits (F= 9.03; p< 0.0001). *Post-hoc* comparisons demonstrated that corneal staining was greater for all follow up visits compared with the initial visit. No significant differences were found for the interaction between groups and scheduled visits (F= 0.93; p= 0.52).

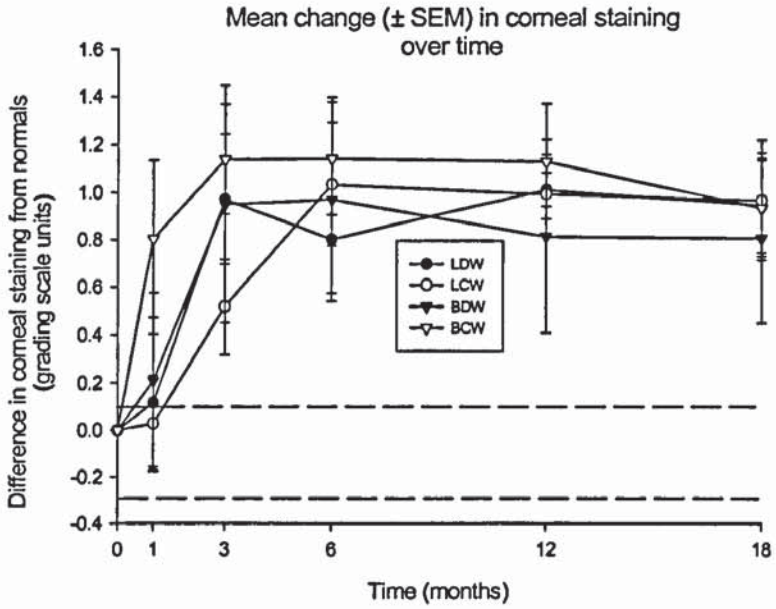


Figure 4.2. Changes in corneal staining over time. The dashed lines represent 1 SEM for the control group.

4.3.2 Objective grading

Bulbar hyperaemia

Bulbar hyperaemia, as assessed with the red extraction technique showed in all contact lens groups an increase over the first twelve months of lens wear and then a decrease between the 12 and the 18-month visit (F= 10.87; p< 0.0001) (Figure 4.3). *Post-hoc* comparisons indicated an increase in bulbar hyperaemia between the 1st month and all follow up visits, except between the 12 and 18-month visit, where a reduction in hyperaemia was observed. No significant changes were found between contact lens groups (F= 0.33; p= 0.80) or for the interaction between time and contact lens groups (F= 0.90; p= 0.55). When bulbar hyperaemia was assessed with the edge detection technique, significant changes were also found over time (F= 5.32; p= 0.0005). These changes did not follow an immediately or

consistent pattern and were found to be statistically significant between months 1 and 6 ($p< 0.0005$) and 6 and 12 ($p< 0.05$). No significant differences were found between contact lens groups ($F= 0.07$; $p= 0.99$) or for the interaction between contact lens groups and time ($F= 1.01$; $p= 0.45$) with the edge detection technique.

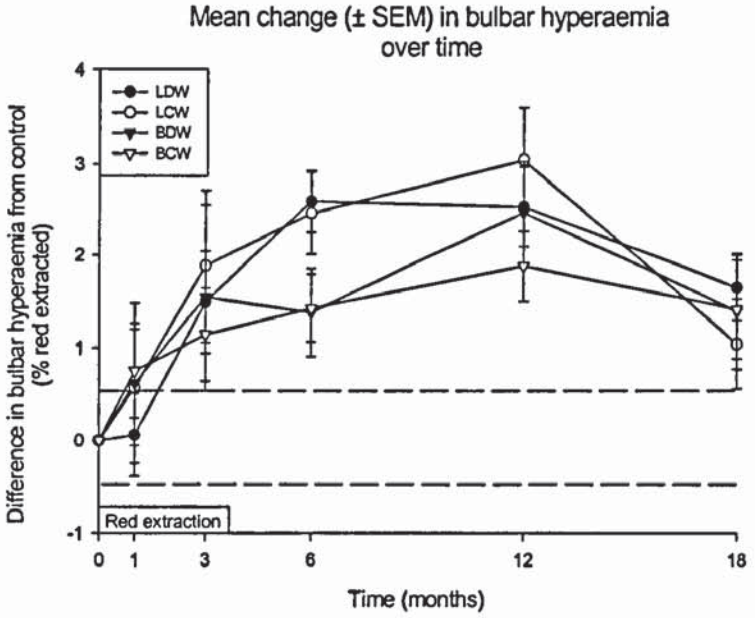


Figure 4.3. Changes in bulbar hyperaemia over time. The dashed lines represent 1 SEM for the control group.

Palpebral hyperaemia

Both Lotrafilcon A groups showed slightly higher levels of palpebral hyperaemia when assessed with the red extraction technique (Figure 4.4). However, no statistically significant differences were found between contact lens groups ($F= 1.20$; $p= 0.32$), over time ($F= 0.99$; $p= 0.42$) or for the interaction between contact lens groups and time ($F= 1.23$; $p= 0.27$). In contrast, when the edge detection technique was employed, a significant difference was found between groups ($F= 3.64$; $p< 0.05$). *Post-hoc* comparisons indicated that BDW showed the highest and BCW the lowest levels of palpebral hyperaemia ($p< 0.05$). A significant change was also found over time ($F=3.80$; $p< 0.01$). Palpebral hyperaemia was found to be significantly lower for the 1st month compared to the 6-month visit ($p< 0.05$). No significant differences were found for the interaction between contact lens groups and time ($F=1.41$; $p= 0.17$).

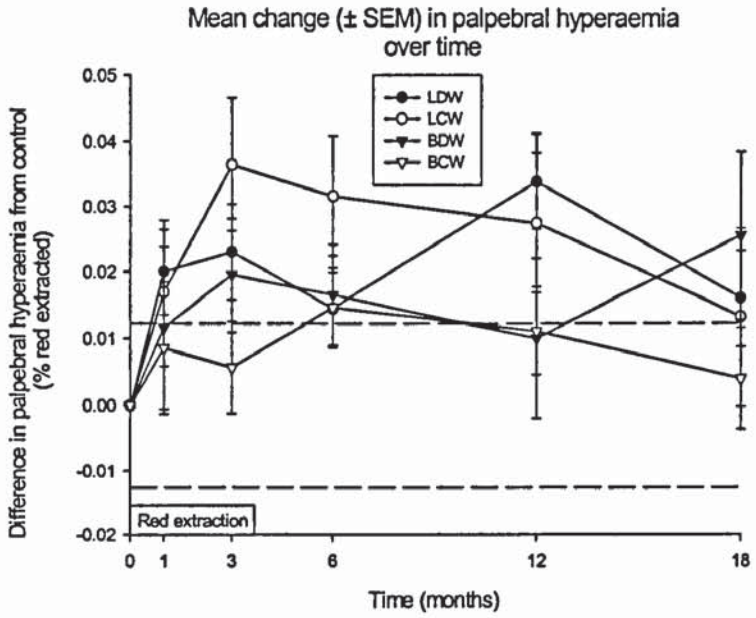


Figure 4.4. Changes in palpebral hyperaemia over time. The dashed lines represent 1 SEM for the control group.

4.3.3 Relationship between subjective and objective grading

Bulbar hyperaemia

A significant positive correlation was found between Efron grading scales and red extraction ($r= 0.46$; $p< 0.0001$) and edge detection techniques ($r= 0.41$; $p< 0.0001$). A significant positive correlation was also found between red extraction and edge detection techniques ($r= 0.28$; $p< 0.0001$).

Palpebral hyperaemia

A weak positive correlation was found between Efron grading scales and red extraction ($r= 0.11$; $p= 0.05$). However, no significant correlation was found between edge detection and Efron ($r=-0.01$; $p= 0.90$) and red extraction ($r=-0.01$; $p= 0.16$). A bias for low values of both bulbar and palpebral hyperaemia was found with the edge detection technique.

4.4 Discussion

4.4.1 Subjective grading

Bulbar and limbal hyperaemia

The results presented here are in agreement with those of Morgan and Efron (2002), who also found no difference in conjunctival and limbal redness between Balafilcon A and Lotrafilcon A SiH materials when assessed with Efron grading scales. However, the increase found in this study in both bulbar and limbal hyperaemia oppose to data from previous SiH trials which found a reduction in the level of ocular redness (Papas *et al.*, 1997; Dumbleton *et al.*, 2001; Morgan and Efron, 2002). Most previous trials have enrolled existing contact lens wearers who switched to SiH materials. Since these materials have a much higher level of oxygen permeability, a reduction in the ocular vascular response is not surprising. The subjects enrolled in the present study were all neophyte contact lens wearers and this might explain the small increase in vascular response found. The vascular response might not be related to hypoxic effects, but the mechanical effect produced by a foreign body (i.e. the contact lens) on ocular tissues may trigger an increase in ocular hyperaemia. It is not clear whether the small variability found between the different study visits was a real change or one due to induced observer noise with the use of the subjective Efron grading scales. Additionally, measurements across the study visits were not taken at the same time of the day and this might also account for the variability found across study visits (Guillon and Shah, 1986). Efron *et al.* (2001) suggested that when applying his grading scales, changes of less than 1.0 unit should not be considered either clinically or statistically significant. The changes found in both bulbar and limbal hyperaemia in the present study are of the order of 0.3 units.

Papillary conjunctivitis

The results presented here are also in agreement with the findings of Morgan and Efron (2002), who did not find significant differences in papillary conjunctivitis between the two lens types nor between visits in a group of 30 pre-existing contact lens wearers using Balafilcon A and Lotrafilcon A, alternatively, for successive eight-week periods. Potvin et al. (1994) failed to detect significant differences between non-wearers and contact lens wearers when an objective image analysis was employed to quantitatively assess the morphometry of the tarsal conjunctiva.

Corneal staining

The amount of corneal staining increased during the study. This finding is not consistent with the report of Sweeney and colleagues (2000) who found less inferior corneal staining associated with SiH wear than that found for hydrogel daily wear. However, the results reported here are in agreement with Morgan and Efron (2002) who, compared to the initial visit, found a significant increase in corneal staining at follow up visits with both Balfilcon A and Lotrafilcon A materials when worn on a continuous wear basis. Possible explanations for increased corneal staining could be attributed to the higher mechanical effect induced by SiH materials which have a greater modulus of rigidity compared to hydrogel materials (Tighe, 2000) and to epithelial microtrauma induced by mucin balls, leaving small surface depressions which stain with fluorescein (Pritchard *et al.*, 2000).

4.4.2 Objective grading

Bulbar hyperaemia

A consistent and significant increase in bulbar hyperaemia was found with the red extraction technique across all study visits except for the last visit where a reduction was found. The data conflicts with previous reports, where a reduction in hyperaemia was found. However, as explained earlier, most trials have enrolled previous contact lens wearers who switched to SiH materials. Since these materials have a much higher level of oxygen permeability they are likely to alleviate the vascular response induced by conventional soft contact lenses. Additionally, these trials have used subjective grading which can be up to 7 times less sensitive than the objective grading system employed here (Wolffsohn and Purslow, 2003). The level of bulbar hyperaemia appears to decrease after the first 12-months of lens wear. It would be interesting to see if bulbar hyperaemia, assessed with the red extraction technique, continues to decrease after 18 months of SiH contact lens wear. The changes found were however very small and not clinically significant. No significant differences were found between materials, which is in agreement with Morgan and Efron (2002).

Edge detection results are less consistent. A significant change in the level of edge detection was found across time, that is, a variation in the number of blood vessels visible, although significant differences between groups were not detected.

Palpebral hyperaemia

Red extraction assessment of palpebral hyperaemia showed that Balafilcon A materials worn either on a daily or continuous wear basis showed a range of effects very similar to those expected in non-contact lens wearers. Conversely, Lotrafilcon A materials worn on either a daily or continuous wear basis showed slightly higher levels of palpebral hyperaemia compared to Balafilcon A. The difference might be due to the different surface treatment of these lenses or to the higher modulus of rigidity of Lotrafilcon A lenses (Tighe, 2000; Lopez-Alemany *et al.*, 2002). However, the changes were not statistically significant over time, between groups or for the interaction between the two, which is again in agreement with Morgan and Efron (2002). These authors did not find significant differences in papillary conjunctivitis between the two lenses, nor between visits in a group of 30 pre-existing contact lens wearers who wore a pair of Balafilcon A and a pair of Lotrafilcon A, alternatively, for successive eight-week periods. Potvin *et al.* (1994), using an objective image analysis, failed to detect significant differences in the tarsal plate of wearers and non-wearers of contact lens. However, direct comparison of our results with those of Morgan and Efron (2002) and Potvin *et al.* (1994) should be interpreted with caution as they employed different grading systems: the former using subjective pictorial grading, the latter objective image analysis.

Edge detection techniques results showed that BDW showed highest and BCW lowest levels of edge detection, suggesting that more blood vessels were visible when Balafilcon A lenses are worn on a daily wear basis. The changes found are minimal and likely to be clinically insignificant.

4.3.3 Relationship between subjective and objective grading

Traditionally, clinical monitoring of changes in ocular physiology has been graded with reference to qualitative textual categories (i.e. mild, severe, etc.). Grading scales have significantly improved diagnosis and monitoring of contact lens-related complications. However, there is still a wide inter-observer variability despite their use and bias toward round numbers. All subjective and objective grading was performed by the author and special care was taken in grading all conditions to one-tenth of a unit in order to increase discrimination (Bailey *et al.*, 1991; Twelker and Bailey, 2000). Objective image analysis techniques have been developed over the past few years to improve sensitivity and repeatability (Simpson *et al.*, 1998; Papas, 2000; Fieguth and Simpson, 2002; Wolffsohn and Purslow, 2003). Previous reports found extraction and detection techniques to be the

most sensitive and repeatable objective techniques. The objective image analysis used in this study was previously validated and red extraction and 3x3 kernel edge detection was chosen for monitoring bulbar and palpebral hyperaemia as they have been found the most sensitive and stable to changes in hyperaemia and image luminance (Wolffsohn and Purslow, 2003).

Bulbar hyperaemia

A significant positive correlation in bulbar hyperaemia was found between Efron grading scales and red extraction and edge detection techniques. This is not surprising, since these techniques have been previously found to have a strong correlation with CCLRU scales (Wolffsohn and Purslow, 2003). Efron grading scales have a very similar design to CCLRU scales, consisting of 5 reference pictures of increasing severity, the main difference being that the former is derived from artistically-rendered drawings and the latter of real eye photographs (Efron *et al.*, 2001). The bias found for low values of bulbar hyperaemia with the edge detection technique may be due to insensitivity in detecting diffuse arteries. Bulbar hyperaemia is characterized by the expansion of small arteries just below the surface of the eye. As the blood vessels swell they become larger and easier to detect as a red line on the white scleral background. An edge detection technique is likely to be very sensitive in detecting changes of expanded arteries. However, the smallest arteries are not resolvable either by the pixels in a charge-coupled device camera, or by the human eye, and a mild onset of hyperaemia therefore begins as a diffuse reddening with no discernible edges. In such cases, a red extraction technique is likely to be more sensitive to detecting changes (Fieguth and Simpson, 2002). Since previous reports found extraction and detection techniques to be the most sensitive and repeatable objective techniques for assessing bulbar hyperaemia, it is not surprising that a significant positive correlation was also found in this study between the two techniques.

Palpebral hyperaemia

The poor correlation found between Efron grading scales and objective grading is not in agreement with the report of Wolffsohn and Purslow (2003), who found a strong correlation with CCLRU scales. However, CCLRU scales provide individual grades of palpebral redness and roughness, while papillary conjunctivitis is graded with the Efron scale in terms of palpebral redness and roughness combined. This difference is likely to account for the weak correlation found. Additionally, examination of the Efron scales

indicates that blood vessels become less distinct with increasing grade, which may also account for the lack of any relationship found. As with bulbar hyperaemia, the bias to low values of palpebral hyperaemia with the edge detection technique may be due to a lack of sensitivity in detecting diffuse arteries by the camera system employed in this study.

Summary of findings

1	An increase in bulbar, limbal and palpebral hyperaemia was observed in most of the contact lens groups and could be attributed to mechanical effects induced by the contact lenses.
2	An increase in corneal staining was also observed in all contact lens groups and could again be attributed to mechanical effects and, in addition, to epithelial microtrauma induced by mucin balls.
3	A significant positive correlation in bulbar hyperaemia was found between Efron grading scales and red extraction and edge detection techniques. However, a poor correlation in palpebral hyperaemia was found between Efron grading scales and red extraction and edge detection techniques.

CHAPTER 5

TEAR FILM CHANGES WITH SILICONE-HYDROGEL CONTACT LENS WEAR

5.1 Introduction

The tear film has several functions which aid in preserving and maintaining a healthy and functional visual system. Adequate tear film structure, stability and volume are essential for succesful contact lens wear (Holly, 1981; Sharma and Ruckenstein, 1985; Guillon and Guillon, 1994). It has been suggested that contact lenses affect tear film characteristics (Tomlinson, 1992) and therefore the study of the tear film is of key importance in understanding the biocompatibility of contact lens materials and the ocular effects induced by contact lens wear. A great deal of clinical and biochemical research has been directed toward determining the effects of contact lenses on the tear film. However, it is not fully understood whether long-term wear of soft contact lenses induce permanent changes in the tear film even when contact lenses are not worn. Guillon *et al.* (1997) found that the pre-ocular tear film characteristics of non-wearers and soft contact lens wearers were very similar in terms of structure, stability and volume, suggesting that soft contact lens wear does not induce permanent changes in clinical tear film characteristics. However, no such studies have been carried out to assess the effect induced by SiH contact lenses in tear film characteristics. The aim of this chapter is to monitor clinical and biochemical changes in tear film characteristics in a group of neophyte SiH contact lens wearers who were followed for 18-months.

5.2 Subjects and methods

5.2.1 Subjects

The subjects, study lenses, care regimes, wearing protocols and scheduled appointments have been described previously in Chapter 3.

5.2.2 Methods

Clinical procedures

Lipid layer pattern grading was carried out as explained in Chapter 2. In some instances a combination of patterns was recorded. However, for simplicity lipid layer grading was re-

classified as seen in figure 5.1 (after Guillon *et al.*, 1997). NITBUT and TMH measurements were also carried out as explained in Chapter 2.

None lipid pattern visible	None
Open Meshwork Close Meshwork	Meshwork
Meshwork & Wave Wave	Wave
Wave & Amorphous Amorphous	Amorphous
Wave & Colours Amorphous & Colours Colours	Colours
Abnormal	Abnormal

Figure 5.1. Tear film characteristics- lipid classification

Biochemical procedures

Tear and contact lens sampling together with the biochemical procedures for the analysis of tear proteins and lipids was carried out as detailed in Chapter 2 (section 2.3).

Statistical analysis

Statistical analyses were performed as detailed in Chapter 3. No statistical analysis was performed for the lipid layer patterns observed and the discussion is based on graphical representations. The bias between subjective and objective measures of TMH (the mean difference, standard deviation, and 95% confidence limits) was calculated and presented graphically (Bland and Altman, 1986). Comparison between subjective and objective measures of TMH was performed using a paired two-tailed t-test.

5.3 Results

5.3.1 Clinical measures

Lipid layer grading

Figure 5.2 shows a graphical representation of the lipid layer patterns found across the study visits. Absent (none) or abnormal lipid layer patterns were not found in any of the groups across all the study visits. Wave and amorphous patterns were by far the most commonly found.

NITBUT

No significant differences in NITBUT from control were found between groups ($F= 0.74$; $p= 0.53$), over time ($F= 1.18$; $p= 0.32$) or in the interaction between time and contact lens groups ($F= 0.95$; $p= 0.50$) (figure 5.3).

TMH

TMH values were found to be very similar between groups ($F= 0.22$; $p= 0.88$). No significant changes were found over time ($F= 1.89$; $p= 0.12$) or in the interaction between time and contact lens groups ($F= 1.31$; $p= 0.22$) (figure 5.4).

Relationship between subjective and objective grading of TMH

TMH, as measured with the subjective eyepiece graticule, was significantly shorter (by approximately 0.02 ± 0.07 mm, $p< 0.0001$) than that measured with the objective image analysis. Eyepiece graticule measures are expected to read approximately as much as 0.05 above or 0.09 below the objective image analysis. There was no significant mean difference (bias) in the accuracy of the instrument for the whole range of TMH evident in this study (that is, 0.05-0.22 mm).

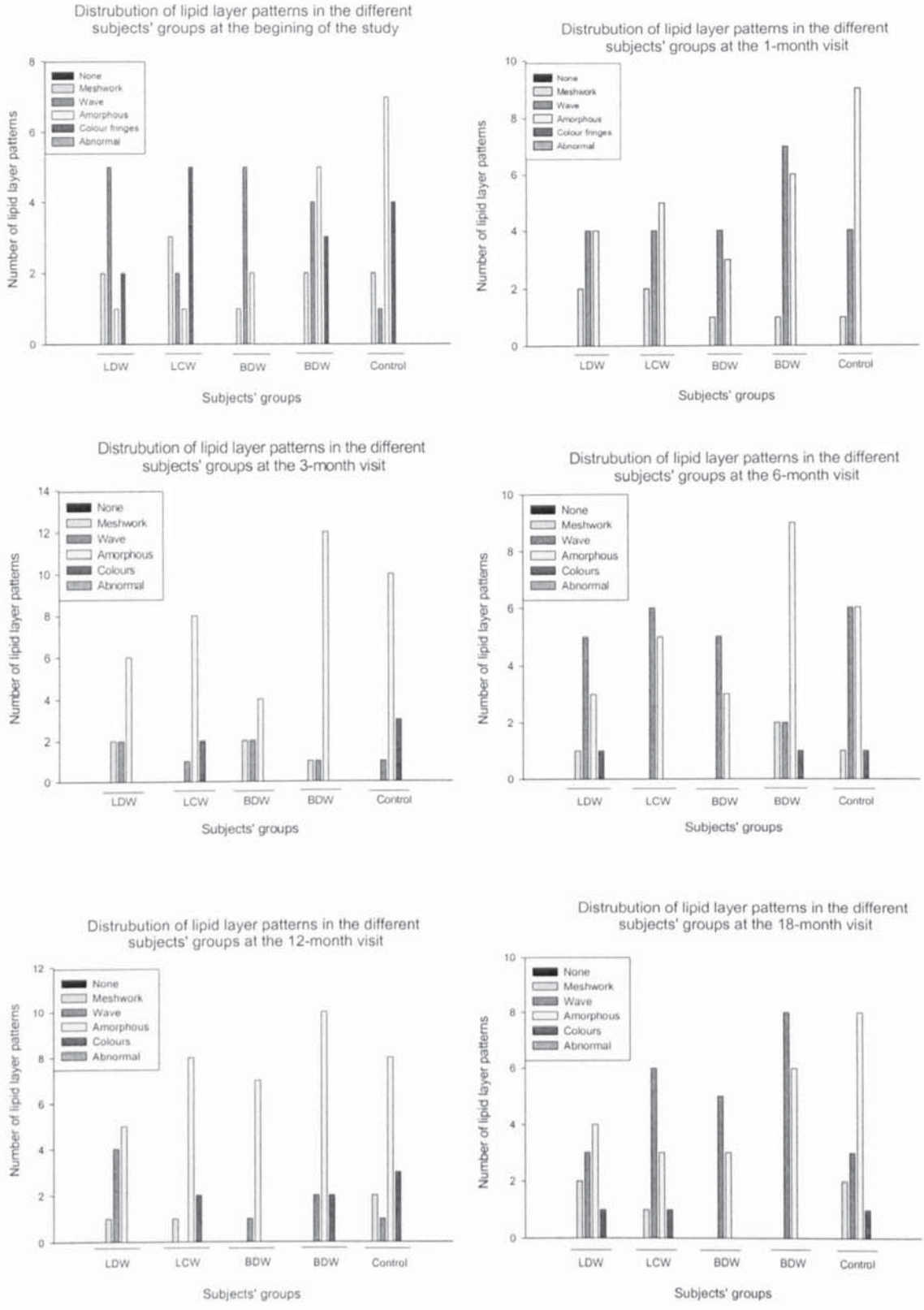


Figure 5.2. Lipid layer patterns found in all subjects' groups across all study visits

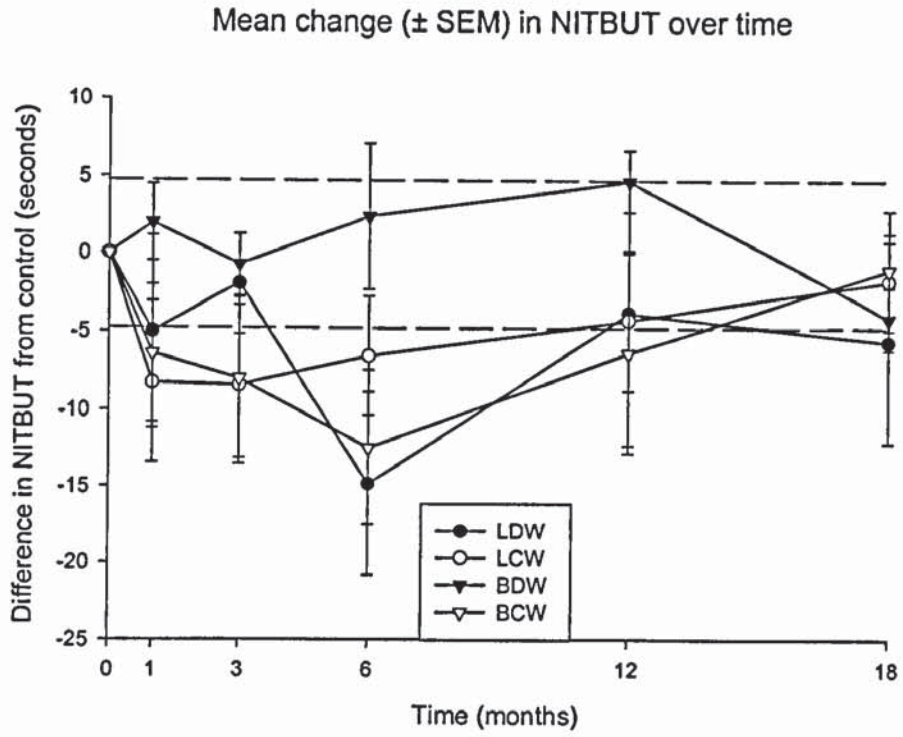


Figure 5.3. Changes over time in NITBUT

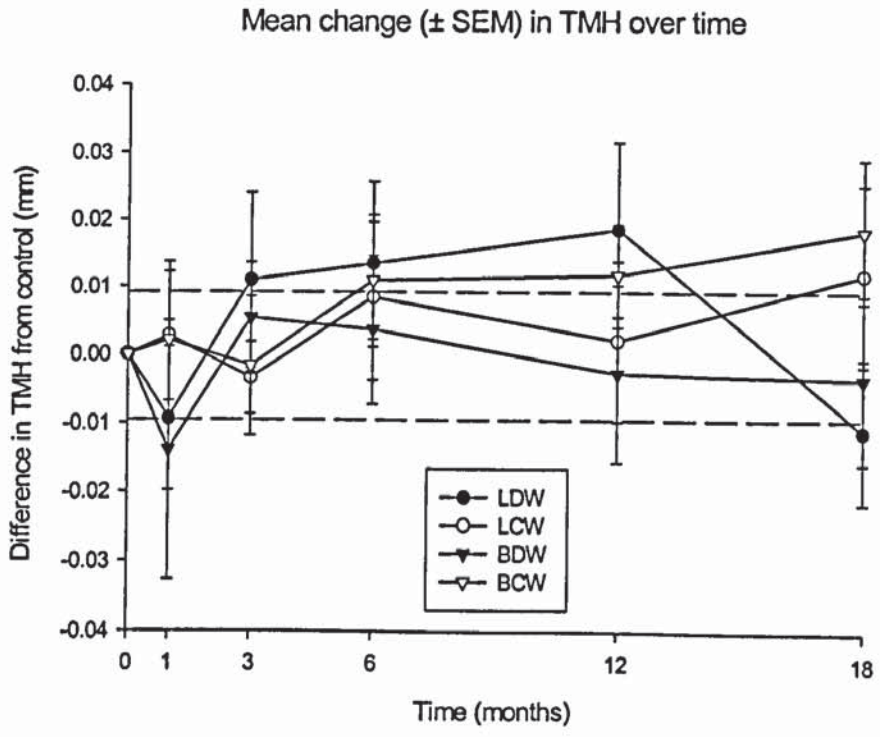


Figure 5.4. Changes over time in TMH

5.3.2 Biochemical measures

Biochemical analyses of the tear samples and contact lenses are time consuming and not all the analysis was completed by the time of the thesis submission date. However, this additional collaborative work done with the Biomaterials Research Unit is currently undergoing. The Biomaterials Research Unit is currently analysing the samples and the relationship between clinical and biochemical measures will be investigated in the near future. Additionally, due to the large amount of data obtained by the Biomaterials Research Unit, only a proportion of the data will be presented in this thesis. It must be remembered that this collaboration with the Biomaterials Research Group was not an initial aim of this work but rather a useful bonus that adds some interesting findings to the main body of research conducted. In the protein analysis three proteins of interest will be included here: high molecular weight kininogen, kallikrein and IgE. Lipid analysis of just two subjects from the LDW and BDW groups is presented in this thesis.

Tear protein analysis

Table 5.2 shows the contact lens tear film protein deposition profiles in all contact lens groups after 1, 6 and 12 months of lens wear. Proteins were removed from lens surfaces by lens extraction and counter inmmunoelectophoresis was employed for analysis of the lens extract eluates as detailed in Chapter 2 (section 2.3.2.b). Kininogen showed the highest positive incidence followed by IgE and kallikrein respectively. An increase in the positive incidence of kininogen and IgE occurred for most contact lens groups over time, whereas kallikrein did not show any significant changes over time.

	LDW			LCW			BDW			BCW		
	Kinin	K'	IgE	Kinin	K'	IgE	Kinin	K'	IgE	Kinin	K'	IgE
Month 1												
Positive	8	3	2	4	2	3	5	0	3	9	1	6
Negative	2	7	8	7	9	8	2	7	4	4	12	7
Total	10	10	10	11	11	11	7	7	7	13	13	13
Month 6												
Positive	4	4	6	9	4	7	5	0	4	11	0	10
Negative	5	5	3	1	6	3	3	8	4	3	14	4
Total	9	9	9	10	10	10	8	8	8	14	14	14
Month 12												
Positive	6	4	5	7	5	9	6	1	6	10	1	10
Negative	1	2	1	4	6	2	2	7	2	2	11	2
Total	7	6	6	11	11	11	8	8	8	12	12	12

Table 5.1. Contact lens tear film protein deposition profiles. Kinin= high molecular weight Kininogen; K'= Kallikrein; Positive= Positive incidence; Negative= Negative incidence.

Table 5.2 shows the incidence of kininogen, kallikrein and IgE in subjects who experienced events of contact lens peripheral ulcer and papillary conjunctivitis. The adverse events as a result of contact lens wear are further discussed in Chapter 7. Kininogen was the most commonly found specific marker, followed by IgE and kallikrein respectively.

	Kininogen				Kallikrein				IgE			
Month	*1*	*6*	*12*		*1*	*6*	*12*		*1*	*6*	*12*	*Occurrence (month)*
Contact lens group												
Contact lens peripheral ulcer												
LDW	Y	N			Y	N			N	N		3
LCW	Y	N	Y		N	N	N		Y	N	Y	6.5
LCW	N	Y	Y		N	N	Y		N	Y	Y	1.25
LCW	Y	Y	Y		Y	Y	N		Y	Y	Y	6
Contact lens papillary conjunctivitis												
LDW	Y	Y			Y	N			Y	Y		6
LCW	N	Y	N		N	Y	N		N	Y	Y	12.5
LCW	N	Y	N		N	Y	N		N	Y		6
LCW	Y	Y	N		N	Y	N		N	N	Y	18
LCW	Y		Y		N		Y		N		Y	18
BDW	Y	Y	Y		N	N	N		N	N	Y	3
BCW	Y	Y	Y		N	N	N		N	Y	Y	12
BCW	Y	Y			N	N			N	Y		12
BCW	Y	Y	Y		Y	Y	N		Y	Y	Y	0, 1, 3, 6, 12, 18

Table 5.2. Incidence of Kininogen, Kallikrein and IgE with contact lens peripheral ulcer and papillary conjunctivitis. Y= Positive incidence; N= Negative incidence

Tear lipid analysis

Table 5.3 shows the surface lipid deposition profiles found at 1 and 6 months of contact lens wear in two subjects, each wearing one of the two SiH contact lenses under investigation in this thesis.

	Surface Lipid 280nm (Fluorescence Units)	Surface Lipid 360nm (Fluorescence Units)
	One month	
LDW	71.14	65.23
BDW	130.1	275.6
	Six months	
LDW	48.22	27.66
BDW	190.7	316.0

Table 5.3. Surface lipid deposition profiles

High performance liquid chromatography analysis was carried out on the lipids extracted from the sponges of 3 subjects at the initial visit. These lipid fingerprints show variations in the quantity of the lipid types between patients and lens types. However, this information is qualitative rather than quantitative.

5.4 Discussion

5.4.1 Clinical measures

Lipid layer pattern

All subjects recruited were young, healthy individuals without any ocular or systemic disease and were free of taking any medication. This may explain why absent or abnormal lipid layer patterns were found in any of the groups across all the study visits. In a study by Craig and Tomlinson (1997), dry eye subjects were included in order to provide the full range of lipid layer structures visible on the human eye. Figure 5.2 shows that wave and amorphous lipid layer patterns were by far the most commonly observed, which is in agreement with previous studies (Craig and Tomlinson, 1997; Guillon *et al.*, 1997). In all contact lens groups, a tendency for a reduction in the number of meshwork and colour fringes patterns and an increase in amorphous patterns was observed in follow up visits compared to baseline visit. Such a change in the lipid layer structure was not observed in the non-contact lens wearing group, suggesting that the contact lens is responsible for the changes observed in the lipid layer structure of contact lens wearers. It has been observed that 30% of contact lens wearers develop some degree of meibomian gland dysfunction (Larke, 1985; Ong and Larke, 1990), which might explain the change from a thinner meshwork pattern to a thicker amorphous lipid layer pattern. However, an increase in the number of colour fringes patterns was not recorded. Contact lens wear might produce mixing of the different lipid layer components into a more stable lipid layer pattern, which might explain the tendency for an increase in the number of well-mixed and very stable amorphous lipid layer patterns.

The results reported here should be interpreted with caution as a large variation in between- and within- groups of observers has been found in the assessment of lipid layer structure with the *Tearscope plus* (Perrigin *et al.*, 2000). Additionally, the small sample sizes and the nature of the measurements were not appropriate for further statistical analysis and therefore more definitive conclusions.

NITBUT

There is no clear agreement on the effect induced by conventional soft contact lenses on pre-ocular NITBUT. Faber *et al.* (1991) and Du Toit *et al.* (2001) found a significant reduction of the pre-corneal NITBUT with hydrogel lens wear. It was hypothesised that the reduction in NITBUT may occur as a result of the disruption of the mucin layer with contact lens wear. In a longitudinal study, Cho and Yap (1995) found a small reduction in pre-corneal NITBUT after 2 and 9 weeks of lens wear, but not after 28 weeks (end of the study) of soft contact lens wear. In a similar study, Chui *et al.* (2000) found a significant reduction at week 2 compared to baseline, but no significant changes from baseline were found at weeks 9 and 28 in a group of neophyte contact lens wearers. Guillon *et al.*, (1997) did not find significant differences in NITBUT between a group of non-contact lens wearers and soft contact lens wearers. A significant decrease in pre-lens compared to pre-corneal NITBUT values has been previously observed (Patel, 1987; Young and Efron, 1991). However, it was out of the scope of this thesis to determinate NITBUT changes with contact lenses *in situ*. The aim of this thesis was to assess ocular changes associated with SiH contact lens wear. The data reported here can not be directly compared with the results of previous studies as SiH materials are very different from conventional hydrogel materials and features, such the high modulus of elasticity and surface coating may result in different tear tribology. The results reported here shows that SiH contact lens did not induce permanent changes in NITBUT in a group of neophyte contact lens wearers monitored over and 18-month period and this finding is in agreement with many previous studies.

TMH

It has been proposed that measurement of the TMH provides a direct estimation of tear volume (Port and Asaria, 1990) and it has been successfully used as an alternative test for the diagnosis of dry eyes (Mainstone *et al.*, 1996). Therefore, clinical monitoring of TMH changes with contact lens wear should provide an estimation of variations in tear volume. The results reported here support the notion that SiH contact lens wear does not induce permanent changes in TMH. This finding is in agreement with Guillon *et al.* (1997), who did not find a significant difference in TMH values between a group of non-contact lens wearers *versus* soft contact lens wearers. Two longitudinal studies did not find a significant change in tear volume as measured by self-prepared cotton thread test, Schirmer test and phenol red thread test in a group of soft contact lens wearers monitored for 28 weeks (Cho

and Yap, 1995; Chui *et al.*, 2000). However, direct comparisons between previous studies and the present study should be interpreted with caution, due to the different methodology and contact lens materials employed. Guillon *et al.* (1997) measured TMH with a modified slitlamp microscope for which the slit opening mechanism was graduated, whereas Cho and Yap (1995) and Chui *et al.* (2000) used invasive methods of assessing tear volume.

The absolute TMH values found in the present study (mean= 0.12 mm; range= 0.06-0.23 mm) correlate well with those reported in recent studies using image analysis techniques (Kwong and Cho, 2001; Doughty *et al.*, 2001, 2002). Assuming a normal TMH to be of the order of 0.1-0.2 mm, precise techniques will need to be employed to detect subtle changes in the TMH. The changes in TMH reported in this study were of the order of 0.01 mm and lie within the range expected in our control group. These were neither statistically or clinically significant. An aim of this chapter was to detect changes in TMH with SiH contact lens wear rather than reporting absolute values. The study of tear meniscus radius of curvature, width and cross-sectional area in addition to TMH might provide a better estimate of tear menicus changes with contact lens wear (Mainstone *et al.*, 1996; Yokoi *et al.*, 1999).

The relationship between subjective and objective measures of TMH

The close match between subjective and objective measures of TMH (0.02 ± 0.07 mm) indicate that both means of assessment are valid. While objective measures were found to be more precise and repeatable, subjective grading of the TMH with an eyepiece graticule inserted in the slitlamp observation system provides an accurate estimate of the TMH which can easily be used in clinical practice.

5.4.2 Biochemical measures

Tear protein analysis

Seven marker proteins were analysed: IgA, IgG, lactoferrin, albumin, IgE, kallikrein and kininogen. However, due to the large amount of data obtained, only three proteins are presented in this thesis: kininogen, kallikrein and IgE. Kininogen and kallikrein are members of the kinin family which constitute a group of bioactive peptides that are closely involved in the modulation of vascular inflammation and local injury, whereas IgE is well known to be prominent in allergic responses, triggering the release of inflammatory mediators from mast cells (Mann *et al.*, 2002; Mann and Tighe, 2002). Therefore, it was not surprising that an increase in the positive incidence of kininogen and IgE was found in

all contact lens groups over time. Thakur and Willcox (2000) also found that contact lens wear alters the production of certain inflammatory mediators in tears. More recently, Michaud and Giasson (2002) found that the overwear of conventional hydrogel contact lenses significantly increased the amount of proteins bound on the contact lenses, as well as the severity of upper conjunctival papillae, upper lid conjunctival hyperaemia, and limbal congestion. The low incidence of kallikrein may be attributed to a progression of the kinin cascade. In the kinin cycle, kininogen is cleaved (i.e. acted upon by breaking bonds) by kallikrein to release the end product bradykinin, which is considered a pain inducer and this occurs when kininogen and kallikrein are bound together on the surface of the contact lens. When kininogen is cleaved and thus activated by kallikrein, kallikrein may diffuse (i.e. leave) the surface of the lens. Thus, finding kininogen and not kallikrein on the lens surface may demonstrate the progression of the kinin cascade and hence the possible release of the pro-inflammatory protein pain inducer (Mann and Tighe, 2002).

The proteins marker response was found to be primarily material-dependent and secondly patient-dependent which is in agreement with the results of Mann *et al.* (2002).

The results show that contact lens wear alters the normal tear film characteristics, reducing lubrication between the cornea and lens and therefore creating friction, and as a result irritation, caused by the lens movement during blink. The friction between the lens and the ocular tissues produces a state of pre-ocular inflammation and consequently an increase in the number of certain tear proteins.

Additionally, an increase in the positive incidence of kininogen, kallikrein and IgE was also found with cases of contact lens peripheral ulcer and contact lens papillary conjunctivitis, with kininogen being the most commonly present specific marker, followed by IgE and kallikrein. Although tear proteins are normally present in the ocular environment, they increase in number before any clinical signs of adverse events are visible. Monitoring of tear protein profiles during contact lens wear is likely to provide valuable information before any adverse event occurs and it can be use as a potential tool in the prevention of adverse events and complications.

None of the proteins investigated could be regarded as being specific to one particular disease or adverse response although the findings presented above would suggest that their assessment may prove useful in the quantification of distinct events in contact lens wear.

Tear lipid analysis

Differences in the deposition profiles of the two lens types reported in this thesis were found and may be attributable to the different surface treatments (Tighe, 2000). More lipid deposition was observed in the subject wearing Balafilcon A lenses and this is in agreement with the results of Jones *et al.* (2001). Lotrafilcon A lenses are surface treated to create a permanent, ultra thin, high refractive index continuous hydrophilic surface (Nicolson and Vogt, 2001), whereas Balafilcon A lenses have silicone components in the surface of the lens which are transformed into hydrophobic compounds (Lopez-Alemany *et al.*, 2002). As a result, the surface of Balafilcon A lenses show glassy, hydrophobic discontinuations of silicate "islands". Hydrophobic surfaces attract lipid deposits and this might explain the higher deposition of lipids found in the subject wearing Balafilcon A lenses.

High performance liquid chromatography analysis showed that there were variations in the quantity of lipids, although the same lipid classes (e.g. cholesterol esters, triglycerides, fatty acids, phospholipids, monoglyercides and cholesterol) were present in the tears of all subjects at the initial visit. The presence of these lipids may be attributed the role of meibomian glands in lubricating the ocular structures. The quantities of the lipid classes extracted from contact lenses are likely to depend on the type of lens material, as certain monomers absorb lipid more strongly than others, and patient lipid spoliation levels vary. The presence and type of lipids in subjects who showed meibomian gland dysfunction is currently under investigation.

Clinical measures of the tear film characteristics showed little differences between materials and regimes of wear, whereas biochemical results appear to be more sensitive in detecting subtle changes in tear film composition. The deposition of contact lenses with substances derived from the tear film is a well-known clinical complication, resulting in reductions in comfort (Pritchard *et al.*, 1996), vision (Gellatly *et al.*, 1988) and increased inflammatory responses (Mondino *et al.*, 1982). The detection of protein and lipid markers in the ocular environment provides extremely valuable information for the development of contact lens materials and solutions as well as for the therapeutic use of drugs for the management of a variety of disorders.

	Summary of findings
1	Clinical measures of tear film characteristics showed little difference between materials and regimes of wear, whereas biochemical results appeared to be more sensitive in detecting subtle changes in tear film composition.
2	An increase in the positive incidence of protein specific markers such as kininogen and IgE was found with contact lens wear and in adverse events of contact lens peripheral ulcer and contact lens papillary conjunctivitis
3	Lipid deposition profiles were higher with Balafilcon A lenses and could be attributed to the higher hydrophobicity of the lens surface compared to Lotrafilcon A lenses.

CHAPTER 6
OCULAR SYMPTOMS WITH SILICONE-HYDROGEL CONTACT LENS WEAR

6.1 Introduction

Knowledge of ocular symptoms, visual quality and comfort is an essential part of contact lens practice. Ocular discomfort and dryness have been proposed as the primary reasons for discontinuation of contact lens wear (Vajdic *et al.*, 1999; Young *et al.*, 2002). The understanding of ocular symptoms in dry eye patients is far from clear (Nichols *et al.*, 1999). This lack of understanding has arisen as a result of the poor association between clinical signs and clinical symptoms (McMonnies, 1986; Schein *et al.*, 1997a; McCarty *et al.*, 1998). The poor association may be due to the limited standardization of diagnostic tests and symptomatology questionnaires (Lemp, 1995). Moreover, the clinical significance of abnormal clinical test results in the absence of symptoms has been questioned (Schein *et al.*, 1997b). Nevertheless, identification and management of contact lens-related symptoms is a requisite for successful contact lens wear and therefore should be carried out routinely in contact lens practice. The purpose of this chapter is to determine whether subjective symptoms/complaints and subjective judgment of lenses were different between silicone-hydrogel materials when worn on a daily and continuous wear basis over an 18-months period and to detect the prevalence of any contact lens-related dry eye.

6.2 Subjects and methods

6.2.1 Subjects

The subjects, study lenses, care regimes, wearing protocols and scheduled appointments have been described previously in Chapter 3.

6.2.2 Methods

Subjective symptoms/complaints and judgements were recorded by the subjects themselves after 1, 2, 3, 4, 12, 24, 48 and 72 weeks of lens wear using a visual analogue scale (Appendix 6). Subjects were asked to mark on the line of a visual analogue scale the position that most adequately described the level at which they had experienced any of the symptoms listed. Subjective symptoms/complaints were graded from 0 (none) to 10 (unbearable) and subjective judgements from 0 (worst) to 10 (best). The subjective

symptoms/complaints of interest in this thesis were: blurred and variable vision, glare, photophobia, lens handling problems, dryness, burning, itching, excess secretion and excessive tearing. The subjective symptoms/complaints, except for lens handling problems, of all contact lens groups were normalized against a control to eliminate some of the variability intrinsic in the use of subjective questionnaires. Subjective judgements of interest in this thesis were overall visual quality, comfort, convenience, ocular health, patient appearance, quality of life and overall satisfaction. Additionally, the CLDEQ and the DEQ were employed at the 12 and 18-month visits to detect any dry eye subjects. An average of the symptoms and subjective judgements across all study visits for each of the contact lens groups was taken as an estimate of the mean grading of symptoms (Tables 6.1 and 6.2).

Statistical analysis

Since visual analogue scales were employed to measure symptoms and subjective judgements, parametric statistics were used using *StatView* (SAS Institute Inc. 1999, Third Edition). A split-plot two-way analysis of variance was used to assess differences between the different groups over time. Scheffe *post-hoc* comparisons were employed to establish the significance or otherwise of within-factor groups.

6.3 Results

6.3.1 Symptoms/complaints

Blurred vision

Symptoms of blurred vision were found to vary significantly over time ($F= 2.94$; $p= 0.006$) (Figure 6.1). However, *post-hoc* comparisons failed to detect any significant differences between time visits ($p> 0.05$). No significant differences were found between contact lens groups ($F= 0.09$; $p= 0.97$) or for the interaction between contact lens groups and time ($F= 1.02$; $p= 0.45$).

Variable vision

Both silicone hydrogel materials when worn on a DW basis induced more glare symptoms compared to subjects wearing their lenses on a CW basis. However, these differences were

not statistically significant (F= 0.85; p= 0.47). No significant differences were found over time (F= 1.63; p= 0.12) or for the interaction between groups and time (F= 0.93; p= 0.55).

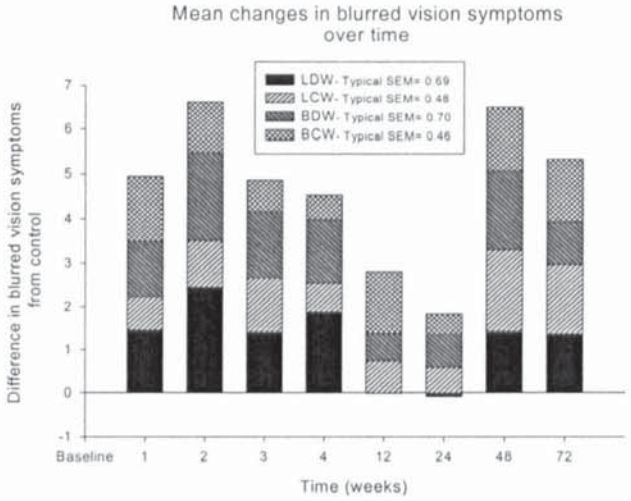


Figure 6.1. Changes in blurred vision symptoms over time.

Glare

All contact lens groups reported similar glare symptoms (F= 0.56; p= 0.64). No significant changes were found over time (F= 1.38; p= 0.22) or for the interaction between contact lens groups and time (F= 1.04; p= 0.42).

Photophobia

Subjects wearing either of the contact lens materials or regimes of wear reported similar symptoms (F= 0.03; p= 0.99). Symptoms of photophobia were also found to be similar over time (F= 1.03; p= 0.41). No significant differences were found for the interaction between contact lens groups and scheduled visits (F= 1.16; p= 0.29).

Lens handling problems

Lens handling problems decreased significantly over time for all contact lens groups, except for LCW who showed an increase in lens handling problems between the 6 and the 18-months of lens wear (F= 3.77; p= 0.0006) (Figure 6.2). *Post-hoc* comparisons showed that significant changes took place between the first and the 3, 6, 12 and 18-month visits (p= 0.02; p= 0.01; p= 0.03 and p= 0.02, respectively). No significant differences were found between groups (F= 0.55; p= 0.65) or for the interaction between groups and time (F= 0.93; p= 0.55).

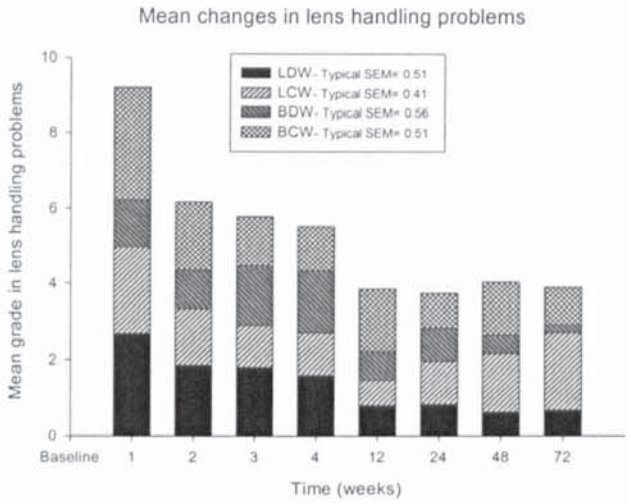


Figure 6.2. Changes in lens handling problems over time

Dryness

Both Lotrafilcon A groups reported slightly higher symptoms of dryness (Figure 6.3). However, no significant changes were found between contact lens groups (F= 0.74; p= 0.53). Changes in dryness over time just reached statistical significance (F=2.10; p= 0.04). However, *post-hoc* comparisons failed to detect any significant differences (p> 0.05). No significant differences were found for the interaction between groups and time (F= 1.23; p= 0.23).

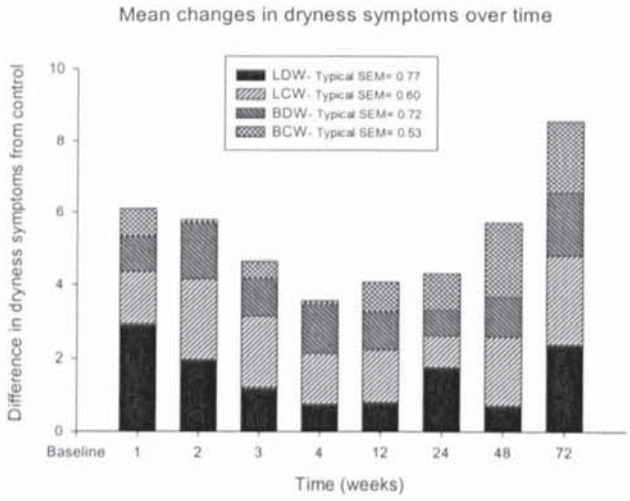


Figure 6.3. Changes in dryness symptoms over time

Burning

Symptoms of burning changed significantly over time (F= 2.28; p= 0.03). However, *post-hoc* comparisons failed to detect any significant differences (p> 0.05). No changes were found between groups (F= 0.08; p= 0.97) or for the interaction between time and contact lens groups (F= 1.47; p= 0.09)

Itching

All contact lens groups reported similar changes in symptoms of itching (F= 0.07; p= 0.98). No significant changes were reported over time (F= 1.19; p= 0.31) or for the interaction between contact lens groups and time (F= 1.34; p= 0.15).

Excess of secretion

The group wearing Lotrafilcon A lenses on a CW basis reported constantly higher levels of excessive secretion symptoms compared to the other contact lens groups (F= 3.00; p= 0.04). *Post-hoc* comparison showed a borderline statistically significant difference between LDW and LCW (p= 0.06). No significant changes were found over time (F= 1.63; p= 0.13) or for the interaction between time and contact lens groups (F= 1.05; p= 0.40).

Excessive tearing

Groups LCW and BDW showed higher symptoms of excessive tearing over the first 6-months of lens wear. In the 12-month visit both CW groups showed the highest excessive tearing symptom levels, whereas for the 18-month visit groups LDW and LCW reported more excessive tearing symptoms than the other contact lens groups. These changes were statistically significant over time (F= 2.21; p= 0.03). However, *post-hoc* comparison failed to detect any significant differences time visits (p> 0.05). Significant differences between contact lens groups did not reach statistical significance (F= 2.68; p= 0.06). No significant changes were found for the interaction between groups and time (F= 1.08; p= 0.37).

Symptoms	LDW	LCW	BDW	BCW
Blurred vision	1.84 ± 0.50	1.66 ± 0.31	1.89 ± 0.46	1.66 ± 0.31
Variable vision	1.68 ± 0.53	0.91 ± 0.24	1.65 ± 0.38	1.27 ± 0.31
Glare	0.41 ± 0.17	0.81 ± 0.15	0.80 ± 0.33	0.85 ± 0.32
Photophobia	0.47 ± 0.21	0.54 ± 0.15	0.50 ± 0.27	0.54 ± 0.18
Lens handling problems	1.38 ± 0.32	1.40 ± 0.20	0.97 ± 0.28	1.52 ± 0.33
Dryness	2.84 ± 0.52	2.95 ± 0.39	2.46 ± 0.54	2.18 ± 0.35
Burning	0.94 ± 0.30	1.08 ± 0.25	1.14 ± 0.50	0.95 ± 0.33
Itching	1.77 ± 0.37	1.94 ± 0.32	1.96 ± 0.54	1.75 ± 0.38
Excess of secretion	0.30 ± 0.13	0.89 ± 0.16	0.46 ± 0.19	0.45 ± 0.11
Excess of tearing	0.35 ± 0.13	0.89 ± 0.11	0.84 ± 0.35	0.43 ± 0.11

Table 6.1. Average grade for each symptom category (± SEM) across all study visits for each of the contact lens groups

6.3.2 Subjective judgements

Visual quality

All contact lens groups graded their visual quality highly throughout the study (Figure 6.4). Subjects wearing Lotrafilcon A lenses on a CW basis reported lower levels of visual quality compared to the other contact lens groups (F= 3.69; p= 0.02). *Post-hoc* comparisons showed significant differences between both CW groups (p= 0.03). Visual quality was reported by most contact lens groups to increase over the first 6-months of lens wear, but then to decrease between the 6 and the 12-month visit; but to increase again between the 12 and 18-month visit. These changes were statistically significant over time (F= 2.50; p= 0.02); however, *post-hoc* comparison failed to detect any significant differences between time visits (p> 0.05). No significant differences were found for the interaction between contact lens groups and time (F= 0.37; p= 1.00).

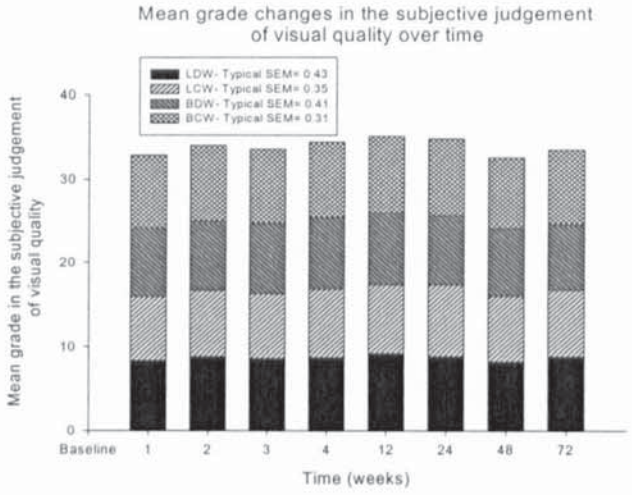


Figure 6.4. Changes in the subjective judgement of visual quality across all study visits

Comfort

The comfort achieved while wearing contact lenses was graded highly throughout the study by all contact lens groups. No significant differences were found between groups (F= 2.20; p= 0.10), over time (F= 1.61; p= 0.13) or for the interaction between groups and time (F= 1.01; p= 0.44).

Convenience

All contact lens groups felt that wearing contact lenses was very convenient (Table 6.2). No significant differences were found between groups (F= 1.17; p= 0.33), over time (F= 1.78; p= 0.09) or for the interaction between groups and time (F= 1.12; p= 0.33).

Ocular health

All contact lens groups reported that their eyes felt healthy throughout the study. However, some differences were found between contact lens groups (F= 3.37; p= 0.03). *Post-hoc* comparisons showed that subjects in the LCW group reported lower levels of ocular health compared to the subjects in the BCW group ($p< 0.05$). No significant differences were found over time (F= 1.19; p= 0.31) or for the interaction between contact lens groups and time (F= 0.51; p= 0.97).

Patient appearance

All contact lens groups reported their appearance as very high while wearing contact lenses, except subjects in the LCW group who reported their appearance to be slightly lower. Significant differences in patient appearance were found between groups (F= 4.99; p= 0.005). *Post-hoc* comparisons showed subjects in the LDW and BCW groups graded their appearance higher than subjects in the LCW groups (p= 0.02 and p= 0.02, respectively). No significant differences were found over time (F= 1.65; p= 0.12) or for the interaction between contact lens groups and time (F= 1.01; p= 0.46).

Quality of life

Subjects of all contact lens groups felt that their quality of life improved with the use of contact lenses. However, some groups reported higher quality of life than others (F= 3.57; p= 0.02). *Post-hoc* comparisons showed that subjects in the LCW group graded their quality of life lower than subjects in the BCW group ($p< 0.05$). Some changes were reported over time although they did not reach statistical significance (F= 1.92; p= 0.07). No significant differences were found for the interaction between groups and time (F= 0.63; p= 0.90).

Overall satisfaction

All contact lens groups were very satisfied with their contact lenses (Figure 6.5). No significant differences were found between groups (F= 1.67; p= 0.19), over time (F= 1.52; p= 0.16) or for the interaction between contact lens groups and time (F= 0.83; p= 0.68).

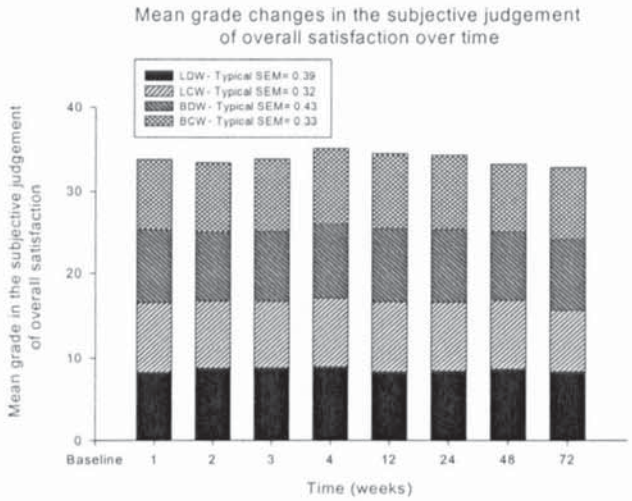


Figure 6.5. Changes in the subjective judgement of overall satisfaction across all study visits

Subjective judgement	LDW	LCW	BDW	BCW
Visual quality	8.79 ± 0.33	7.81 ± 0.22	8.37 ± 0.27	8.89 ± 0.24
Comfort	8.10 ± 0.28	7.46 ± 0.21	8.35 ± 0.30	8.31 ± 0.30
Convenience	8.89 ± 0.42	8.20 ± 0.22	8.83 ± 0.27	8.78 ± 0.24
Ocular health	8.59 ± 0.26	7.61 ± 0.28	8.48 ± 0.35	8.69 ± 0.24
Patient appearance	9.35 ± 0.14	7.97 ± 0.31	8.57 ± 0.52	9.23 ± 0.20
Quality of life	9.14 ± 0.24	8.19 ± 0.21	8.69 ± 0.38	9.14 ± 0.20
Overall satisfaction	8.61 ± 0.23	8.01 ± 0.17	8.57 ± 0.33	8.71 ± 0.25

Table 6.2. Average of the subjective judgement (± SEM) across all study visits for each of the contact lens groups

6.3.3 Detection of dry eye subjects

When the CLDEQ was applied individually to each of the contact lens subjects and the DEQ to the non-contact lens subjects, no dry eye subjects were identified in either of the groups.

6.4 Discussion

The subjects enrolled in the study were not representative of the normal population as all exhibited some degree of refractive error. However, the study group are most likely to attend a contact lens practice for a contact lens consultation. It could be argued that since all subjects were neophyte contact lens wearers they are likely to experience more symptoms than previously adapted contact lens wearers. However, most symptoms reported in this study were very similar across all scheduled visits. It could also be argued that since subjects recruited in the study were getting free contact lenses, contact lens solutions and cases and after care, they might be predisposed to under grade and over grade their symptoms/complaints and subjective judgements respectively. However, this predisposition was likely to be similar in all contact lens groups.

6.4.1 Symptoms/complaints

Dryness was the most commonly reported symptom in this study and this is in agreement with previous studies with conventional hydrogel lenses (Vajdic, 1999; Du Toit *et al.*, 2001). However, symptoms of dryness were mild and reported by a few subjects only. In a study of 504 subjects wearing Balafilcon A lenses on an extended or CW basis, dryness, the most commonly reported symptom, was also found to be mild (Nilsson, 2001). Fonn and Dumbleton (2003) found that symptoms of dryness over time were experienced equally by Lotrafilcon wearers compared to conventional hydrogel wearers. Both groups wearing Lotrafilcon A lenses in this study reported higher levels of dryness compared to subjects wearing Balafilcon A lenses. Possible explanations for increased dryness symptoms in subjects wearing Lotrafilcon A lenses could be attributed to the different characteristics of the lens materials, such as the modulus of rigidity and surface treatments (Tighe, 2000). Additionally, higher levels of lipid deposition were found in Lotrafilcon A lenses compared to Balafilcon A lenses (see Chapter 5). One of the Lotrafilcon A groups, LDW, showed the lowest male/female ratio (2:8). Previous studies in adult populations have also shown a higher prevalence of dry eye symptoms in females compared to males (Doughty *et al.*, 1997; McCarty *et al.*, 1998; Du Toit *et al.*, 2001).

Dry eye symptoms could be related to mechanical irritation of the bulbar conjunctiva by the lens edge, or of the palpebral conjunctiva by the anterior lens surface owing to the presence of a depleted or unstable pre-lens tear film.

Other symptoms commonly reported by all contact lens groups in this study are itching and blurred and variable vision, which is also in agreement with previous studies (Vajdic, 1999; Du Toit *et al.*, 2001; Nilsson, 2001). Blurred and variable vision have been reported as a common symptom of dry eye (Begley *et al.*, 2000). Additionally, since all contact lens groups showed an increase in myopia as the study progressed, the reported symptoms of blurred and variable vision could also be attributed to a gradual progression of myopia (uncorrected) driven by a low level of retinal defocus. More variable symptoms were reported by the groups wearing lenses on a DW basis. Variable vision might occur as a result of lens movement. Subjects wearing lenses on a CW basis are likely to show less lens movement than those wearing lenses in the DW basis and this could be attributed to contact lenses moulding to the corneal shape of the CW subjects as a result of the higher number of hours of lens wear.

More lens handling problems were reported at the beginning of the study. This is not surprising since all contact lens groups had been newly introduced to contact lens wear and therefore they were more likely to have greater initial problems when handling their lenses. As the study progressed and subjects gained more experience handling their lenses, the handling problems decreased. Interestingly, the two CW groups showed an increase in their reported lens handling problems towards the end of the study. This was probably due to the reduced time spent by these subjects handling their lenses as lenses were worn on a continuous wear basis. The remaining symptoms investigated (i.e. glare, photophobia, burning and excess of secretion and tearing) were not commonly reported.

6.4.2 Subjective judgement

All the subjective judgements sampled in this thesis were rated very favourable. Nilsson (2001) and Iruzubieta *et al.* (2001) also found very favourable subjective judgements in subjects wearing silicone hydrogel lenses on either an extended or continuous basis in terms of comfort, visual quality and overall satisfaction. Siegel and Spilkin (2000) found subjective comfort and overall satisfaction to be significantly better for Balafilcon A lenses than for Lotrafilcon A lenses, which is in agreement with the results reported here. The LCW group reported worst subjective judgements compared to the other contact lens groups. Using the objective red extraction technique, both Lotrafilcon A groups, especially LCW, showed slightly higher levels of palpebral hyperaemia compared to both Balafilcon A groups. The LCW group also showed a higher rate of adverse reactions compared to the

other contact lens groups (see Chapter 7). A higher rate of localized contact lens-induced papillary conjunctivitis has been previously reported with Lotrafilcon A lenses and it has been suggested that it could be due to mechanical trauma between the lens and the anterior palpebral conjunctiva (Skotnitsky *et al.*, 2002). A higher degree of corneal flattening was also observed in the LCW group compared to the other groups. Previous studies have also found a higher degree of corneal flattening with Lotrafilcon A lenses (Dumbleton *et al.*, 1999; González-Meijome *et al.*, 2003). Indentation ring marks at the lens edge on the bulbar conjunctiva were most commonly seen also in the LCW group. Additionally, higher levels of lipid deposition were found in Lotrafilcon A lenses compared to Balafilcon A lenses (see Chapter 5). Higher levels of lipid deposition are likely to induce changes in the tear film components that, even if small, can disturb the nature and dynamics of the tear film and predispose patients to increased symptomatology (Glasson *et al.*, 2002).

Lotrafilcon A lenses when worn under closed-eye conditions appear to induce more unwanted effects compared to other groups. The mechanisms responsible for these effects are not clearly understood. The different characteristics of the lens materials, such as the modulus of rigidity and surface treatments may explain some of the differences found. However, subjects wearing Lotrafilcon A lenses on a CW basis showed more adverse reactions, higher levels of vascular response and more symptomatology than subjects wearing the same lenses on a DW basis. Careful analysis of the LCW group showed that 6 out of 11 subjects were Chinese in origin, whereas the other groups showed between none to two Chinese subjects per group. Lam and Loran (1991) reported than oriental eyes differ significantly from Caucasian eyes, in terms of corneal curvature, sensitivity and peripheral flattening. Contact lens design is invariably based on Caucasian eyes and hence one could anticipate that the performance of contact lenses in Oriental eyes is unlikely to be optimal. It is clear that continuous wear of Lotrafilcon A lenses produce a special environment responsible for these unwanted effects and the higher symptomatology reported. However, the mechanisms responsible for it are not clearly understood and further research will need to be carried out to reveal the possible reasons.

6.4.3 Detection of dry eye subjects

No dry eye subjects were detected by means of subjective questionnaires in any of the groups examined. This finding correlates well with the tear film clinical measures carried out in this study. No permanent changes in tear film volume as measured by tear menicus height and stability as measured by non-invasive tear break-up time were found in this

thesis. Whilst symptoms of dry eye have been found to be commonly reported in non-contact and contact lens wearers, the prevalence of dry eye is relatively low. Dry eye syndrome has been found to increase with age, being higher in females aged 40 to 60 years (McCarty *et al.*, 1998; Jamaliah and Fathilah, 2002). To date, no studies have assessed the prevalence of dry eye in young populations, probably due to its low incidence.

The mild symptoms and high subjective acceptance judgements reported by all contact lens groups suggest that the performance of SiH lenses is very high according to these criteria. However, understanding symptomatology as a result of contact lens wear can be very difficult. The findings reported in this chapter could assist practitioners to anticipate those patients who are likely to develop contact lens-related symptoms and those likely to become unsuccessful contact lens wearers.

Summary of findings

1	Dryness was the most commonly reported symptom followed by itching and blurred and variable vision. Dry eye symptoms could be related to mechanical irritation of the bulbar conjunctiva by the lens edge, or of the palpebral conjunctiva by the anterior lens surface owing to the presence of a depleted or unstable pre-lens tear film.
2	All the subjective judgements sampled in this thesis were rated very favourable by all contact lens groups.
3	No dry eye subjects were detected by means of subjective questionnaires in any of the groups examined and this could be attributed to the low prevalence of dry eye subjects in young populations.
4	Generally, symptoms were mild and the high subjective acceptance judgements reported by all contact lens groups suggest that overall the clinical performance of SiH lenses is very high according to these criteria.

CHAPTER 7

ADVERSE EVENTS AND COMPLICATIONS ASSOCIATED WITH SILICONE HYDROGEL-CONTACT LENS WEAR

7.1 Introduction

The use of contact lenses has increased considerably in recent years. One of the barriers to their widespread use has been adverse events and complications, especially with extended wear. In general terms, an adverse event may be defined as an "unwanted, often unexpected and sometimes dangerous reaction that require immediate attention" and a complication as a "morbid process" (Stedman's medical dictionary, 2000). Both may occur as result of treatment or disease, in this case the correction of ametropia with SiH contact lenses. Silicone-hydrogel contact lenses have overcome many of the hypoxic problems commonly associated with EW of traditional low-Dk hydrogel lenses, allowing continuous wear (of contact lenses to be a convenient and safe option. The adverse reactions frequently found with EW of low-Dk hydrogel lenses include neovascularization, striae, microcysts and an increase in bulbar and limbal hyperaemia. Whereas these events do not commonly occur with CW of SiH lenses, many other problems still need to be solved with these new materials (Keay *et al.*, 2000; Nilsson, 2001; Fonn *et al.*, 2002). Inflammatory conditions such as contact-lens induced peripheral ulcers (CLPU), contact lens acute red eye (CLARE), infiltrative keratitis and contact lens papillary conjunctivitis (CLPC) occur at similar rates than those previously reported with conventional hydrogel lenses (Skotnitsky *et al.*, 2000; Fonn *et al.*, 2002; Holden, 2002). Due to the higher stiffness of SiH compared to hydrogel lenses, other adverse events associated with mechanical trauma (e.g. superior epithelial arcuate lesions and localized contact lens-induced papillary conjunctivitis) may have a higher rate of incidence (Skotnitsky *et al.*, 2000; Fonn *et al.*, 2002; Holden, 2002).

The key to successful management of an adverse event and/or complication lies in prompt detection, correct diagnosis and use of appropriate management and treatment strategies.

The aim of this chapter is to discuss the symptoms, signs, diagnosis, management and treatment of the complications seen in a group of forty-three neophyte SiH contact lens wearers and fourteen non-contact lens wearing subjects (control group) who were monitored over an 18-month period.

7.2 Subjects and methods

7.2.1 Subjects

The subjects, study lenses, care regimes, wearing protocols and scheduled appointments have been described previously in Chapter 3.

7.2.2 Methods

Adverse events were evaluated by detailed collection of reported symptoms and observable signs. Pictures of the adverse events were taken with a camera attached to a slit-lamp biomicroscope (as described in 2.2.1) and stored into a computer with the help of specialized software (WinTV, Version 4.6, Hauppauge!®). Diagnosis was based on symptommatology and signs. The management and treatment procedures adopted for each of the adverse events/complications are also described. Recurrences of the same adverse events or complications in the same or fellow eye at any of the subsequent study visits were considered to be a single event. Bilateral events of a different nature in each eye were counted as two individual events.

An emergency 24- telephone number was provided to all contact lens wearers in the study.

7.3 Results

The adverse reactions/complications found in this study are summarized in the table below.

	CLPU	CLPC	CLARE	SEAL	SI	MGD	OTHER
LDW	1	1	-	-	1	2	BDIM
LCW	4	4	1	1	2	7	-
BDW	-	1	-	-	1	2	-
BCW	-	3	-	1	1	4	-
CONTROL	-	-	-	-	-	5	-

Table 7.1 Adverse reactions/complications observed in all groups throughout the study. CLPU= contact-lens induced peripheral ulcers; CLPC= contact lens papillary conjunctivitis; CLARE= contact lens acute red eye; SEAL= superior epithelial arcuate lesions; SI= Scleral indentation; MGD= Meibomian gland dysfunction; BDIM= Bilateral drug-induced myopia

None of the subjects was permanently discontinued from contact lens wear and best-corrected visual acuity was unaffected in all subjects.

Contact lens peripheral ulcer

Five events of CLPU were found in this study, all associated with the wear of Lotrafilcon A lenses. However, they were more commonly observed in the continuous wear group. All events were characterized by the presence of a focal, circumscribed, dense, round, corneal infiltrate. The infiltrate typically exhibits a single peripheral or mid-peripheral white/gray lesion in the anterior stroma.

In the LDW group one single subject was found to experience an episode of CLPU. This 20-years old Caucasian male was found to be asymptomatic and two typical scars were seen at the 11 and 1 o'clock positions at the 3rd month scheduled visit. No treatment was required and just close monitoring was carried out. Scars were present at the 6 and 12-month follow-up visits, but they were no longer visible at the 18-month visit (end of the study).

The LCW group showed 4 events of CLPUs. In a follow-up visit, two typical scars were seen at the 7 and 10 o'clock positions in the left eye of an 18.5-year old Caucasian female after 6.5 months of lens wear. She was asymptomatic. No treatment was required and just close monitoring was carried out. No recurrences were observed and corneal scars were no longer present at the 12-month visit.

A 19-year old male Caucasian symptomatic subject experienced 1 occurrence of CLPU in his left eye after 5 weeks of lens wear. At the time of the emergency visit, a corneal infiltrate was observed at the 12 o'clock position in the mid-peripheral cornea. Mild blockage of the meibomian glands was also observed in this subject in previous aftercare visits. The scar disappeared by the end of the study and no re-occurrences were reported. The symptommatology reported by this subject included eye redness, discomfort, excessive tearing and secretion, glare and symptoms of itching. Treatment included discontinuation of lens wear for 7 days. Afterwards, he reassumed lens wear on in a daily wear basis for a second week and then he restarted CW. No recurrences were found. He also was instructed on how treat the mild blockage of his meibomian glands.

A third case of CLPU in the LDW group was experienced by an 18-year old Malaysian Chinese female who showed bilateral recurrences associated with mild to moderate symptoms (Figure 7.1 and 7.2). The symptoms in order of severity included excessive

tearing, itching, photophobia, blurred vision, burning, excess of secretion and ocular redness. The first CLPU occurred in the right eye at the 7 o'clock position after 6-month of CW and was accompanied with a strong bulbar and limbal vascular response. A recurrence was observed at the 6 o'clock position in the fellow eye at the 12-month visit. Both corneal scars were still present at the end of the study. Treatment for both events was the same and included discontinuation of lens wear for 6 days. Afterwards, she reassumed lens wear in a daily wear basis for a week and then she restarted CW. Scars were still visible by the end of the study.

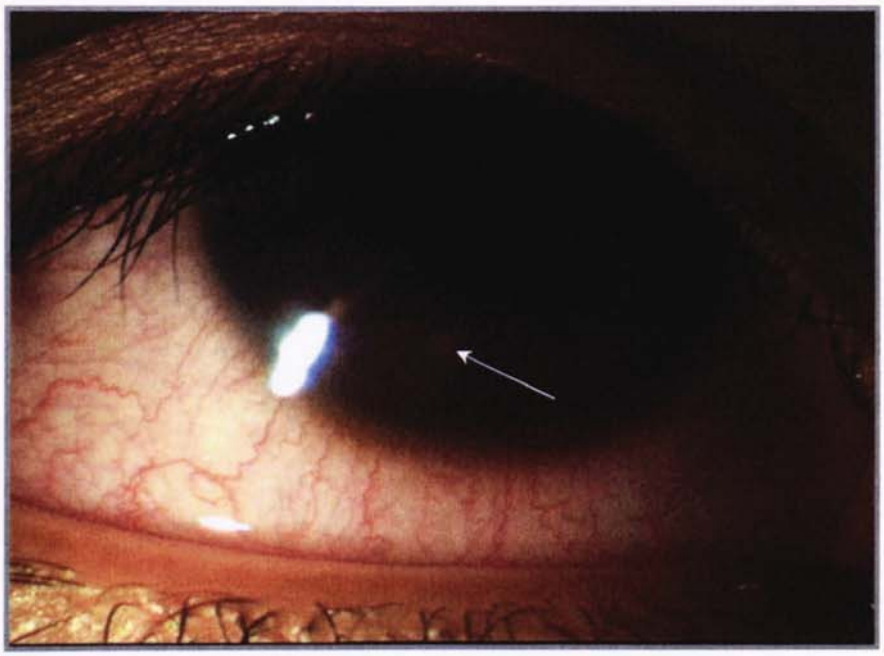


Figure 7.1. Round, dense focal infiltrate on the right eye at the 7 o'clock position associated with a strong bulbar and limbal vascular response (white arrow). A magnified picture of the same infiltrate is seen Figure 7.2.

Figure 7.2. Stained infiltrate as a result of full-thickness epithelial loss.

The last event of CLPU in the LDW group occurred in an 18-year old Hong-Kong Chinese male after 6 weeks of lens wear (Figure 7.3). This subject reported symptoms of pain, excessive tearing, foreign body sensation, bulbar redness and the need to remove his contact lenses. A typical corneal infiltrate at the 11 o'clock position was seen in the anterior stroma which stained with fluorescein as a result of a full-thickness epithelial loss. The corneal scar disappeared by the 12-month visit. Meibomian gland dysfunction was also observed in this subject at most follow-up visits. Treatment included discontinuation of lens wear for 6 days. Afterwards, he reassumed lens wear on a daily wear basis for a week and then he restarted CW. No recurrences were found and he was advised to regularly clean his eyelids and lashes using a baby shampoo and instructed on how to apply hot compresses and lid scrubs.

Figure 7.3. Typical scar of a corneal infiltrate one month after occurrence.

Contact lens papillary conjunctivitis

Several cases of CLPC were found in this study, being more common in subjects wearing lenses on a CW basis. The characteristic feature of CLPC observed was the presence of elevated papillae and increased hyperaemia and roughness of the everted lid. The papillae was either localized to one quadrant or seen involving the entire tarsus (general). Contact lens papillary conjunctivitis was classified as either general or localized.

The LDW group showed only one event of CLPC in a 21-year old Asian female. The condition was bilateral, recurrent and localized. The localized event was detected in both eyes at the 6-month after care visit, being more severe in the right eye. At this time the subject was asymptomatic and signs were very subtle. No discontinuation of lens wear was advised but close monitoring over the following weeks was carried out. The condition did not change over the following 4 weeks and the subject was discharged. At the 12-month visit a worsening of the condition was observed being again more severe in the right eye. At this point the subject complained of, in order of severity, discomfort, foreign body sensation, burning, blurred and variable vision and dryness. Discontinuation of lens wear over the following 2 weeks alleviated the signs and symptoms reported and contact lens wear was reassumed. The importance of contact lens cleaning procedures was emphasized for this subject. At the 18-month study visit bilateral localized CLPC was again observed. However, the signs were not as severe as at previous visits and were accompanied by mild symptoms of dryness and itching. This subject was advised to change to a different contact lens material.

Four localized events of CLPC were found in the LCW group. A 24-year old Hong-Kong Chinese male experienced a unilateral event which was detected in the nasal side of the tarsal plate after 12.5 months of lens wear. Symptoms included pain, discomfort, blurred vision and discharge. Daily wear of contact lenses during the following two weeks alleviated signs and symptoms and CW was reassumed. A similar sign of less severity and without any associated symptoms was observed in the same eye after 18 months of lens wear. This subject was advised to switch to a daily wear regime.

A second localized event was found in a 21-year old Caucasian male. The event was found to be bilateral and asymmetric, with the right eye being more involved than the left. This subject complained of discomfort and dryness being more severe in the right eye. He also reported that the right contact lens was removed at earlier intervals than the left contact lens due to discomfort. The event was detected after 6 months of lens wear and disappeared without discontinuation of continuous wear of contact lenses but with the help of ocular lubricants (*Opti-Free* lubricant eye drops, Alcon Laboratories, Inc., TX, USA).

A third localized event was detected in a 21-year old Asian female at the 18-month follow-up visit. It was unilateral and only affected a small part of the nasal side of the tarsal plate.

The subject complained of mild symptoms of, in order of severity, itching, blurred vision, dryness, burning and excessive tearing. Daily wear of contact lenses for 3 weeks eliminated the signs and symptoms observed. Contact lens wear was reassumed but she was advised that if recurrent events occurred, she would need to change to a daily wear regime or to a different contact lens material.

Finally, the fourth event occurred at the 18-month visit in the left eye of a 22-year old Chinese female and was associated with blockage of the upper lid meibomian glands of the same eye (Figure 7.4). This subject was mainly asymptomatic and only complained of mild dryness. Daily wear of contact lenses together with treatment of the meibomian glands over the following two weeks alleviated signs and symptoms.

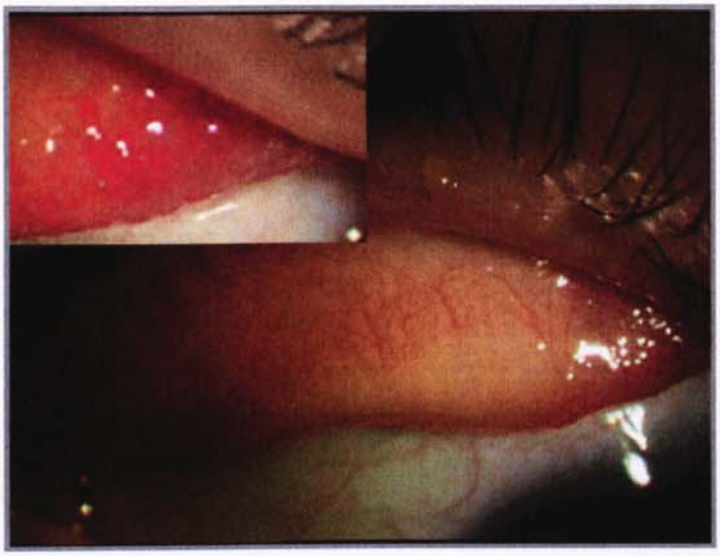


Figure 7.4. Localized CLPC associated with MGD. A magnified picture of the palpebral changes of the nasal conjunctiva is seen on the top left corner of the picture.

A single general event of CLPC was found in the BDW group and included a bilateral, general and asymmetrical event, detected in a 20.5-years old Hong-Kong Chinese female at the third month visit (Figure 7.5). This subject reported symptoms of blurred and variable vision, glare, photophobia, dryness, burning, itching and excess of secretion and tearing. Most of the symptoms were given a grade 5 on a scale of 0 (none) to 10 (unbearable). A reduction in wearing times together with the use of tear lubricants alleviated signs and symptoms over the following 4 weeks. A recurrence in the left eye was observed at the 6-month visit which also was alleviated by reducing wearing times and the use of tear lubricants. No recurrences were observed at subsequent visits.

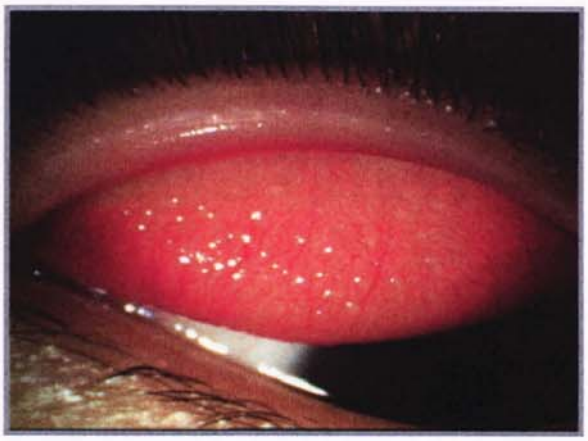


Figure 7.5. General CLPC involving the entire tarsus.

Three events were found in the BCW group, all of them being localized in nature. One unilateral localized event was detected on the nasal side of the tarsal plate of an 18.5-year old Caucasian asymptomatic female at the 12-month visit. Since this subject was asymptomatic and the signs were mild, no intervention was carried out at that time, but 6 weeks after, she complained of discomfort and soreness in the same eye. Lid eversion revealed similar clinical signs to those found at the 12-month visit. This subject was advised to discontinue lens wear for a week and then to start in a daily wear regime for another week. After these two weeks all signs and symptoms regressed. No signs or symptoms were found at the 18-month visit.

Another event of localized CLPC was observed in a 22-year-old Asian male at the 12-month visit and was associated with mild anterior blepharitis (Figure 7.6). Only the nasal and temporal sides of the tarsal plate of the right eye were involved. Slit-lamp examination revealed the presence of hyperaemia and scaling of the lid margins. Symptoms included varying levels of foreign body sensation and discomfort for the last 2.5 months. This subject was advised to promote lid hygiene and reduce wearing times. All signs and symptoms of CLPC and blepharitis disappeared within 5 weeks. No signs of symptoms were found at the 18-month visit.

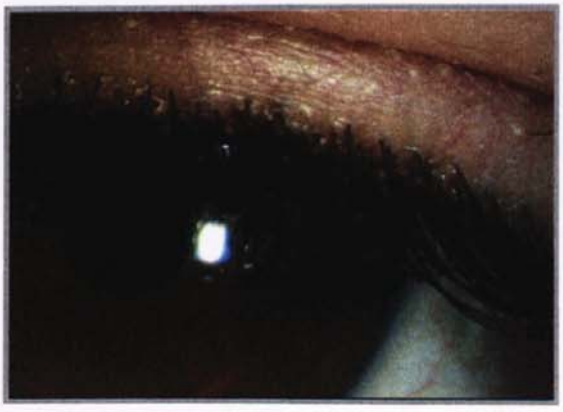


Figure 7.6. Mild blepharitis with brittle scales on the lid margin.

The last event observed in the BCW group included a bilateral CLPC in an asymptomatic 22-years old Asian female (Figure 7.7 and 7.8). Mild palpebral redness and roughness was observed in both tarsal plates *prior* to contact lens fitting. An increase in palpebral redness, roughness and elevated papillae was found by the end of the first month. The subject was asymptomatic and monitored over the next few months. The clinical signs remained the same at all following visit and the subject reported symptoms of dryness only for which artificial tears were dispensed (*Opti-Free* lubricant eye drops).

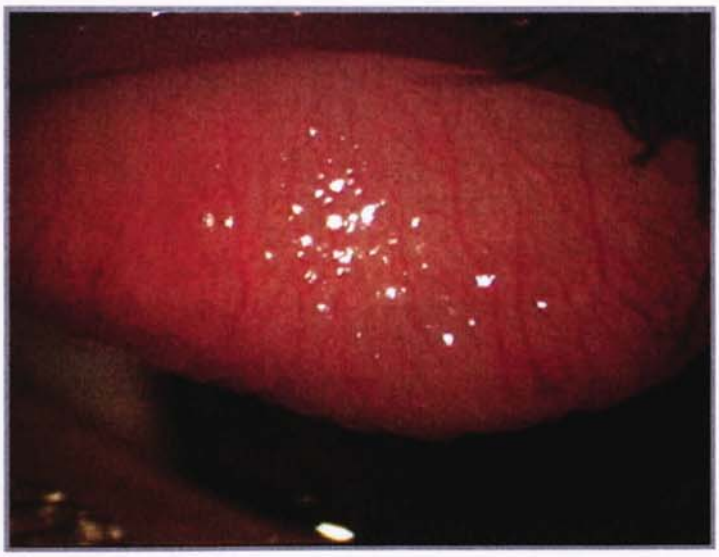


Figure 7.7. Localized CLPC. Elevated papillae and increased hyperaemia and roughness of the palpebral conjunctiva is localized to the central region.

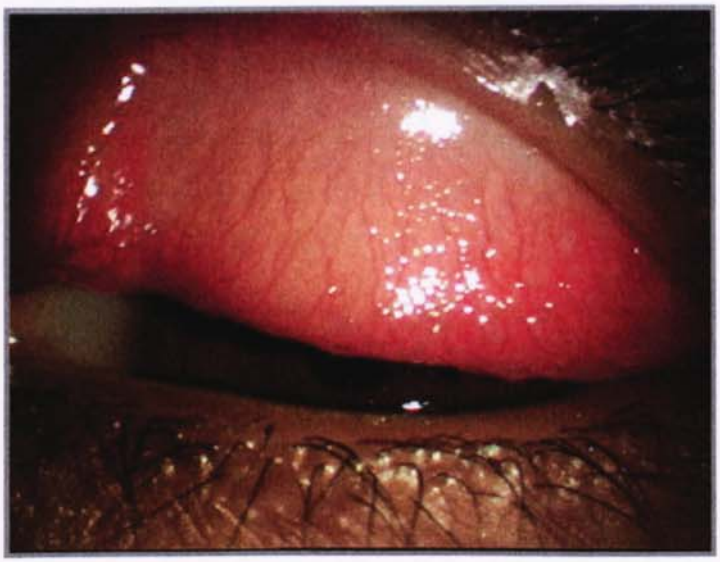


Figure 7.8. Localized CLPC affecting the nasal and temporal sides of the tarsal plate, possibly as a result of mechanical trauma induced by the lens edges.

Finally, a 19-year old Kenyan female from the non-contact lens wearing control group consistently showed bilateral general papillary conjunctivitis starting at the initial visit and lasting throughout the study period. This subject was asymptomatic and signs remained unchanged at follow-up visits. The condition was considered just a physiological feature and not an adverse event. No intervention was carried out.

Contact lens acute red eye

One single case of CLARE was found in a 19-year old male Caucasian subject from the LCW group. The adverse event occurred in the right eye after 9 weeks of lens wear and was associated with the presence of large amounts of mucin balls and probably post-lens tear film debris. This subject reported that on the night before the event occurred, he was experiencing some redness and discomfort on his right eye, but he went to sleep in his lenses. Next morning, the eye was very red and painful. The symptoms reported at the emergency visit were, in order of severity excessive secretion, excessive tearing, itching, dryness, photophobia and glare. Fine diffuse infiltrates were observed in the superior peripheral cornea. This subject also experienced an event of CLPU after 5 weeks of lens wear.

Superior epithelial arcuate lesions

Two events of SEALs were found in a 19 and 18.5-year old Caucasian male (Figure 7.9) and female (Figure 7.10), respectively. Both subjects were asymptomatic and both corneal lesions were detected at the 6-month follow-up visit. The lesions were seen in the superior limbus between the 10 and 2 o'clock positions and characterized by a thin white limbal arcuate lesion which stained with fluorescein. Injection of the limbal vessels around the SEALs was also observed, but there was no associated inflammation or infiltrates. No recurrent SEALs were detected. Subjects were temporary discontinued from lens wear and resolution occurred within 6 days for the female subject and 3 days for the male subject. No prophylactic medication or artificial tears were required. Subjects were then restarted with contact lens wear and advised that if recurrent episodes were observed they might have to be changed to a daily wear regime.

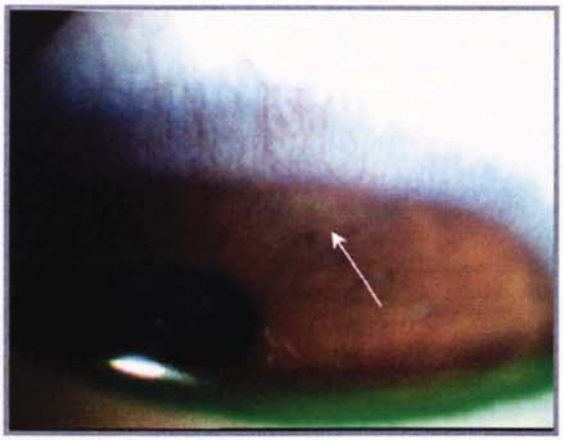


Figure 7.9. Corneal SEAL (white arrow).

Figure 7.10. Stained corneal SEAL associated with injection of the limbal vessels.

Meibomian gland dysfunction

Several cases of MGD were observed in all experimental groups. They were more commonly observed in subjects wearing lenses in a continuous wear basis and in the control group. All cases were mild and not associated with symptomatology, except for four cases. These four cases included three severe blockages of the meibomian glands in the LCW group and a fourth case of an internally blocked meibomian gland in the BDW group.

An 18-year old Hong-Kong Chinese male from the LCW group showed severe MGD associated with frothing of the tear film and tear film debris (possibly mucus) and excessive secretions around lid margins. The subject was asymptomatic and also experienced an episode of CLPU ten days after the severe MGD was observed. Unsatisfactory hygiene was suspected as the cause.

A second complication of MGD was found in a 20-year old Asian male after 6 months of continuous wear (Figures 7.11 and 7.12). At the follow-up visit he complained of discomfort, blurred vision and a foreign body sensation. He was unable to wear his lenses to the same extent. Slit-lamp examination revealed two severely blocked meibomian glands in the upper lid of the left eye. Careful expression of the blocked meibomian glands succesfully unblocked the glands. The subject was advised to regularly clean his eyelids and lashes and was instructed on how to apply hot compresses and lid scrubs. No recurrences were found.

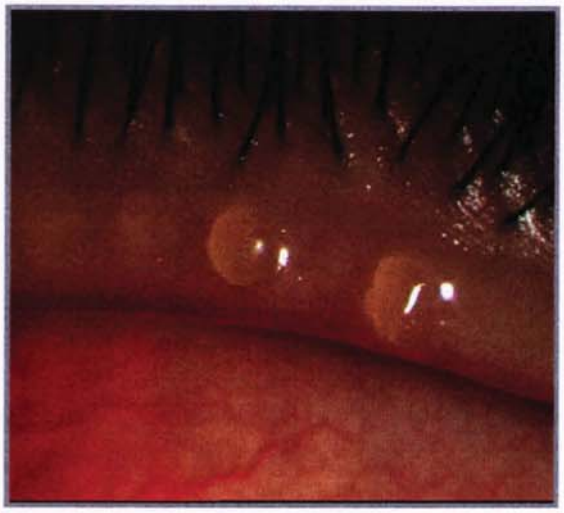


Figure 7.11. Blockage of two meibomian glands of the upper lid.

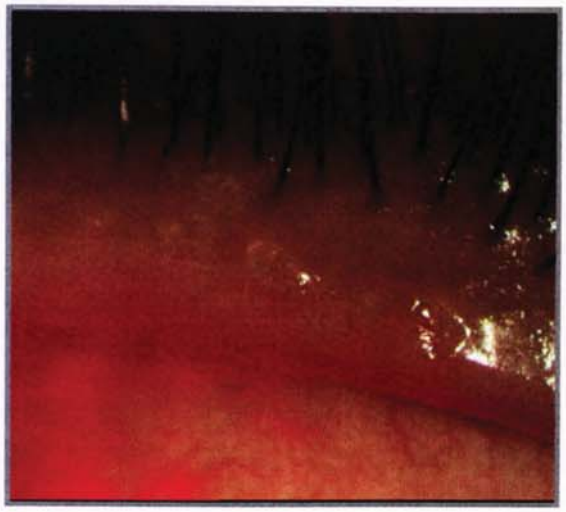


Figure 7.12. View of the meibomian glands seen in Figure 7.11 after successful mechanical expression of the glands.

A third complication was found in a 22-year old Chinese female from the LCW group. She showed mild blockage of the meibomian glands at all study visits with no assocciated symptomatology. A severe blockage of one gland from the upper lid associated with localized CLPC was observed at the 18-month visit. At the time of complication she was asymptomatic and only complained of slight dryness. Daily wear of contact lenses, hot compresses, increased lid hygiene and artificial tears alleviated signs and symptoms of the meibomian gland dysfunction and CLPC. She was re-instructed on the standard protocol for the treatment of MGD.

An internally blocked meibomian gland was observed in the right eye of a 24-year old Chinese male from the BDW group (Figure 7.13). The blocked gland was easily observed through the slit-lamp and was located on the palpebral conjunctiva of the lower lid. This subject reported a sore, painful red eye. Hot compresses and mechanical expression together with incision of a sterile needle failed to unblock the gland. The subject came back a few days later reporting that a small solid mass had come out of his eye. Slit-lamp observation revealed a small hole in the palpebral conjunctiva together with an unblocked gland, suggesting that this solid piece of mass was somehow blocking the normal release of meibomian lipids from the gland.

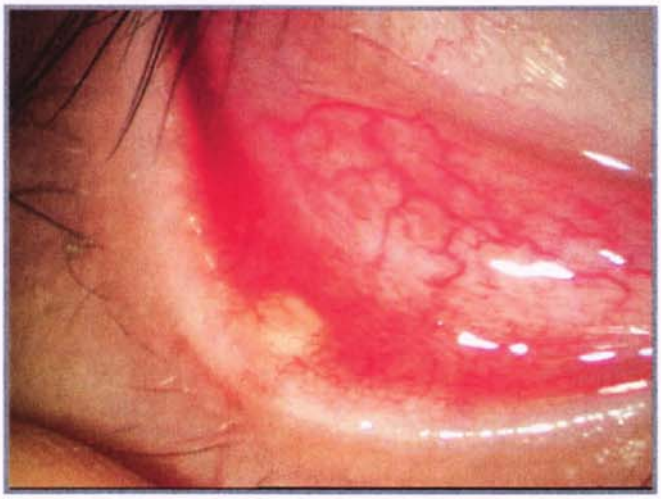


Figure 7.13. Internally blocked meibomian gland.

Scleral indentation

Four cases of scleal indentation in the bulbar conjunctiva by the lens edge were observed in 3 males and 1 female wearing their lenses in a CW basis (Figure 7.14 and 7.15). All subjects were asymptomatic and identations dissappared with discontinnuation of lens wear anytime between a few hours to 2 days.

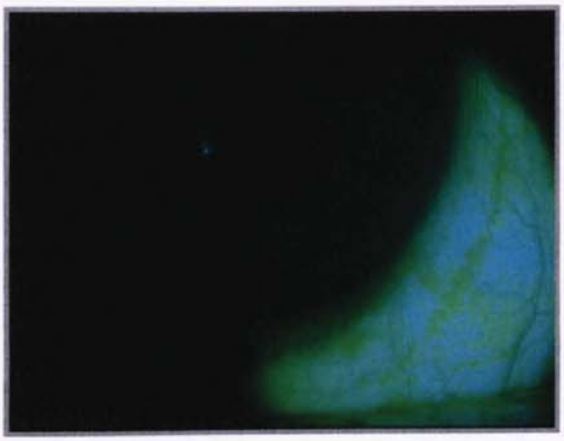


Figure 7.14. Scleral indentation associated with the use of Lotrafilcon A lenses in a continuous wear basis.

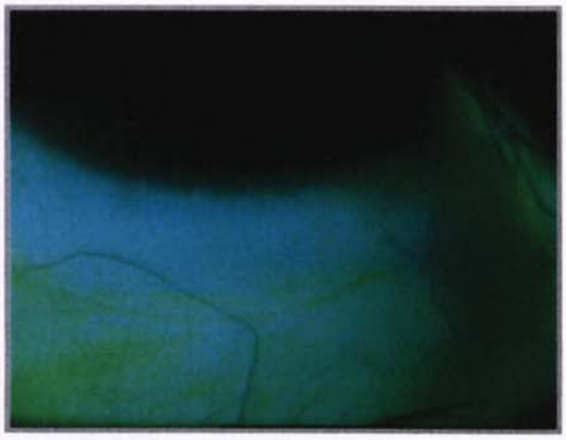


Figure 7.15. Scleral indentation associated with the use of Balafilcon A lenses in a continuous wear basis.

Other adverse events

An interesting drug-induced bilateral transient myopia with the use of sulphonamide sulfasalazine was found in a 22-year old female from the LDW group (Figure 7.16). This subject presented with a sudden bilateral onset of –1.0 DS of myopia (from -3.0 DS to -4.0 DS) following the addition of a sulphonamide (sulfasalazine) to her oral non-steroidal anti-inflammatory treatment (meloxicam) for rheumatoid arthritis. The myopia regressed to -3.50 DS after two weeks when all medication was withdrawn and stabilised at this level

when subsequent treatment was resumed after eight weeks with the non-steroidal anti-inflammatory drug celecoxib.

A full account of this work is given in the attached publication Santodomingo-Rubido *et al.* (2003).

7.4 Discussion

Although, clearly of clinical relevance and interest the present study was not specifically designed *per se* to examine the type and incidence of adverse events and complications that occur with SiH contact lens wear and therefore the number of subjects does not warrant prevalence and average onset figures. However, since a number of adverse events and complications were observed and recorded, they have been included in this thesis to further understand the ocular response to SiH contact lenses. None of the adverse events/complications caused any loss of best-corrected visual acuity or discontinuation of lens wear.

Contact lens peripheral ulcer

Contact lens peripheral ulcers are thought to be an inflammatory response which occurs as a result of corneal exposure to high numbers of Gram-positive bacteria, in particular *Staphylococus spp.* (Willcox *et al.*, 1995). These pathogenic bacteria colonize the lens surface and release toxins. It is thought that for a CLPU to occur, the contact lens may act as either: (1) a vector for the delivery of the antigen to the corneal surface or (2) a trap for antigen material against the cornea. Presumably, the antigen material releases chemical signals within the compromised epithelium, triggering the inflammatory response. A compromised epithelium could simply occur as a result of mechanical trauma from the contact lens. (It should be noted here that Chapter 4 shows a significant increase in corneal staining in all contact lens groups in the first 6 months of lens wear, hence leaving the cornea more prone to events of CLPU). Since the release of chemical signals is via the corneal periphery, the proximity of the limbus allows the delivery of antigens more efficiently than in the central cornea thus eliciting a rapid and effective immune response which consists of inflammatory cells homing to the site of the antigen and possibly preventing infection (Holden *et al.*, 2000).

Most subjects who experienced CLPUs in this study complained of mild pain, described as a foreign body or general discomfort. Excessive tearing and secretion and itching were also

commonly reported. The typical sign observed was a focal, circumscribed, dense, round, corneal infiltrate. The infiltrate typically exhibits a single peripheral or mid-peripheral white/grey lesion in the anterior stroma. The signs and symptoms reported match closely those previously reported (Holden *et al.*, 2000). It has been shown that the lesion represents and area of dense infiltration by polymorphonuclear leucocytes and stains in the early stages due to a full-thickness loss of epithelium (Holden *et al.*, 1999). Epithelium regeneration occurred over the lesion in all affected subjects within 1-3 days and no more staining was observed. However, a well-defined circular scar remained in all subjects for at least 6 months, which is in agreement with the findings Holden *et al.* (2000). Recurrences were observed in 1 out of 5 subjects which was consistent with the findings of Dumbleton *et al.* (2000) and Holden *et al.* (1999) who reported that approximately 10-25 % of the events show recurrent episodes. Third time reoccurrences were not observed. One subject was asymptomatic and scars were only detected at follow-up visits, suggesting that in some cases CLPU can be experienced with very mild symptoms and subjects might be unaware of the occurrence of the adverse event. It has been previously reported that up to 50% of CLPUs are not associated with symptoms and present simply as scars (Grant *et al.*, 1998; Dumbleton *et al.*, 2000). It is not surprising that several of the CLPU events were associated with MGD as it has been previously reported that subjects who exhibit MGD also harbour high levels of gram positive organisms (Dougherty and McCulley, 1984).

All adverse events of CLPU were found in subjects wearing Lotrafilcon A lenses, being much more common in the CW regime. Grant *et al.* (1998) also found that most CLPUs occurred with extended wear of contact lenses, with a few events in daily wear. Possible explanations for the occurrence of CLPUs in Lotrafilcon A wearers could only be attributed to the different material characteristics between SiH materials, that is with regard to the modulus or rigidity and surface treatment. The stiffer Lotrafilcon A lens (compared to Balafilcon A lenses) may induce more mechanical trauma to the corneal epithelium thus leaving the cornea more prone to adverse events. However, this was not shown to be the case (see Chapter 4). Whether the type, extent and depth of corneal stain were different between contact lenses was not investigated in this thesis. The different surface treatment of Lotrafilcon A lenses compared to Balafilcon A lenses might also allow greater colonization of bacteria (Lopez-Alemany *et al.*, 2002). Several studies have shown that bacterial colonization still occurs with Lotrafilcon A lenses in a similar way to that seen with conventional hydrogel lenses (Keay *et al.*, 2001; Willcox *et al.*, 2002). However,

whether Lotrafilcon lenses allow greater colonization than Balafilcon lenses still needs to be demonstrated.

The different lens design of the two SiH materials might also induce different lens movement and tear flushing. A reduction in lens movement and therefore tear flushing in Lotrafilcon compared to Balafilcon lenses could also explain the higher incidence of CLPC in subject wearing Lotrafilcon lenses. However, whether Lotrafilcon A lenses show less lens movement and therefore less tear flushing also needs still to be shown. A recent study by Morgan and Efron (2002) found no significant differences between the two SiH materials when worn in a CW basis in terms of horizontal and vertical centration, corneal coverage and lens movements. Finally, a large number of subjects in the LCW group were of Chinese origin and the performance of the contact lenses in these subjects might not be optimal compared to Caucasian eyes. The data found in this thesis show that the combination of contact lens wear of Lotrafilcon A lenses and eyelid closure during sleep affect significantly ocular defence mechanisms and thus leave the cornea more prone to CLPU events.

Contact lens papillary conjunctivitis

Contact lens associated papillary conjunctivitis is an inflammatory condition affecting the palpebral tarsal plates and is thought to be mechanical and/or inmmunologically mediated (Efron, 2000). However, it has been recently proposed that events of CLPC with SiH lenses are likely to be localized as a result of the mechanical effects induced by the contact lenses on the palpebral conjunctiva (Skotnitsky *et al.*, 2002). This finding is in agreement with the data from this study as all the events found, except one, were localized and likely to be mechanical in nature. The only general event found in this thesis could also be attributted to mechanical effects. The mechanical nature of the events could be attributted to the slightly stiffer nature of SiH materials compared to low Dk materials. Compromised lens surface wettabilities are also likely to play an important role in the development of CLPC. The fact that many of the CLPCs found in this thesis were seen at the nasal and temporal margins of the tarsal plate suggests that the mechanical effect induced by the lens edge on the palpebral conjucntiva may be an important precursor in the development of the events and provides further support for the theory that CLPC is mechanically rather than immunologically mediated. Additionally, the few symptoms, mild signs and rapid recovery reported by the subjects in this study also lends support to the fact that the events were mechanically induced. All signs and symptoms of CLPC found in the subjects of this study

were very similar to those previously reported (Holden *et al.*, 2000). The incidence of CLPC between materials was very similar and might be attributed to similar lens edge designs and wettabilities. Continuous wear of contact lenses produced more events than daily wear of lenses and this again could be attributed to larger wearing times. Additionally, subjects wearing lenses continuously showed more MGDs than those wearing lenses in a daily wear basis. These subjects are more likely to show higher deposition profiles and hence poorer lens wettabilities. It is envisaged that poor lens weattability is likely to result in a higher mechanical impact of the lens surface on the palpebral conjunctiva.

One subject in the control group consistently showed mild bilateral general papillary conjunctivitis throughout the whole study period from the initial visit and since she was asymptomatic, and clinical signs remained unchanged at follow-up visits, no intervention was carried out. A report by MacKinven and colleagues (2001) showed that, although rare, some non-contact lens wearers have significant redness and roughness of the palpebral conjunctiva.

Superior epithelial arcuate lesions

The exact nature for the development of SEAL is not well understood. It has been previously suggested that SEAL are thought to occur due to the inability of the stiff nature of SiH materials to conform the limbus thus causing mechanical pressure with poor lens wettability and tight eyelids. Certain corneal irregularities have also been implicated. Therefore, the aetiology of SEAL is likely to be multifactorial and affected by lens material, design and individual patient characteristics (Holden *et al.*, 2001).

The signs and symptoms of SEAL found in this study closely match those previously reported (Hoden *et al.*, 2000). It is not surprising that the two events found occurred in subjects wearing lenses continuously and this might be attributed to the longer wearing times and poor lens wettabilities. No significant differences in the incidence of SEAL were found between SiH materials and this is in agreement with the results of Morgan and Efron (2002). Since SEAL are typically asymptomatic, it is possible that more events occurred but resolved before the next study visit.

Meibomian gland dysfunction

It is not surprising that two cases of severe MGD reported in this thesis were associated with CLPU events. It has been previously reported that subjects with MGD present high

levels of gram-positive organisms which are likely to induce ocular inflammatory responses (Dougherty and McCulley, 1984). As a general rule, subjects who exhibit MGD should be considered as poor candidates for CW of SiH contact lenses and fitting of this modality of wear should only be carried out with detailed monitoring. Similar incidences of MGD were found with the two SiH materials under investigation in this thesis. However, MGD was more common with CW than with daily wear of contact lenses. The exact mechanism for the development of MGD is not known and may be attributed to mechanical effects. The constant rubbing of the contact lenses on the lid margins during the act of blinking is a source of mechanical irritation to the lid and may disrupt the normal characteristics of the meibomian glands. The effect is likely to be more pronounced with CW of contact lenses due to longer wearing times. It is not surprising that MGD was also found in non-contact lens wearing control subjects However, the signs observed were not as severe as those seen in contact lens wearers. No severe blockage of the meibomian glands was found in any of the subjects from the control group. Ong and Larke (1990) found that 30% of contact lens wearers develop some degree of meibomian gland dysfunction after 6 months of lens wear whereas only 20 % of non-lens wearers have a similar problem. However, they failed to detect any significant differences in the composition of the fluid secreted by the blocked glands compared to normal unblocked glands. The Biomaterial Research Unit at Aston University is currently analysing differences in MGD composition between materials, regimes of wear as well as between non-lens wearers and contact lens wearers. All complications were successfully managed with standard treatment including hot compresses, lid scrubs, mechanical expression, increased lid hygiene and artificial tears.

Scleral indentation

Four cases of scleal indentation on the bulbar conjunctiva by the lens edge were observed. A detailed search through the literature did not revealed any reports of this complication, which might be due to the relatively inocuous nature of this complication, as indentations dissappeared on ceasing lens wear anytime between a few hours to 1-2 days and were asymptomatic in all cases. Scleral indentations might be attributted to longer wearing times, poor lens wettability and lens edge design. The higher incidence in Lotrafilcon wearers compared to Balafilcon wearers is likely to be due to Lotrafilcon's higher modulus of rigidity.

Other adverse events

Although ocular adverse reactions to sulphonamides have included uveitis and Stevens-Johnson syndrome, most previous studies have reported bilateral reduced visual acuity and a subjective increase in myopia (Chirls and Norris, 1984; Hook *et al.*, 1986). Whereas, the exact mechanism underlying the myopic shift found with sulphonamide was not clear, it was conjectured that the refractive changes induced by sulfasalazine were associated with posterior central corneal oedema as there was no detectable keratometric and objective refraction changes. Additionally, a number of features indicate that the myopic shift is genuinely associated with the addition of a sulphonamide to the medication regimen: the increase in myopia was too rapid to be caused by structural change; the onset and regression of myopia was coincident with changes in medication; if a normal increase in axial length (invariably the structural correlate of myopia) was the cause of the myopic shift then this should have been evident from *IOLMaster* measures as its resolution is equivalent to 0.03 D change in refractive error (Santodomingo-Rubido *et al.*, 2002).

Several adverse events and complications have been reported in this thesis. Problems of hypoxia have been virtually eliminated with the wear SiH materials. However, high rates of mechanically induced effects has been observed. Mechanical events are likely to occur as a result of the stiffer nature of SiH materials compared to conventional hydrogel lenses. Poor lens wettabilitties are also likely to be implicated. Inflammatory events were also found in this study and they are likely to occur as a result of bacteria which have either been trapped between the cornea and contact lens or bound to the contact lens surface. With a compromised epithelium, filtration of toxins released by bacteria could trigger the inflammatory response. Other complications such as scleral indentations and increased MGD with SiH have not been previously reported and are also likely to be mechanically mediated. Events and complications were more commonly found with continuous wear of contact lenses, especially with Lotrafilcon A lenses. Close monitoring of CW of SiH contact lenses is a prerequisite for convenient and safe wear.

New generations of SiH contact lenses should overcome problems related to the stiffer material, lens wettability and flushing mechanisms found in current materials. The results of this thesis will help contact lens practitioners and manufacturers to further understand the impact of SiH lenses on ocular health and thus develop better and safer contact lenses.

Summary of findings

1	Mechanically induced events, such as contact lens papillary conjunctivitis and superior epithelial arcuate lesions were found and are likely to occur as a result of the slightly stiffer nature of SiH materials compared to conventional hydrogel lenses together with poor lens wettability.
2	Inflammatory conditions such as contact lens peripheral ulcers were also found possibly as a result of bacteria infiltration through a compromised epithelium.
3	Other complications such as scleral indentation and increased meibomian gland dysfunction with SiH have not been previously reported and may be related to mechanical moulding.
4	A case of drug-induced bilateral transient myopia with the sulphonamide sulfasalazine was also identified.
5	Events and complications were more commonly found with continuous wear of contact lenses, especially with Lotrafilcon A lenses.

CHAPTER 8

CONCLUSIONS AND PROPOSALS FOR FUTURE WORK

8.1 Summary of conclusions from the present studies

Refraction and biometry

Myopia increased significantly in subjects wearing Lotrafilcon A lenses on a daily wear basis. The increase was accompanied by a correlated increase in axial length. However, no significant relationships were found between change in refractive error and near work and axial length/corneal curvature ratios. Possible reasons for the increase in myopia include a directly induced physical/physiological contact lens effect, a higher rate of progression for the lower level of myopia evident in the group, and finally the interesting postulate that compromised immunology due to contact lens wear may trigger ocular growth in the posterior segment. There is also the possibility that contact lenses may induce more myopia by virtue of generating a different peripheral image shell compared to spectacles.

Keratometric analysis revealed a small but not statistically significant degree of central corneal flattening of both meridians (flatter and steeper) in the Lotrafilcon A groups and this could be attributed to the higher modulus of rigidity of Lotrafilcon A compared to Balafilcon A materials. The other biometric measures showed very little change.

Ocular physiology

An increase in bulbar, limbal and palpebral hyperaemia was observed in most of the contact lens groups and could be attributed to the mechanical effect induced by the contact lenses. An increase in corneal staining was also observed in all contact lens groups and could be attributed to the mechanical effect induced by the contact lenses and to epithelial microtrauma induced by mucin balls. A significant positive correlation was found between subjective and objective measures of bulbar hyperaemia. A poor correlation was found between subjective and objective measures of palpebral hyperaemia.

Tear film characteristics

Clinical measures of the tear film characteristics showed little difference between materials and regimes of wear, whereas biochemical results appear to be more sensitive in detecting subtle changes in tear film composition. An increase in the positive incidence of certain protein specific markers such as kininogen and IgE was found with contact lens wear and in certain adverse events. Lipid deposition profiles were higher with Balafilcon A lenses

and could be attributed to the higher hydrophobicity of the lens surface compared to Lotrafilcon A lenses.

Symptomatology

Dryness was the most commonly reported symptom. However, the mild symptoms and high subjective acceptance judgements reported by all contact lens groups suggest that overall the clinical performance of SiH lenses is very high.

Adverse events and complications

Mechanically induced effects, such as contact lens papillary conjunctivitis and superior epithelial arcuate lesions were found. Mechanical events are likely to occur as a result of the slightly stiffer nature of SiH materials compared to conventional hydrogel lenses. Poor lens wettability is also likely to be implicated. Inflammatory conditions such as contact lens peripheral ulcers were also found and they are likely to occur as a result of bacteria infiltration through a compromised epithelium. Other complications such as scleral indentations and increased MGD with SiH have not been previously reported and are also likely to be due to mechanical moulding. A case of drug-induced bilateral transient myopia with the sulphonamide sulfasalazine was also found. Events and complications were more commonly found with continuous wear of contact lenses, especially with Lotrafilcon A lenses.

8.2 Critical analysis of experimental work and suggestions for improvement

Refraction and biometry

The small sample of subjects used in each group limited the robustness of statistical analysis and may account in part for the poor correlation between change in refractive error and near work and axial length/corneal curvature ratios. Differences in the level of myopia, ethnicity and gender between the different groups could also be responsible for differences in the progression of myopia between groups. Ideally, matched groups for number of subjects, level of myopia, ethnicity and gender would have given the study more statistical power but this was not possible given the constraints of clinical selection.

Ocular physiology

For practical reasons, measurements across the study visits were not taken at the same time of the day as subjects were not always willing to attend at the same time to the scheduled visits. Additionally, the inhomogenity of samples mentioned above, might account for the variability in the vascular response found. Guillon and Shah (1996) using an objective method of measuring conjunctival redness found that for not contact lens wearers, redness in the evening was similar to that upon waking, and greater than redness 2 hrs post waking. In contrast, in daily soft contact lens wearers, redness was maximal in the evening and greater than before insertion or during wear in the morning. In extended soft contact lens wearers, redness was maximal upon waking. Measurement of bulbar and palpebral hyperaemia was objectively quantified by means of an objective image analysis. The objective image analysis employed in this study has been found to be up to 7 times more repeteable than subjective grading (Wolffsohn and Purslow, 2003). Effective application of this objective technique to the measurement of limbal hyperaemia and corneal staining is promising and is likely to provide a better insight of the effect of SiH contact lenses on ocular physiology.

Tear film characteristics

Consistent with the results of Perrigin *et al.* (2000) the measurements of tear film lipid layer patterns found in this thesis were very variable. Jones *et al.* (2000) found more stable results when grading previously recorded video observations of bulbar and limbal hyperaemia with reference to direct observation and recording. Analysis of digital photographs of the tear film lipid layer interference patterns might provide a more accurate and repeatable means of assessment.

Only a relatively small proportion of the large number of biochemical analyses of the tear samples and contact lenses were completed by the time of the thesis submission date. Although the data available have provided several interesting insights into the ocular changes observed with SiH contact lens wear, future analysis of the complete data set will consolidate our understanding of the biochemical bases of continuous wear.

Symptomatology

Subjective responses to contact lens wear can be very variable and difficult to assess (Nichols *et al.*, 1999). The questionnaire used in this thesis was based on those used in previous studies on silicone hydrogel contact lenses (e.g. Iruzubieta *et al.*, 2001; Nilsson, 2001). Since the questionnaire did not have the same design than those previously used, direct comparisons with other studies should be interpreted with caution. Additionally, since the questionnaires were not completed by the subjects at the same time of the day, this could affect the outcome of the results found. A more popular subjective questionnaire, such as the McMonnies' questionnaire (McMonnies, 1986) would allow comparison of the symptoms reported in this study with those studies which have previously used this popular test.

Adverse events and complications

Although clearly of clinical relevance and interest, this thesis was not specifically designed *per se* to examine the type and incidence of adverse events and complications which occur with SiH contact lens wear. Furthermore, the sample sizes used do not permit reliable estimates of prevalence and average onset figures. A useful template for further work in this area would be the study by Sankaridurg and co-workers (1999).

8.3 Proposals for future work

Refraction and biometry

A study with a larger sample of subjects and with all groups matched for number of subjects, level of myopia, ethnicity and gender would provide a better insight into the refractive and biometric effects induced by SiH contact lenses. Since some of the effects induced by contact lens wear in refraction and biometry may be temporary, it would be interesting to monitor a group of subjects for a period of time without contact lens wear to show whether changes are temporary or permanent. It would be also of value to assess whether contact lenses might induce more myopia by virtue of generating a different peripheral image shell compared to spectacles.

Ocular physiology

The objective image analyses used in this thesis could be applied to a wider range of ocular physiology parameters. For example, it would be interesting to use the method of analysis to assess changes in other ocular physiology parameters, such as limbal hyperaemia and corneal staining. Since there is likely to be diurnal variations in ocular physiology, measurements should be carried out at the same time of the day. The search for a standard, objective and accurate means of assessing ocular physiology is clearly of value for clinical and research purposes.

Tear film characteristics

The results of this thesis have shown that biochemical analysis of tear film components can be used as a potential tool for further understanding the effect of SiH contact lenses on ocular physiology. Similar findings with conventional hydrogel lenses have been reported by Michaud and Giasson (2002). Additionally, biochemical analyses of tear film components might be able to estimate whether an individual is likely to be a successful candidate for contact lens wear and prevent unwanted adverse events and complications. Research in how to apply biochemical tests to clinical practice and to relate the results to clinical findings still need to be addressed.

Symptomatology

Research needs to be carried out to compare different subjective questionnaires in order to find the most accurate and repeatable one allowing standardization of results and therefore comparison between studies.

Adverse events and complications

To date, no large studies have been carried out to assess the type and incidence of the adverse events and complications which can occur with SiH contact lenses. A well-designed study to examine accurately the type and incidence of adverse events and complications will be very valuable for clinicians involved in SiH contact lens fitting. Additionally, from the data analysed in this thesis, it is concluded that most of the adverse events and complications found were induced by the rigidity and inadequate lens wettability and movement of SiH materials. Research aimed at developing a new generation of softer, more wettable and mobile SiH lenses will facilitate the ultimate clinical objective of producing a biocompatible contact lens which is free of ocular adverse events and complications.

Concluding statement

This thesis has addressed a number of clinical issues with regard to the effects of SiH contact lenses on ocular physiology and function. Evidence has been presented to show that different effects than those found with conventional hydrogel materials are likely to occur with SiH contact lens wear. The findings reported in this thesis will enable contact lens practitioners and manufacturers to understand further the optical, physiological and biochemical nature of the ocular response to SiH contact lenses and hence facilitate the development of this important generation of contact lens material.

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APPENDIX 1

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria-Patient must:

- Be 18-25 years of age and have full legal capacity to volunteer
- Have read, understood, and be willing to sign a Statement of Informed consent
- Be free of any anterior segment disorders which, in investigator's opinion, contraindicate contact lens wear
- New contact lens wearer
- Normal binocular vision
- A low to moderate level of refractive error (± 3.00 D) and astigmatism (< 0.75 D), requiring correction and be correctable through spherical refraction to 6/9 or better in each eye
- Have a reasonable expectation of improvement in visual acuity with the study lenses
- No previous ocular health complications including dry eye and highly atopic individuals
- Be willing and able to follow patient instructions and meet the protocol-specified schedule of follow-up visits
- Agree to wear the study lenses on any of the wear schedules (daily wear vs. continuous wear)

Exclusion criteria.

- Corneal infiltrates
- Systemic disease affecting ocular health, e.g., exophthalmos/ lagophthalmos, blepharitis, meibomitis, diabetes, allergies, hay fever, dry eyes
- Use of any systemic or topical medications that will affect ocular physiology or the performance of the contact lenses
- Active ocular disease
- Any lid or anterior segment abnormalities which, in the investigator's opinion, contraindicate contact lens wear
- Any "graded" finding (epithelial edema, epithelial mycrocysts, corneal staining, limbal injection, bulbar injection, tarsal conjunctival abnormalities, corneal neovascularisation or corneal infiltrates) based on *Efron grading scales for contact lens complications* with the exception of grade 1 limbal injection, grade 1 bulbar injection, grade 1 corneal staining, grade 1 tarsal conjunctival abnormalities.
- Any "present" corneal striae, conjunctivitis, or other anterior segment finding that in the Investigator's judgment, may interfere with successful contact lens wear.
- Any "adverse effect" finding listed (corneal ulcer, anterior uveitis, other ocular infections and inflammations, corneal scarring, or permanent loss of vision)
- Refractive astigmatism greater than 0.75 D
- Myopes and hyperopes with a mean sphere greater than 3.00 D
- One eye corrected for near and the other eye corrected for distance vision (monovision not allowed)
- Wearing of contact lenses within the last 6 months
- Prism required horizontally or >3 vertically
- Patient is aphakic
- Patient is amblyopic
- Patient has had corneal refractive surgery
- Pregnancy

APPENDIX 2

HUMAN SCIENCE ETHICAL COMMITTEE

The following shows a duplicate of the forms submitted to the Human Sciences Ethical Committee, Aston University, for the approval of the research project carried out in order to produce this thesis on human volunteers.

ASTON UNIVERSITY **PROJECT NO.....**

THE SENATE REG/88/273

HUMAN SCIENCE ETHICAL COMMITTEE

Application for approval of a research project involving human volunteers

Please read the enclosed guidelines before completing this form - in typescript or black ink - and return the form to: The Secretary of the Human Science Ethical Committee, Registry. If you intend to administer any substance or expose the subjects to a physical procedure other than simple venepuncture **you must also submit an experimental protocol.**

Project title:

Investigator(s):	**Department/address:**	**Telephone:**
Prof. B. Gilmartin	**Optometry, Life and Health Sciences**	**X 5159**
Dr. J. Wolffsohn	**Optometry, Life and Health Sciences**	**X 5160**
Mr J. Santodomingo	**Optometry, Life and Health Sciences**	**X 5159**
.....	.....	
.....	.....	

A
Details of sponsoring/collaborating organisation (if any)

1. Name: **The Neuroscience Research Institute**

2. Does the sponsoring/collaborating organisation provide insurance? **NO**

3. If drugs are used, do any require a clinical trials certificate or clinical trials exemption certificate? **NO**

B
Summary of Project

1 Starting date: **September 2001.**

2 Duration: **2 years.**

3 Location: **Optometry, Life and Health Sciences, Aston University.**

4 Physical procedures:

Fitting different types of commercially available contact lenses
Measurement of different ocular parameters with commercially available devices:

1. **Refractive error using standard auto-refractor (*Shin-Nippon Co*)**
2. **Axial length using a non-contact partial coherence interferometer (*IOL Master, Zeiss*)**
3. **Corneal topography using the non-contact *EyeSys* instrument (*Texas Instruments*)**
4. **Tear film parameters using a non-contact instrument (*Tearscope plus, Keeler*).**

5 Substances to be administered:*

1. Fluorescein sodium administered via commercially available sterile single use applicators (*Fluorets, Chauvin Pharmaceuticals Ltd*). Fluorescein is an indicator diagnostic dye commonly used in general optometric practice, which allows checking of rigid lens fitting and stained damaged corneal or conjunctival tissue. Fluorescein is normally entirely washed out of the eye within one hour.

2. Commercially available contact lens care solutions (i.e., Sensitive Eye Plus Saline from Bausch and Lomb; Optifree express saline from Alcon)

*A substance is anything other than normal food. Chemical constituents of food stuffs, ethanol and variation of the diet should be included here.

6 Psychological assessment:

N/A.

C
Subjects

1 Number of subjects to be used: **150.**

2 Over what time span? **2 years.**

3 Age of subjects: **18-25 years.**

4 Sex of subjects: **Mixed.**

5 Source: **Neuroscience Research Institute undergraduate (N~= 130) and postgraduate students (N~= 20).**

6 Will payments be made to the subjects and if so, how much will each be paid? **No.**

7 Are the subjects patients or healthy volunteers? (If patients, give diagnosis, clinic/responsible practitioner). **All subjects are healthy volunteers.**

8 Will any subjects be excluded and if so, on what grounds?

Due to the nature of the study the following subjects will be excluded, as they are unlikely to have good quality of vision:

1. **Subjects with strabismus**
2. **Subjects with corneal astigmatism greater than 0.75 D**
3. **Myopes with a mean sphere greater than 3.00 D**

Additionally, previous contact lens wearers, or subjects with previous allergies or intolerances to contact lens wear and/ or contact lens solutions will be excluded. Previous contact lens wearers will be excluded because contact lens wear is likely to have produced some degree of ocular change.

9 Is the activity of the subject to be restricted in any way before or after the procedure? (eg diet, driving) **No. None of the procedures proposed normally affect visual function.**

10 Consent: Please attach a copy of the consent form you intend to use, detailing how procedures and hazards will be explained. **Attached.**

D

Hazards

1. Please give full details of any hazards which could affect the health, safety or welfare of any subject.

1. Adverse reaction to contact lenses or contact lens solutions. However, the type of reaction and management procedures are well documented in the clinical literature.

2. Ocular infection or adverse reaction as a result of poor hygiene.

3. Although previous extended wear lens designs were likely to produce corneal swelling due to the hypoxia produced as a result of poor oxygen transmissibility, (particularly when contact lenses were worn during sleep), new extended wear materials and lens designs have much higher oxygen transmissibility, and hence reducing the risk significantly. The risks are considered to be less than conventional daily soft lens wear (Efron, 1999).

2. How do you propose to minimise these hazards?

1. Subjects with a previous history of reaction to contact lenses or contact lens solution, or those who appear unlikely to comply with hygiene protocols will be excluded from the study. If an adverse reaction occurs, the patient's condition will be closely monitored until visual acuity returns to normal levels and the reaction has ceased.

2. Use commercially-available single-use disposable soft contact lenses to eliminate the risk of cross-infection (i.e., *Acuvue* from *Vistakon, Johnson and Johnson*; *Soflens* from *Bausch and Lomb*; *Focus dailies* from *Ciba Vision*; *PureVision* from *Bausch and Lomb*; *Focus night and day* from *Ciba Vision*).

3. Subjects showing adverse reactions as a result of contact lens wear will be required to discontinue contact lens wear, and they will be monitored closely until the reaction has ceased.

4. Corneal integrity will be checked at the end of each experiment by slit lamp examination in conjunction with the use of fluorescein as an indicator dye. Visual acuity will be checked with a standard Snellen chart.

3. Is there any precedent for these experiments? If so, please give details with references if possible.

Inaba, M. (2000). 1-Day Acuvue vs. Focus Dailies: a comparison of comfort, user preference, and incidence of corneal complications. *CLOA J.* 26 (3), 141-145.

Dumbleton, K.A., Chalmers, R.L., Richter, D.B., Fonn, D. (1999). Changes in myopic refractive error with nine months' extended wear of hydrogel lenses with high and low oxygen permeability. *Optom. Vis. Sci.* 76, 845-849.

Efron, N. and Brennan, N.A. (1999). Will increased oxygen really decrease extended wear infections? *Optom. Vis. Sci.* 76, 435-436.

Horner, D.G., Soni, P.S., Salmon, T.O. and Swartz, T.S. (1999). Myopia progression in adolescent wearers of soft contact lenses and spectacles. *Optom. Vis. Sci.* 76, 474-479.

Guillon, M., Styles, E., Guillon, J.P. and Maïssa, C. (1997). Preocular tear film characteristics of nonwearers and soft contact lens wearers. *Optom. Vis. Sci.* 74, 273-279.

Horner, D.G., Soni, P.S., Salmon, T.O. and Schroeder, T.L. (1996). Junior high age children's myopia progression in soft contact lenses vs. spectacles. *Invest. Ophthalmol. Vis. Sci.* 37, 4610.

NOTE: Three similar projects (Ref. 99N, ref. 87 xi, ref. 87 viii) have been approved by the Aston University Human Science Ethical Committee. They were successfully completed or are ongoing without adverse consequences, and used similar procedures that will be used in this study.

4. Has this project been considered/ is it being considered by any other Ethical Committee? If so, please give details and decision made. **No**

E

STATEMENT BY NAMED INVESTIGATORS, HEAD OF DEPARTMENT AND (if necessary) RESEARCH SUPERVISOR

I consider that the details given constitute a true summary of the project and that the hazards and potential risks to any subject are accurately described.

Investigator.....
date.....

Investigator.....
date.....

Investigator.....
date.....

Investigator.....
date.....

Investigator.....
date.....

Head of Department.....
date.....

Supervisor.....
date.....

The following should be attached:

- subject consent form
- insurance certificate (if available)
- clinical trials certificate or clinical trials exemption certificate (if appropriate)
- experimental protocol

FOR OFFICE USE ONLY

Date form received:
Assessors: (1) (2) (3)

Were any changes to the project agreed? YES/NO If yes, details are attached.

Date project approved by Chairman:

Date project approved by Committee:

Date project finished:

APPENDIX 3

INFORMATION AND CONSENT FORMS FOR EXPERIMENTAL PARTICIPANTS

Following are information and consent forms for subjects participating in experiments where invasive procedures were employed.

EXPLANATION AND CONSENT FORM FOR VOLUNTEER SUBJECTS

DESCRIPTION OF PROJECT

TITLE: The effect of contact lenses on anterior segment physiology and function

RESEARCH WORKERS AND SCHOOL RESPONSIBLE:

Supervisor: Professor B. Gilmartin, B.Sc. (Hons.), Ph.D., FCOptom., FAAO;
Associate supervisor: Dr. J. Wolffsohn, B.Sc. (Hons.), Ph.D., PGDipAdvClinOptom., MCOptom., FAAO;
Postgraduate: Mr. J. Santodomingo, D.O.O., M.Sc., MCOptom.;
Neurosciences Research Institute, School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham. B4 7ET.

EXPLANATION OF PROCEDURES:

This study will examine the effects of different commercially available soft contact lenses on the eye over a two-year period. If interested in participating the study, you will be assessed prior to any experiment to ascertain whether you satisfy the following criteria:

- New contact lens wearer
- Normal binocular vision
- A low to moderate level of refractive error and astigmatism
- No previous ocular health complications including dry eye and highly atopic individuals
- 18-25 years old

If you agree to take part in the study you will be fitted with contact lenses which will either be worn for a day and disposed, with a new lens for each day or worn for 30 days continuous wear without removal with a new lens every month. The wearing schedule will be allocated randomly. Subjects will get free lenses and solutions to take part in the study for a 2 year period. A further group of people will be invited to take part in the study, but will wear their usual spectacle correction.

Measurements of ocular parameters, taking approximately one hour, will include:

- Refractive error using the Shin-Nippon SRW-5000 autorefractor
- Axial length and anterior chamber depth using the Zeiss *IOLMaster*
- Corneal topography using the EyeSys system
- Corneal thickness profile using image analysis techniques
- Slit lamp grading of anterior eye health
- Subjective questionnaire
- Clinical measures of the tear film such as keratometry mires, slit lamp specular reflection, tear prism and the Tearscope.

All measurements taken do not come in contact with the eyes and do not involve the use of eye drops. For students who are not aware of any of these procedures, a further explanation will be carried out by the researchers and on their lectures.
Measurements will be performed:

- Before the beginning of lens wear
- After one week
- After one month
- After three months
- After six months
- After twelve months
- After twenty four months

Hazards which may affect the health, safety or welfare of any subject include adverse reactions to contact lenses and solutions, ocular infection or adverse reaction as a result of poor hygiene and corneal swelling due to poor oxygen transmissibility. In order to minimise these hazards, subjects with a previous history of reaction to contact lenses or contact lens solutions, or those who appear unlikely to comply with hygiene protocols will be excluded from the study. If an adverse reaction occurs, the patient's condition will be closely monitored until visual acuity returns to normal levels and the reaction has ceased. The use commercially-available single-use disposable soft contact lenses will eliminate the risk of cross-infection. Subjects showing adverse reactions as a result of contact lens wear will be required to discontinue contact lens wear, and they will be monitored closely until the reaction has ceased. Corneal integrity will be checked at the end of each experiment by slit lamp examination in conjunction with the use of fluorescein as an indicator dye. Visual acuity will be checked with a standard Snellen chart.

All the data collected and your identity will remain confidential.

STATEMENT OF VOLUNTEER

I have read and understood the above explanation. I have had the opportunity to discuss it with the investigators and to ask any questions and I understand that I am free to withdraw at any time. I understand that partaking in this experiment is not a requirement of my undergraduate or postgraduate course and that no sanctions will be taken against me if I refuse to participate or withdraw from the project. Consent to participate does not compromise my rights in law. I agree to take part in the above project.

Name of volunteer:.....

Signed:.....

Date:.....

APPENDIX 4

LONGITUDINAL DATA

A4.1 Longitudinal refractive and biometric data relating to Chapter 3.

Refraction (mean spherical equivalent) (D)

GROUP	1M	3M	6M	12M	18M
LDW	-0.32	-0.38	-0.44	-0.27	-0.47
LDW	-0.44	-0.7	-0.78	-0.39	-0.29
LDW	-0.13	0.14	-0.18	-0.04	-0.12
LDW	-0.26	-0.51	-0.63	-0.94	-1.22
LDW	0.07	0.41	0.24	0.42	-0.26
LDW	-0.5	-0.48	-0.93	-0.48	-1.28
LDW	-0.07	-0.55	-0.72	-0.3	-0.41
LDW	-0.07	0.07	0.04	-0.2	-0.22
LDW	-0.42	-0.27	-0.52	-0.41	-0.33
LDW	-0.04	0.29	-0.15	-0.21	-0.38
LCW	0	-0.27	0.19	-0.1	0.11
LCW	0.19	-0.16	-0.58	-0.8	-0.98
LCW	0.31	-0.03	0.08	-0.03	-0.49
LCW	-0.13	-0.28	-0.1	-0.02	0.14
LCW	0.19	0.14	-0.32	-0.09	-0.55
LCW	1.81	-0.39	0.21	-0.42	-0.48
LCW	0.01	-0.59	-0.28	0.16	-0.22
LCW	0.38	0.17	-0.08	0.29	0.36
LCW	0.13	-0.14	0.63	-0.41	0.36
LCW	-0.1	-0.2	0.19	0.33	-0.04
LCW	-0.33	-0.08	-0.23	-0.24	-0.52
BDW	0.13	0.07	-0.25	0.24	-0.15
BDW	-0.23	0.01	-0.34	-0.33	-0.22
BDW	-0.25	-0.23	-1.48	-0.41	-0.7
BDW	0.21	0.41	-0.2	0.3	0.48
BDW	-0.26	-0.12	-0.23	0	-0.47
BDW	0	0.36	0	-0.01	0.06
BDW	0.01	0.01	-0.42	-0.26	0.47
BDW	0.18	0.14	0.37	-0.44	-0.32
BCW	-0.13	-0.4	-0.35	-0.39	-0.47
BCW	-0.22	-0.5	-0.4	0.22	-0.22
BCW	0.25	-0.03	0.04	-0.1	0.14
BCW	-0.07	0.26	-0.13	0.07	0.21
BCW	0.35	0.04	0.1	-0.2	-0.05
BCW	-0.91	-0.53	-0.51	0.01	0.14
BCW	-0.41	-0.45	-0.57	-0.72	-1
BCW	0.06	0.12	-0.1	-0.08	0.14
BCW	0.22	-0.07	-0.56	0.07	-0.18
BCW	0.07	-0.26	-0.54	-0.12	-0.42
BCW	-0.21	-0.04	-0.29	-0.09	-0.26
BCW	-0.13	0.24	0.18	0.12	-0.2
BCW	-0.05	-0.13	-0.04	-0.4	-0.53
BCW	0.01	0.02	-0.04	-0.11	-0.04
CON	-0.63	-0.24	-0.17	-0.15	-0.47
CON	0.02	0.04	-0.22	0.27	0.27
CON	0.75	0.6	0.42	0.9	0.35
CON	0.16	-0.11	0.1	-0.02	-0.35
CON	-0.01	-0.47	0.17	0.07	0.15
CON	0.39	0.08	-0.25	-0.18	-0.21
CON	-0.69	-0.33	-0.97	-0.16	-0.66
CON	0.1	0.04	-0.26	-0.25	0.04
CON	0.04	0.22	-0.06	0.04	0.03
CON	0.07	0.13	-0.01	-0.23	-0.44
CON	0.36	0.13	0.16	0.29	1.02
CON	0.23	0.34	0.38	0.46	0.7
CON	-0.09	-0.36	-0.16	-0.08	-0.23
CON	-0.55	-0.41	-0.54	-0.72	-0.14

Abbreviations	
M	Month
LDW	Lotrafilcon daily wear
LCW	Lotrafilcon continuous wear
BDW	Balafilcon daily wear
BCW	Balafilcon continuous wear
CON	Control
N	None
M	Meshwork
W	Wave
A	Amorphous
C	Colours
AB	Abnormal
WK	Week

Table A4.1.1. Longitudinal refractive error data.

Axial length (mm)

GROUP	1M	3M	6M	12M	18M
LDW	0.06	0.09	0.14	0.09	0.15
LDW	0.01	0.01	-0.01	-0.03	0.03
LDW	0.03	0.04	0.06	0.06	0.07
LDW	3.33E-03	0.16	0.21	0.17	0.31
LDW	-0.03	0.03	-0.05	-0.01	0.2
LDW	0.06	0.06	0.02	0.07	0.14
LDW	0.05	0.12	0.2	0.05	0.2
LDW	0.01	0.02	0.03	3.33E-03	0.02
LDW	0.02	0.06	0.08	0.12	0.18
LDW	0.03	0.03	0.1	0.12	0.13
LCW	-3.33E-03	-0.01	-3.33E-03	0.13	0.07
LCW	0.02	0.07	0.12	0.19	0.3
LCW	0.03	0.07	-0.02	0.03	0.07
LCW	3.33E-03	0.05	0.03	0.04	0.06
LCW	-0.01	-0.01	-0.05	-3.33E-03	-0.03
LCW	0.02	0.01	-0.02	0.02	0.03
LCW	0.07	0.05	0.12	3.33E-03	0.03
LCW	3.33E-03	3.33E-03	-0.08	-0.08	-0.04
LCW	0.02	0	0.01	0.02	0.03
LCW	0.02	0.05	0.01	0.02	0.08
LCW	0.06	0.01	0.06	0.08	0.06
BDW	-0.02	0.02	0.02	0.02	-3.33E-03
BDW	-0.04	-0.03	3.33E-03	0.01	0.02
BDW	-3.33E-03	-3.33E-03	0.03	0.05	0.09
BDW	0.05	0.04	-0.01	0.05	0
BDW	0.03	-0.03	-0.01	0.02	0.07
BDW	0.02	-0.01	0.02	0.05	0.05
BDW	0.02	0.03	0.06	0.06	0.15
BDW	0.02	0.05	0.14	0.15	0.17
BCW	0.01	0.03	0.05	0.06	0.14
BCW	0.02	0.01	0.07	0.1	0.17
BCW	0.01	0.01	0.03	3.33E-03	0.06
BCW	-0.02	-0.05	-0.11	-0.17	-0.02
BCW	-0.06	3.33E-03	0.02	0.01	0.06
BCW	-0.02	-0.11	0.01	0.11	0.04
BCW	-0.02	-0.03	0.03	0.17	0.31
BCW	-0.01	-0.02	-0.01	-0.07	-3.33E-03
BCW	0	0.04	0.02	0.05	0.05
BCW	0.02	0.04	0.1	0.12	0.04
BCW	3.33E-03	0.02	0.01	0.03	0.04
BCW	0.05	0.02	-0.01	0.05	0.08
BCW	0.01	-0.05	0.03	0.08	0.08
BCW	0.01	0.01	0.05	-0.01	-0.02
CON	-0.01	-0.03	-0.01	-0.03	-0.02
CON	0.07	0.13	-0.01	0.02	-0.02
CON	0.02	0.01	0.04	3.33E-03	0.05
CON	0.01	-0.04	-0.05	-0.01	-0.06
CON	0.03	0.1	0.11	0.2	0.35
CON	0.02	0.01	0.1	0.08	0.09
CON	0	-3.33E-03	0.04	0.01	0.12
CON	-0.02	-0.12	3.33E-03	0.04	0.11
CON	0.04	0.03	0.07	0.04	0.05
CON	0.06	0.03	0.03	0.06	0.21
CON	0.01	0.04	0.01	-0.01	0.04
CON	0.01	0.02	0.05	0.05	0.06
CON	-0.05	-0.06	0.08	0.07	0.13
CON	0.05	0.09	0.07	0.11	0.1

Table A4.1.2. Longitudinal axial length data.

Anterior chamber depth (mm)

GROUP	1M	3M	6M	12M	18M
LDW	4.00E-03	-0.05	-0.05	-2.00E-03	-0.01
LDW	-0.09	0.03	-0.03	-0.04	-0.06
LDW	0.04	0.09	0.04	0.01	0.06
LDW	0.01	-0.02	-0.02	-0.01	-0.02
LDW	0.38	0.3	0.22	0.3	0.33
LDW	0.16	0.01	0.1	-0.01	0.11
LDW	-0.03	-0.02	-0.04	-0.02	-0.05
LDW	-0.18	-0.13	-0.11	-0.14	-0.13
LDW	-0.05	-0.07	-0.08	-0.02	-0.03
LDW	-0.08	0.05	-4.00E-03	-0.01	-0.05
LCW	0.05	0.09	0	-0.02	0.04
LCW	0	-0.02	-0.02	-0.03	-0.04
LCW	-0.04	0.05	0.06	0.12	0.01
LCW	-0.01	-0.03	-0.04	-0.03	0.04
LCW	0.01	-0.02	-0.02	-0.04	-0.06
LCW	0.02	0.05	0.04	0.08	0.06
LCW	4.00E-03	0.04	-0.01	0.01	4.00E-03
LCW	0.01	0.08	-0.08	-0.04	0.02
LCW	0.02	0.04	2.00E-03	-0.07	-0.03
LCW	0.03	0.05	0.02	0	-0.02
LCW	0.06	0.02	0.06	-0.02	-0.03
BDW	0.01	0.06	0.06	0.01	0.01
BDW	-0.01	0.04	0.04	-0.01	0.02
BDW	0.07	-0.02	-0.1	-0.03	0.01
BDW	-0.01	-4.00E-03	0.01	-0.02	-0.02
BDW	-0.04	-0.14	-0.13	-0.03	-0.03
BDW	0.08	0.03	-0.03	0.02	0.06
BDW	-0.04	-0.09	-0.09	-0.03	-0.02
BDW	-0.06	0.04	0.07	4.00E-03	0.07
BCW	0.02	-4.00E-03	0.03	-0.02	-0.01
BCW	0.01	0.03	-0.01	-0.02	-4.00E-03
BCW	-0.07	-0.09	-0.09	-0.08	-0.19
BCW	0.04	-0.04	-0.02	-0.15	-0.11
BCW	-0.05	-0.2	-0.11	-0.04	-0.07
BCW	-0.09	0.05	0.03	-0.04	0
BCW	-0.03	-0.09	-0.01	-0.03	-0.04
BCW	-0.04	-0.06	0.04	-0.01	-0.08
BCW	-0.08	-0.1	-0.09	-0.08	-0.16
BCW	-0.06	-0.11	-0.07	-0.03	0.05
BCW	-0.02	-0.02	-0.07	-0.1	-0.08
BCW	0.02	0.01	-0.03	-0.07	-0.03
BCW	-0.23	-0.02	-0.14	0.04	-0.04
BCW	-0.02	-0.05	0.03	-0.07	-0.05
CON	2.00E-03	-0.01	-0.01	-2.00E-03	0.01
CON	0	0	0.07	4.00E-03	0.1
CON	0.02	4.00E-03	-0.01	-2.00E-03	0.01
CON	-0.02	0.04	-0.07	0.01	-0.02
CON	0.09	0.02	4.00E-03	0.02	0.02
CON	0.01	-0.04	0.07	0.05	0.05
CON	-0.01	-0.06	-0.03	-0.04	-0.01
CON	0.01	0.1	0.02	0.05	0.05
CON	-0.02	-0.07	-0.07	-0.05	-0.14
CON	-0.02	0.06	0	-0.02	-0.01
CON	0.19	0.21	0.19	0.12	0.16
CON	0.02	0.02	-4.00E-03	0.07	0.05
CON	-0.09	0	0.05	0.03	0.04
CON	-0.05	-0.05	-0.06	-0.03	-0.03

Table A4.1.3. Longitudinal anterior chamber depth data.

Flatter corneal radius (mm)

GROUP	1M	3M	6M	12M	18M
LDW	0.07	0.03	-0.01	0.32	-0.03
LDW	-0.01	0.01	0.02	-0.03	0
LDW	0.04	-0.04	0	0.05	0.07
LDW	-0.03	-0.03	-0.04	-0.02	-0.03
LDW	-0.02	0.01	0.03	0.03	0.04
LDW	0.01	-0.01	0.03	0.02	0.04
LDW	-0.05	-0.03	0	-0.06	0
LDW	0.01	0.01	-0.02	-0.01	0.01
LDW	0.02	0.04	0.05	-0.01	0.09
LDW	0.02	0.01	0.01	0.03	0.01
LCW	0.07	0.01	0.04	-0.01	-0.02
LCW	0.05	0.01	0.01	0	0.02
LCW	0.02	-0.02	0.03	0.06	0.03
LCW	0.03	0.05	0.04	0.05	0
LCW	0.04	0.04	0	0.05	0.05
LCW	0.07	0.01	0.01	0.02	0.01
LCW	0.03	0.02	0.01	-0.01	-0.03
LCW	0.01	-0.01	0.03	0	0.02
LCW	0.06	0.05	0.13	0.05	0.04
LCW	0	0	0.06	0.03	0.09
LCW	0	0.04	0.01	0	0.01
BDW	0.06	0.01	0.01	0.05	0
BDW	-0.02	-0.08	-0.07	-0.07	0.01
BDW	0.03	0.02	0.03	0.01	0.03
BDW	-0.01	-0.01	0.01	0.03	0.02
BDW	0.02	0.06	0	0.02	0.01
BDW	-0.01	-0.04	0.01	0.02	0.01
BDW	0.03	0.05	-0.01	0.02	0.02
BDW	-0.02	-0.01	-0.04	-0.02	0.01
BCW	-0.03	-0.01	-0.07	-0.02	-0.02
BCW	0.02	-0.01	-0.04	-0.02	-0.01
BCW	0.02	0.05	0.04	0.01	0.02
BCW	0.01	0.02	0.02	0.01	-0.01
BCW	0.02	-0.01	0.03	0.01	0.01
BCW	0.01	0.02	0.03	0.04	-0.02
BCW	-0.03	-0.02	-0.03	-0.04	0
BCW	0.03	0.03	0.04	0.04	0.05
BCW	0.02	0.07	0.05	0.07	0.04
BCW	-0.07	-0.08	-0.11	-0.05	0
BCW	0	0.02	-0.02	0.04	0.01
BCW	0.03	0.02	0.01	0.01	0.02
BCW	0.02	0.01	0.01	0.01	0.04
BCW	-0.01	-0.02	0.01	0.02	0.03
CON	-0.02	-0.03	0.01	0.01	-0.02
CON	-0.01	-0.03	-0.04	-0.02	-0.05
CON	0.01	0.01	0	-0.01	-0.09
CON	0.01	0.01	0.01	0.01	0.01
CON	0.02	-0.01	0	-0.02	-0.05
CON	-0.01	0	0.02	0	0.01
CON	0	0.03	0.01	0.06	0.04
CON	-0.01	0.03	-0.01	-0.02	-0.03
CON	0.01	-0.02	0.01	0.02	-0.02
CON	-0.03	0.02	0.05	-0.02	-0.01
CON	-0.06	-0.08	-0.05	-0.13	-0.01
CON	-0.01	0	0	0	-0.01
CON	0.06	0.05	0.07	0.04	0.05
CON	-0.04	-0.06	-0.04	-0.06	-0.05

Table A4.1.4. Longitudinal flatter corneal radius data.

Steeper corneal radius (mm)

GROUP	1M	3M	6M	12M	18M
LDW	0.22	0.14	0.05	0.22	0.14
LDW	0.03	0.01	0	0	-0.07
LDW	-0.02	-0.02	0.04	0.07	0.06
LDW	0.01	-0.07	-0.05	-0.06	-0.08
LDW	-0.09	-0.04	-0.03	-0.04	-0.04
LDW	0.01	0.01	0.01	0.01	-0.01
LDW	-0.04	-0.01	-0.05	-0.03	-0.05
LDW	0.11	0.08	0.05	-0.01	0
LDW	0.01	0.04	0.01	-0.01	0.01
LDW	-0.01	-0.01	-0.02	0	-0.01
LCW	0.04	-0.03	0.03	0.04	0.01
LCW	0.05	0.02	0.03	0.02	0
LCW	-0.02	-0.02	-0.01	0	-0.02
LCW	0.01	0.02	0.04	0.03	0.04
LCW	0.07	0.06	0.03	0.09	0.07
LCW	0.06	0.02	0.01	0.04	0.04
LCW	0.05	0.06	0.05	0.04	0.04
LCW	0.02	0	0.06	0.03	0
LCW	0.05	0.04	0.1	0.03	-0.01
LCW	0	-0.01	0.01	0	0
LCW	-0.07	0	-0.04	-0.02	-0.06
BDW	0.03	0.02	0.01	0.05	0.01
BDW	-0.05	-0.06	-0.03	-0.04	-0.05
BDW	-0.01	-0.01	0	0	-0.02
BDW	-0.04	-0.04	-0.03	-0.01	-0.03
BDW	0.01	0	-0.04	0	-0.03
BDW	0	-0.03	-0.03	-0.03	-0.04
BDW	0.03	0.05	0.07	0.09	0.09
BDW	-0.01	-0.02	-0.03	0.01	0.04
BCW	-0.01	-0.01	-0.04	-0.02	0
BCW	0.01	-0.06	-0.02	0.05	0.02
BCW	-0.01	-0.01	0.02	0.01	0.03
BCW	0.01	0.02	0	0.01	0.03
BCW	0.03	-0.01	0.02	0.02	0
BCW	-0.01	0.02	0.03	0.03	0.01
BCW	-0.02	-0.02	-0.03	-0.03	0
BCW	0.01	0	-0.05	0	-0.01
BCW	0.03	0.04	0.04	0.05	0.04
BCW	-0.07	-0.05	-0.04	-0.03	-0.01
BCW	0.02	-0.01	-0.01	0.02	-0.01
BCW	0.01	0.03	-0.21	0.03	-0.04
BCW	0.04	0.01	0.05	0.05	0.06
BCW	-0.01	-0.03	-0.01	-0.01	0.03
CON	-0.03	-0.03	-0.02	-0.01	-0.05
CON	-0.01	-0.03	-0.04	-0.02	-0.02
CON	0.01	-0.04	0.02	0.05	0.03
CON	0	-0.01	-0.01	-0.01	0.01
CON	0.01	0.01	-0.02	-0.01	0
CON	-0.03	-0.04	-0.01	-0.02	-0.03
CON	0.01	0.02	-0.03	0.02	0.02
CON	-0.03	0.02	0.03	0	0.01
CON	0.03	0.02	0.02	0.05	0.03
CON	-0.01	0.02	-0.01	-0.02	0.01
CON	0.06	0.04	0	-0.08	0.04
CON	-0.01	0	0.03	0.01	-0.01
CON	0.07	-0.05	0.08	0.11	0.05
CON	-0.06	-0.06	-0.05	-0.06	-0.07

Table A4.1.5. Longitudinal steeper corneal radius data.

p-value (units)

GROUP	1M	3M	6M	12M	18M
LDW	0.22	0.14	0.05	0.22	0.14
LDW	0.03	0.01	0	0	-0.07
LDW	-0.02	-0.02	0.04	0.07	0.06
LDW	0.01	-0.07	-0.05	-0.06	-0.08
LDW	-0.09	-0.04	-0.03	-0.04	-0.04
LDW	0.01	0.01	0.01	0.01	-0.01
LDW	-0.04	-0.01	-0.05	-0.03	-0.05
LDW	0.11	0.08	0.05	-0.01	0
LDW	0.01	0.04	0.01	-0.01	0.01
LDW	-0.01	-0.01	-0.02	0	-0.01
LCW	0.04	-0.03	0.03	0.04	0.01
LCW	0.05	0.02	0.03	0.02	0
LCW	-0.02	-0.02	-0.01	0	-0.02
LCW	0.01	0.02	0.04	0.03	0.04
LCW	0.07	0.06	0.03	0.09	0.07
LCW	0.06	0.02	0.01	0.04	0.04
LCW	0.05	0.06	0.05	0.04	0.04
LCW	0.02	0	0.06	0.03	0
LCW	0.05	0.04	0.1	0.03	-0.01
LCW	0	-0.01	0.01	0	0
LCW	-0.07	0	-0.04	-0.02	-0.06
BDW	0.03	0.02	0.01	0.05	0.01
BDW	-0.05	-0.06	-0.03	-0.04	-0.05
BDW	-0.01	-0.01	0	0	-0.02
BDW	-0.04	-0.04	-0.03	-0.01	-0.03
BDW	0.01	0	-0.04	0	-0.03
BDW	0	-0.03	-0.03	-0.03	-0.04
BDW	0.03	0.05	0.07	0.09	0.09
BDW	-0.01	-0.02	-0.03	0.01	0.04
BCW	-0.01	-0.01	-0.04	-0.02	0
BCW	0.01	-0.06	-0.02	0.05	0.02
BCW	-0.01	-0.01	0.02	0.01	0.03
BCW	0.01	0.02	0	0.01	0.03
BCW	0.03	-0.01	0.02	0.02	0
BCW	-0.01	0.02	0.03	0.03	0.01
BCW	-0.02	-0.02	-0.03	-0.03	0
BCW	0.01	0	-0.05	0	-0.01
BCW	0.03	0.04	0.04	0.05	0.04
BCW	-0.07	-0.05	-0.04	-0.03	-0.01
BCW	0.02	-0.01	-0.01	0.02	-0.01
BCW	0.01	0.03	-0.21	0.03	-0.04
BCW	0.04	0.01	0.05	0.05	0.06
BCW	-0.01	-0.03	-0.01	-0.01	0.03
CON	-0.03	-0.03	-0.02	-0.01	-0.05
CON	-0.01	-0.03	-0.04	-0.02	-0.02
CON	0.01	-0.04	0.02	0.05	0.03
CON	0	-0.01	-0.01	-0.01	0.01
CON	0.01	0.01	-0.02	-0.01	0
CON	-0.03	-0.04	-0.01	-0.02	-0.03
CON	0.01	0.02	-0.03	0.02	0.02
CON	-0.03	0.02	0.03	0	0.01
CON	0.03	0.02	0.02	0.05	0.03
CON	-0.01	0.02	-0.01	-0.02	0.01
CON	0.06	0.04	0	-0.08	0.04
CON	-0.01	0	0.03	0.01	-0.01
CON	0.07	-0.05	0.08	0.11	0.05
CON	-0.06	-0.06	-0.05	-0.06	-0.07

Table A4.1.6. Longitudinal p-value data.

A4.2 Longitudinal ocular physiology data relating to Chapter 4.

Subjective grading (efron)

Bulbar hyperaemia (units)

GROUP	1M	3M	6M	12M	18M
LDW	-0.39	0.16	-0.9	-0.4	-0.54
LDW	-0.59	0.51	0.05	-1.43E-03	0.01
LDW	0.31	0.86	0.45	0.55	0.71
LDW	0.51	0.86	0.6	0.7	0.74
LDW	0.41	0.61	0.4	0.55	0.54
LDW	0.11	0.41	0.05	0.4	0.09
LDW	0.61	0.96	0.65	0.45	0.46
LDW	-0.09	-0.14	-0.35	0.3	-0.39
LDW	0.31	0.36	-0.15	-0.2	0.28
LDW	-0.14	-0.39	-0.15	0.07	-0.24
LCW	-0.99	0.21	-0.4	0.15	-0.19
LCW	0.11	0.41	0.25	0.4	0.26
LCW	0.31	0.91	0.15	0.75	-0.16
LCW	0.51	1.26	0.75	0.6	0.68
LCW	0.41	1.46	0.25	1.45	0.9
LCW	0.41	-0.29	-0.2	1.22	0.31
LCW	0.21	0.01	-0.45	-0.05	-0.19
LCW	0.01	0.16	-0.1	-0.03	-0.06
LCW	-0.39	-0.04	-0.1	-0.05	-0.14
LCW	-0.09	-0.04	0.1	0.1	-0.32
LCW	0.01	-0.19	-0.25	-0.23	-0.02
BDW	0.41	0.61	0.75	0.45	0.61
BDW	1.11	0.86	0.2	1.4	0.78
BDW	-0.29	-0.09	-0.1	-1.43E-03	-0.34
BDW	0.51	0.66	0.4	0.05	0.41
BDW	-0.04	0.41	-0.05	0.07	0.31
BDW	0.21	0.01	-0.2	0.02	-0.04
BDW	0.11	0.06	-0.2	0.14	-0.06
BDW	-0.04	0.06	-0.25	-0.35	-0.31
BCW	0.01	-0.04	0.4	0.07	-0.06
BCW	0.61	0.81	0.6	0.1	0.29
BCW	-0.19	0.11	-0.6	-0.08	-0.38
BCW	-0.39	-0.09	-0.15	0.17	-0.04
BCW	0.46	0.06	0.1	-0.1	0.26
BCW	0.41	0.51	0.25	0.35	0.21
BCW	0.21	0.26	-0.25	0.23	-0.04
BCW	-0.39	-0.14	-0.6	-0.63	-0.44
BCW	0.11	0.01	0.15	0.15	0.26
BCW	0.06	-0.04	-0.25	-0.13	0.51
BCW	-0.24	0.71	0.3	-0.07	0.61
BCW	0.16	0.81	0.5	0.62	0.58
BCW	0.41	0.76	0.55	0.11	0.14
BCW	-0.04	0.11	-0.2	-0.05	-0.04

Table A4.2.1. Longitudinal bulbar hyperaemia data.

Limbal hyperaemia (units)

GROUP	1M	3M	6M	12M	18M
LDW	-0.46	0.77	0.11	0.16	-0.07
LDW	0.04	0.27	1.21	0.51	0.38
LDW	0.64	1.57	0.81	0.96	1.03
LDW	-0.26	0.17	0.31	0.01	-0.17
LDW	-0.36	-0.03	0.31	-0.09	-0.19
LDW	-0.36	-0.03	0.56	0.24	-0.27
LDW	-0.06	0.07	0.11	0.51	0.21
LDW	-0.16	0.17	0.11	0.31	0.03
LDW	-0.21	0.27	0.16	0.26	0.43
LDW	0.84	0.77	0.86	0.28	1.08
LCW	0.04	-0.23	-0.54	-0.49	-0.55
LCW	1.14	0.62	1.01	0.46	0.8
LCW	0.44	0.07	0.41	0.56	-0.72
LCW	-0.16	0.87	0.51	0.46	0.61
LCW	0.14	1.07	0.51	0.86	0.48
LCW	0.14	0.52	0.01	1.46	0.11
LCW	-0.06	-0.13	0.21	0.01	0.08
LCW	-0.96	-0.43	-0.24	-0.39	-0.57
LCW	-0.26	0.07	0.11	0.34	0.03
LCW	0.19	0.57	0.81	0.46	0.43
LCW	-0.36	-0.63	-0.49	-0.66	-0.44
BDW	0.74	1.17	1.11	0.26	0.63
BDW	1.64	0.47	0.46	0.76	0.28
BDW	-0.06	0.02	0.31	0.11	0.01
BDW	-0.36	-0.08	0.41	-0.14	-0.07
BDW	-0.21	0.97	0.31	0.41	1.38
BDW	-0.46	-0.63	-0.29	-0.42	0.53
BDW	-0.06	0.07	0.01	0.66	0.28
BDW	0.74	0.67	0.46	0.04	-0.17
BCW	-0.16	0.77	0.91	1.48	0.33
BCW	0.74	1.57	0.61	0.61	0.41
BCW	-0.86	-0.33	-0.59	-0.36	-0.47
BCW	-0.26	-0.33	0.31	0.23	0.08
BCW	0.54	0.32	0.41	0.16	0.43
BCW	0.54	0.92	0.51	0.41	0.53
BCW	0.84	1.07	0.76	0.86	0.23
BCW	0.04	1.07	0.46	0.16	0.23
BCW	0.94	-0.03	0.21	0.11	0.33
BCW	0.19	0.22	0.56	0.06	0.61
BCW	0.49	0.87	0.51	0.26	1.03
BCW	-0.16	0.07	0.26	0.51	0.08
BCW	0.04	0.52	0.51	0.28	0.33
BCW	0.19	0.57	-0.19	0.06	0.13

Table A4.2.2. Longitudinal limbal hyperaemia data.

Papillary conjunctivitis (units)

GROUP	1M	3M	6M	12M	18M
LDW	1.03	1.35	0.93	0.47	0.53
LDW	0.53	1.5	1.08	1.02	1.18
LDW	0.03	1.1	0.93	0.94	0.63
LDW	0.43	1.15	0.13	0.69	1.03
LDW	0.43	0.65	0.13	1.12	1.18
LDW	-0.17	0.3	-0.38	-0.43	0.53
LDW	0.23	-0.05	-0.28	-0.33	-0.17
LDW	0.03	-0.05	-0.58	0.87	0.33
LDW	0.03	-0.2	-0.13	-0.11	-0.19
LDW	0.13	0.3	-0.03	-0.23	-0.52
LCW	-0.17	0.95	0.97	0.62	0.63
LCW	0.03	1.35	1.13	0.92	0.83
LCW	0.03	0.85	0.23	0.77	0.93
LCW	1.23	0.95	1.02	0.87	1.03
LCW	0.03	0.95	0.42	0.57	1.03
LCW	0.83	0.95	1.02	1.02	1.18
LCW	-0.63	-0.81	-1.13	-1.03	-1.33
LCW	0.33	0.65	0.68	0.37	0.33
LCW	-0.07	0.1	0.42	-0.27	0.03
LCW	-0.02	-0.2	-0.38	-0.43	0.08
LCW	0.28	0.05	0.07	0.1	0.13
BDW	0.43	0.45	0.53	0.12	0.53
BDW	0.03	0.15	-0.07	-0.68	-0.52
BDW	0.93	1.05	0.88	0.97	1.08
BDW	0.33	0.2	0.63	-0.16	1.63
BDW	0.63	0.45	0.42	0.59	0.88
BDW	0.53	0.1	0.07	0.09	0.13
BDW	0.23	0.3	-0.58	0.52	-0.22
BDW	0.73	0.55	1.08	0.97	1.08
BCW	1.33	0.65	0.53	0.22	0.78
BCW	0.23	0.25	0.63	0.92	0.98
BCW	0.13	0.05	0.03	-0.38	0.21
BCW	1.33	0.6	0.93	1.43	1.23
BCW	0.23	-0.2	-0.07	0.02	0.33
BCW	0.18	0.25	-0.13	0.12	0.43
BCW	1.23	0.55	0.83	1.02	1.08
BCW	0.43	0.65	0.63	0.37	0.63
BCW	0.73	0.6	0.23	1.05	0.58
BCW	-0.57	-0.45	-0.58	-0.73	-0.57
BCW	0.13	0.15	0.03	-0.63	0.38
BCW	0.78	0.45	0.88	0.9	0.15
BCW	0.73	0.85	0.83	0.72	0.78
BCW	-0.07	-0.25	-0.68	0.02	-0.57

Table A4.2.3. Longitudinal papillary conjunctivitis data.

Corneal staining (units)

GROUP	1M	3M	6M	12M	18M
LDW	0.6	1.39	1.31	0.97	1.31
LDW	-0.4	-0.21	0.37	0.82	0.86
LDW	-0.4	1.94	-0.29	1.15	0.77
LDW	-0.5	1.09	0.86	0.77	-0.09
LDW	-0.4	1.49	1.41	0.87	0.88
LDW	-0.4	2.39	1.91	1.19	0.64
LDW	-0.4	0.69	1.36	1.22	0.91
LDW	0.1	-0.21	-0.29	0.82	0.51
LDW	2.4	0.89	0.71	1.44	2.33
LDW	0.6	0.29	0.71	0.85	1.27
LCW	-0.4	0.99	-0.29	0.57	2.01
LCW	0.8	-0.21	1.61	1.27	0.66
LCW	-0.4	0.29	1.71	2.27	1.49
LCW	-0.4	1.79	1.36	1.22	1.41
LCW	-0.4	1.04	1.41	0.95	0.61
LCW	-0.4	-0.21	1.06	0.85	0.64
LCW	1.5	0.54	-0.69	0.25	0.11
LCW	-0.4	-0.21	1.91	1.39	0.79
LCW	0.6	0.29	1.21	0.84	1.42
LCW	0.35	1.24	1.71	0.85	2.11
LCW	-0.5	0.19	0.41	0.44	-0.69
BDW	-0.4	2.09	2.46	1.77	0.81
BDW	2	0.79	1.11	1.81	1.81
BDW	-0.4	2.09	1.61	1.47	0.64
BDW	0.6	-0.21	0.31	1.25	1.41
BDW	0.9	1.79	1.31	0.87	0.89
BDW	-1.3	-1.91	-1.64	-1.7	-1.49
BDW	0.7	1.94	1.51	0.23	0.83
BDW	-0.4	1.04	1.11	0.8	1.51
BCW	-0.4	1.39	0.86	1.62	0.88
BCW	-2.1	-0.51	-0.59	-1.47	-1.31
BCW	1.8	1.89	2.31	1.82	1.71
BCW	-0.4	1.19	0.71	0.57	0.89
BCW	1.3	1.14	1.91	1.23	1.31
BCW	1.1	1.89	0.71	1.42	0.63
BCW	-0.4	-0.21	0.11	0.85	1.01
BCW	0.9	1.69	0.71	1.25	1.57
BCW	1.6	-0.01	1.31	0.77	0.89
BCW	2.4	1.59	2.11	2.07	1.39
BCW	1.95	2.34	1.86	1.77	1.79
BCW	1.45	0.59	0.86	2.07	0.71
BCW	1.7	1.64	2.46	1.25	0.61
BCW	0.4	1.39	0.71	0.57	0.91

Table A4.2.4. Longitudinal corneal staining data.

Objective grading

Bulbar hyperaemia (red extraction) (% red extracted)

GROUP	1M	3M	6M	12M	18M
LDW	3.65E-03	0.02	0.03	0.05	0.02
LDW	-0.02	0.02	0.02	0.02	-0.01
LDW	0.01	0.05	0.03	0.03	0.03
LDW	-0.01	0.02	0.02	-3.20E-03	0.02
LDW	-0.01	0.01	0.03	0.02	0.03
LDW	-0.01	-0.02	3.07E-03	0.02	0.02
LDW	-2.85E-03	4.92E-03	0.02	0.02	0.02
LDW	0.01	0.02	0.04	0.02	1.34E-03
LDW	0.01	0.01	0.03	0.04	0.02
LDW	0.03	0.01	0.04	0.03	0.02
LCW	-0.01	0.04	0.01	0.03	0.02
LCW	3.15E-03	2.92E-03	0.03	0.08	0.04
LCW	0.02	0.07	0.02	0.04	-1.61E-04
LCW	-3.85E-03	0.05	0.06	0.03	0.01
LCW	0.02	0.04	0.04	0.05	0.04
LCW	-0.04	-0.03	-2.93E-03	0.02	-0.01
LCW	0.03	0.02	0.02	0.02	-2.83E-03
LCW	-3.85E-03	0.02	0.03	0.01	1.51E-03
LCW	0.01	-0.01	0.02	0.03	0.01
LCW	-3.35E-03	2.92E-03	0.03	0.01	0.01
LCW	0.03	4.92E-03	0.02	0.02	-0.01
BDW	0.02	0.05	0.03	0.04	0.02
BDW	0.01	0.01	0.01	0.05	0.01
BDW	0.01	9.17E-04	0.03	0.03	0.02
BDW	-0.02	-8.33E-05	0.01	0.01	-0.02
BDW	0.06	0.07	0.01	0.03	0.04
BDW	-0.02	-0.01	-3.43E-03	0.01	0.01
BDW	-1.35E-03	0.01	0.03	0.02	0.03
BDW	-0.01	-0.01	2.57E-03	3.30E-03	8.39E-04
BCW	0.01	-8.33E-05	0.02	0.01	0.01
BCW	-0.01	-3.08E-03	1.07E-03	-0.01	-0.02
BCW	-4.85E-03	0.01	0.01	0.03	0.01
BCW	0.02	0.03	0.04	0.04	0.02
BCW	0.01	0.01	0.02	0.01	0.02
BCW	0.05	0.02	3.07E-03	0.03	0.02
BCW	0.02	0.05	4.07E-03	0.03	0.01
BCW	0.01	0.03	0.02	0.01	0.03
BCW	-3.85E-03	-0.02	-0.01	0.01	-0.01
BCW	0.01	-3.08E-03	0.01	0.03	0.06
BCW	-0.01	0.01	0.01	0.02	0.03
BCW	-0.02	-0.01	0.03	0.04	-1.16E-03
BCW	0.03	0.04	0.04	0.02	3.39E-04
BCW	-0.01	-4.08E-03	0.01	-0.01	0.03

Table A4.2.5. Longitudinal bulbar hyperaemia data (red extraction).

Bulbar hyperaemia (edge detection) (% area of blood vessel coverage)

GROUP	1M	3M	6M	12M	18M
LDW	-1.44E-03	-1.32E-03	-8.94E-04	-3.85E-03	-1.03E-03
LDW	1.56E-03	2.68E-03	0.02	-3.85E-03	2.54E-04
LDW	1.56E-03	6.78E-04	-3.94E-04	-2.85E-03	2.68E-03
LDW	2.56E-03	6.78E-04	1.61E-03	-1.85E-03	0.01
LDW	2.56E-03	1.68E-03	6.06E-04	-1.85E-03	2.11E-03
LDW	2.56E-03	6.78E-04	2.61E-03	-8.46E-04	2.58E-03
LDW	5.65E-04	-3.22E-04	2.61E-03	-1.85E-03	2.18E-03
LDW	2.56E-03	4.68E-03	-3.94E-04	-2.85E-03	1.24E-03
LDW	1.67E-03	-3.22E-04	6.06E-04	-1.85E-03	2.18E-03
LDW	0.01	6.78E-04	0.01	0.01	2.74E-03
LCW	-4.35E-04	-3.22E-04	2.61E-03	-8.46E-04	1.93E-03
LCW	0.02	2.68E-03	2.61E-03	1.15E-03	2.67E-03
LCW	-4.19E-03	-0.01	-0.01	-0.02	-0.02
LCW	0.01	0.02	0.03	-3.85E-03	1.39E-03
LCW	0.01	0.01	1.61E-03	1.15E-03	2.46E-03
LCW	0.01	0.01	1.61E-03	0.02	4.78E-03
LCW	2.40E-03	1.11E-05	-7.27E-04	-1.26E-03	-6.34E-04
LCW	1.56E-03	6.78E-04	1.61E-03	-1.85E-03	3.24E-03
LCW	5.65E-04	-1.32E-03	6.06E-04	-2.85E-03	1.44E-03
LCW	6.46E-05	-1.32E-03	1.61E-03	0.01	-2.05E-03
LCW	-0.01	-0.01	-0.01	-0.01	-0.01
BDW	0.01	0.02	0.01	-8.46E-04	4.56E-03
BDW	0.02	0.02	2.61E-03	0.01	3.34E-03
BDW	2.56E-03	2.68E-03	6.06E-04	-1.85E-03	2.78E-03
BDW	6.46E-05	-1.32E-03	1.61E-03	-2.85E-03	1.53E-03
BDW	0.01	1.68E-03	-0.01	1.54E-04	-3.92E-03
BDW	-0.01	-0.01	-0.01	-0.01	-0.01
BDW	6.46E-05	-1.32E-03	-3.94E-04	1.54E-04	1.15E-03
BDW	-2.69E-03	-4.57E-03	-3.64E-03	-0.01	-2.67E-03
BCW	1.56E-03	-3.22E-04	3.61E-03	-8.46E-04	2.71E-03
BCW	-0.01	-0.01	-0.01	-0.01	-0.01
BCW	0.01	1.68E-03	2.61E-03	-8.46E-04	2.12E-03
BCW	-3.44E-03	-3.22E-04	-1.39E-03	1.54E-04	-3.93E-04
BCW	0.01	2.68E-03	0.01	0.01	-9.07E-04
BCW	0.01	1.68E-03	0.02	3.15E-03	2.49E-03
BCW	0.01	-2.32E-03	1.61E-03	-0.01	-2.36E-03
BCW	6.46E-05	-3.22E-04	-3.94E-04	-1.85E-03	1.15E-03
BCW	0.01	-0.01	-1.39E-03	-2.85E-03	-4.21E-04
BCW	-1.44E-03	-0.01	-1.39E-03	-4.85E-03	2.62E-03
BCW	2.56E-03	2.68E-03	3.61E-03	1.54E-04	2.80E-03
BCW	-6.85E-04	-2.07E-03	-1.44E-04	-3.60E-03	6.94E-04
BCW	1.06E-03	6.78E-04	1.61E-03	-1.85E-03	3.24E-03
BCW	1.06E-03	6.78E-04	2.61E-03	2.15E-03	1.52E-03

Table A4.2.6. Longitudinal bulbar hyperaemia data (edge detection).

Palpebral hyperaemia (red extraction) (% red extracted)

GROUP	1M	3M	6M	12M	18M
LDW	-0.01	-0.02	-0.02	0.02	0.04
LDW	0.01	-0.01	0.01	0.01	-0.01
LDW	0.05	0.04	0.04	0.03	0.02
LDW	-0.01	0.04	0.03	0.03	0.03
LDW	0.02	0.04	0.02	0.04	1.67E-03
LDW	0.02	0.03	0.02	0.01	0.03
LDW	0.01	0.01	-0.01	0.01	-0.02
LDW	0.04	0.03	0.02	0.06	0.03
LDW	0.02	0.02	0.02	0.03	-2.00E-03
LDW	0.05	0.04	0.01	0.08	0.04
LCW	0.04	0.03	0.08	0.06	0.02
LCW	-0.04	0.02	3.68E-04	0.01	-0.03
LCW	0.06	0.07	0.04	0.02	-0.02
LCW	0.06	0.06	0.03	0.03	-0.01
LCW	3.81E-03	0.06	0.06	0.08	0.11
LCW	0.02	0.07	0.03	0.04	0.04
LCW	-0.02	0.01	0.02	8.20E-04	-0.01
LCW	-0.04	-0.04	-0.02	-0.04	-0.05
LCW	0.03	0.06	0.05	0.07	0.03
LCW	0.02	0.04	1.37E-03	0.01	0.04
LCW	0.03	0.01	0.06	0.05	0.03
BDW	2.81E-03	-0.01	1.37E-03	-0.05	2.67E-03
BDW	0.02	0.02	0.02	0.02	-0.01
BDW	0.08	0.05	0.06	0.06	0.02
BDW	-0.04	0.02	0.01	-3.85E-03	0.1
BDW	1.81E-03	1.45E-03	0.02	0.01	0.02
BDW	-0.02	0.01	-0.01	-0.02	1.17E-03
BDW	0.03	0.06	0.02	0.03	0.05
BDW	0.02	-2.55E-03	0.02	0.02	0.02
BCW	0.05	0.05	0.05	0.06	0.06
BCW	0.01	0.03	0.02	-2.85E-03	-0.02
BCW	0.05	-0.02	-0.01	-0.01	-0.04
BCW	0.08	0.03	0.05	0.03	0.03
BCW	-0.02	-0.01	4.37E-03	0.03	-0.01
BCW	-0.02	-0.01	-3.63E-03	-0.02	0.02
BCW	0.03	-0.01	-0.01	-0.01	-0.02
BCW	0.02	-0.02	3.37E-03	0.01	-0.01
BCW	-0.01	-0.02	-0.02	3.15E-03	-0.03
BCW	-0.02	0.01	0.03	0.05	0.03
BCW	-0.04	-0.01	2.37E-03	0.03	-0.02
BCW	0.01	0.02	0.02	0.03	0.01
BCW	-0.05	-0.01	0.03	-0.02	0.02
BCW	0.03	0.05	0.03	-0.01	0.03

Table A4.2.7. Longitudinal palpebral hyperaemia data (red extraction).

Palpebral hyperaemia (edge detection) (% area of blood vessel coverage)

GROUP	1M	3M	6M	12M	18M
LDW	0.02	0.05	0.04	0.02	0.01
LDW	-0.01	-1.83E-03	2.58E-04	0.01	0.01
LDW	-0.01	-3.83E-03	-7.42E-04	-4.49E-03	0.01
LDW	-0.01	2.17E-03	0.01	0.02	0.01
LDW	-0.01	-0.01	3.26E-03	-0.01	0.01
LDW	-0.01	-0.01	-1.74E-03	-4.49E-03	0.01
LDW	-0.01	-4.83E-03	4.26E-03	-0.01	0.01
LDW	-0.01	-0.01	1.26E-03	-0.01	0.01
LDW	-0.01	-0.01	-4.74E-03	-0.01	4.93E-03
LDW	-0.01	-1.33E-03	0.02	-0.01	-2.59E-03
LCW	-0.01	-3.83E-03	2.58E-04	1.51E-03	0.01
LCW	4.90E-03	4.17E-03	0.03	0.02	0.01
LCW	-0.01	-0.01	0.01	0.01	0.01
LCW	1.90E-03	0.01	2.58E-04	-0.01	0.01
LCW	-0.02	-0.01	-0.01	0.02	-0.01
LCW	-0.01	-8.26E-04	0.01	3.51E-03	3.69E-03
LCW	0.02	-2.29E-03	0.01	2.51E-03	-2.10E-03
LCW	-2.10E-03	0.01	-7.42E-04	0.02	0.01
LCW	-0.01	-0.01	-2.74E-03	-0.01	3.41E-03
LCW	-0.01	-1.83E-03	0.01	-4.49E-03	2.09E-03
LCW	9.05E-04	-0.01	-0.01	-0.01	1.97E-03
BDW	-0.01	-0.01	-7.42E-04	0.01	0.01
BDW	-2.10E-03	0.01	-7.42E-04	-0.01	0.01
BDW	3.90E-03	0.02	0.01	0.03	-0.01
BDW	0.04	-0.02	0.04	0.04	-0.01
BDW	0.03	0.01	-3.74E-03	0.03	2.63E-03
BDW	-4.10E-03	-0.01	0.04	0.02	2.32E-03
BDW	-0.01	-0.01	-3.74E-03	-3.49E-03	2.22E-03
BDW	0.01	0.02	0.01	0.03	3.89E-03
BCW	-0.01	4.17E-03	0.01	0.02	0.01
BCW	-1.10E-03	-0.01	-0.01	-0.01	3.28E-03
BCW	-0.01	-0.01	-0.01	-0.01	-0.01
BCW	-0.04	-0.02	-0.02	-3.49E-03	-0.02
BCW	-0.02	-0.01	0.01	2.51E-03	-0.01
BCW	-4.10E-03	0.01	0.01	3.51E-03	-0.01
BCW	-0.02	0.01	-0.01	-0.01	-1.62E-03
BCW	-0.01	-0.01	-2.74E-03	-4.49E-03	0.01
BCW	1.90E-03	0.01	2.26E-03	-0.01	0.01
BCW	-0.01	-0.01	0.02	0.01	-0.01
BCW	2.90E-03	-0.01	-1.74E-03	-4.49E-03	0.01
BCW	-0.01	-0.01	-0.01	0.02	1.80E-03
BCW	0.03	0.02	-4.74E-03	-0.02	-0.01
BCW	-0.01	-2.83E-03	-3.74E-03	-3.49E-03	0.01

Table A4.2.8. Longitudinal palpebral hyperaemia data (edge detection).

A4.3 Longitudinal tear film data relating to Chapter 5.

Lipid layer pattern (Tearscope)

	INITIAL	1M	3M	6M	12M	18M
			LDW			
N	0	0	0	0	0	0
M	2	2	2	1	1	2
W	5	4	2	5	4	3
A	1	4	6	3	5	4
C	2	0	0	1	0	1
AB	0	0	0	0	0	0
			LCW			
N	0	0	0	0	0	0
M	3	2	0	0	1	1
W	2	4	1	6	0	6
A	1	5	8	5	8	3
C	5	0	2	0	2	1
AB	0	0	0	0	0	0
			BDW			
N	0	0	0	0	0	0
M	1	1	2	0	0	0
W	5	4	2	5	1	5
A	2	3	4	3	7	3
C	0	0	0	0	0	0
AB	0	0	0	0	0	0
			BCW			
N	0	0	0	0	0	0
M	2	1	1	2	0	0
W	4	7	1	2	2	8
A	5	6	12	9	10	6
C	3	0	0	1	2	0
AB	0	0	0	0	0	0
			CON			
N	0	0	0	0	0	0
M	2	1	0	1	2	2
W	1	4	1	6	1	3
A	7	9	10	6	8	8
C	4	0	3	1	3	1
AB	0	0	0	0	0	0

Table A4.3.1. Longitudinal lipid layer pattern data.

Non-invasive tear break-up time (sec)

GROUP	1M	3M	6M	12M	18M
LDW	-41.52	1.94	-44	5.64	-17.22
LDW	11.22	2.08	-1.92	49.9	12.64
LDW	-23.74	-28.72	-33.08	-26.8	-19.44
LDW	6.58	1.66	1.52	5.08	13.16
LDW	1.86	-2.5	0.58	4.7	14.27
LDW	1.9	-2.4	-38.92	-35.3	-30.42
LDW	11.78	4.16	-14.02	-13.66	-17.5
LDW	5.68	3.24	2.54	4.72	12.06
LDW	7.58	7.28	5	9.38	12.66
LDW	-31.4	-6.26	-25.94	-42.08	-36.92
LCW	3.36	1.12	1.4	3.42	-8.52
LCW	3.76	1.22	-1.14	13.04	-6.64
LCW	1.5	-2.94	2.08	2.1	8.12
LCW	-36.82	-33.98	-14.74	-5.7	25.2
LCW	-28.32	-22.98	-24.34	-20.84	1.84
LCW	5.34	15.88	4.4	3.5	-8.44
LCW	-33.44	-37.64	-32.54	-37.62	-4.22
LCW	-0.14	-5.82	-8.58	-2.56	-6.92
LCW	-16.78	-13.88	-5.44	-15.14	-3
LCW	6.16	3.52	-0.44	8.62	-8.82
LCW	4.56	2.98	7.18	4	-8.16
BDW	10.32	0.02	0.56	7.7	-6.4
BDW	-7.08	-1.44	-1.34	-0.28	-4.72
BDW	4.94	2.98	0.1	5.2	-4.74
BDW	2.58	-2.58	-2.88	7.18	-8.7
BDW	-10.38	-13.18	-12.44	-5.56	-4.04
BDW	3.24	0.56	1.82	3.02	-3.78
BDW	7.46	5.72	33.58	13.02	8.78
BDW	4.7	1.92	-0.16	7.38	-9.84
BCW	1.6	-26.3	-12.82	-24.34	-8.12
BCW	2.3	-0.92	-1.74	4.52	-8.12
BCW	12.82	7.22	6.38	10.32	-5.3
BCW	-41.02	1.94	-47.96	-40.04	45.56
BCW	-10.18	-4.42	-5.78	-4.4	-1.9
BCW	-16.96	-41.36	-40.08	-39.22	-6.76
BCW	-9.34	-12.08	-7.32	-6.62	-4.5
BCW	-37.82	-49.12	-48.58	-45.2	-5.04
BCW	-4.86	2.66	0.3	-1.28	-2.58
BCW	1.84	4.34	-1	4.84	12.82
BCW	3.9	-1.54	-0.28	2.9	-7.3
BCW	-2.72	-4.12	-6.1	-1.26	-8.64
BCW	-4.8	-10.3	-12.8	44.74	-7.02
BCW	15.38	22	3.28	5.72	-7.76

Table A4.3.2. Longitudinal non-invasive tear break-up time data.

Tear meniscus height (mm)

GROUP	1M	3M	6M	12M	18M
LDW	-41.52	1.94	-44	5.64	-17.22
LDW	11.22	2.08	-1.92	49.9	12.64
LDW	-23.74	-28.72	-33.08	-26.8	-19.44
LDW	6.58	1.66	1.52	5.08	13.16
LDW	1.86	-2.5	0.58	4.7	14.27
LDW	1.9	-2.4	-38.92	-35.3	-30.42
LDW	11.78	4.16	-14.02	-13.66	-17.5
LDW	5.68	3.24	2.54	4.72	12.06
LDW	7.58	7.28	5	9.38	12.66
LDW	-31.4	-6.26	-25.94	-42.08	-36.92
LCW	3.36	1.12	1.4	3.42	-8.52
LCW	3.76	1.22	-1.14	13.04	-6.64
LCW	1.5	-2.94	2.08	2.1	8.12
LCW	-36.82	-33.98	-14.74	-5.7	25.2
LCW	-28.32	-22.98	-24.34	-20.84	1.84
LCW	5.34	15.88	4.4	3.5	-8.44
LCW	-33.44	-37.64	-32.54	-37.62	-4.22
LCW	-0.14	-5.82	-8.58	-2.56	-6.92
LCW	-16.78	-13.88	-5.44	-15.14	-3
LCW	6.16	3.52	-0.44	8.62	-8.82
LCW	4.56	2.98	7.18	4	-8.16
BDW	10.32	0.02	0.56	7.7	-6.4
BDW	-7.08	-1.44	-1.34	-0.28	-4.72
BDW	4.94	2.98	0.1	5.2	-4.74
BDW	2.58	-2.58	-2.88	7.18	-8.7
BDW	-10.38	-13.18	-12.44	-5.56	-4.04
BDW	3.24	0.56	1.82	3.02	-3.78
BDW	7.46	5.72	33.58	13.02	8.78
BDW	4.7	1.92	-0.16	7.38	-9.84
BCW	1.6	-26.3	-12.82	-24.34	-8.12
BCW	2.3	-0.92	-1.74	4.52	-8.12
BCW	12.82	7.22	6.38	10.32	-5.3
BCW	-41.02	1.94	-47.96	-40.04	45.56
BCW	-10.18	-4.42	-5.78	-4.4	-1.9
BCW	-16.96	-41.36	-40.08	-39.22	-6.76
BCW	-9.34	-12.08	-7.32	-6.62	-4.5
BCW	-37.82	-49.12	-48.58	-45.2	-5.04
BCW	-4.86	2.66	0.3	-1.28	-2.58
BCW	1.84	4.34	-1	4.84	12.82
BCW	3.9	-1.54	-0.28	2.9	-7.3
BCW	-2.72	-4.12	-6.1	-1.26	-8.64
BCW	-4.8	-10.3	-12.8	44.74	-7.02
BCW	15.38	22	3.28	5.72	-7.76

Table A4.3.3. Longitudinal tear meniscus height data.

A4.4 Longitudinal symptoms data relating to Chapter 7.

Symptoms/complaints

Blurred vision

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	0.41	0.91	0.41	-0.39	-0.09	-0.59	0.81	-0.59
LDW	3.41	4.21	1.61	3.91	-0.59	-0.39	3.01	1.61
LDW	1.91	2.41	4.91	6.91	1.41	1.41	5.81	5.31
LDW	1.91	-0.09	1.41	0.41	0.41	-0.59	0.81	2.11
LDW	2.91	8.11	0.31	0.01	-0.29	0.41	0.61	-0.59
LDW	-0.59	3.91	-0.59	1.41	-0.59	-0.59	-0.59	0.21
LDW	6.41	6.41	7.41	7.41	1.41	-0.59	-0.59	4.61
LDW	-0.59	-0.59	-0.59	-0.59	-0.59	1.41	5.61	-0.09
LDW	-0.59	-0.59	-0.59	-0.59	-0.59	-0.59	-0.59	-0.59
LDW	-0.59	-0.09	-0.09	0.41	-0.59	-0.59	-0.59	1.81
LCW	-0.59	-0.59	-0.59	-0.59	4.41	1.41	2.81	6.41
LCW	-0.59	0.91	0.71	-0.29	0.01	-0.09	2.81	1.21
LCW	-0.59	-0.59	-0.59	0.41	0.41	-0.59	-0.59	1.11
LCW	-0.59	-0.59	1.41	-0.59	-0.59	-0.59	3.21	-0.09
LCW	0.41	1.41	1.41	1.41	1.41	1.41	0.21	0.01
LCW	1.91	2.91	5.91	0.91	-0.59	2.91	6.21	4.11
LCW	3.41	2.91	1.91	1.41	0.41	0.41	0.71	0.91
LCW	1.41	2.41	2.41	2.91	3.41	1.41	3.11	2.21
LCW	1.41	1.41	0.41	1.41	-0.59	0.41	2.41	1.41
LCW	2.91	2.16	1.41	0.91	0.41	-0.59	0.01	0.51
LCW	-0.59	-0.59	-0.59	-0.59	-0.59	0.41	-0.19	-0.29
BDW	2.41	7.41	7.41	7.41	4.41	-0.59	3.91	-0.09
BDW	-0.59	1.41	1.91	2.41	-0.59	3.41	4.61	-0.59
BDW	0.41	0.41	-0.59	0.41	0.41	0.41	1.01	1.11
BDW	3.41	1.41	0.41	0.41	0.41	2.41	1.71	2.51
BDW	2.41	0.41	-0.09	-0.59	-0.59	-0.59	-0.49	-0.09
BDW	0.41	0.41	0.41	0.41	0.41	1.41	2.01	1.21
BDW	0.41	-0.09	-0.34	-0.34	-0.59	0.41	1.81	-0.59
BDW	1.41	4.41	2.91	1.41	1.41	-0.59	-0.39	4.31
BCW	2.41	6.41	1.61	3.41	2.61	2.21	4.61	1.41
BCW	-0.59	-0.59	1.41	0.41	-0.59	-0.59	0.81	1.41
BCW	-0.59	-0.59	-0.59	-0.59	-0.59	-0.59	-0.59	0.81
BCW	2.41	0.41	0.41	-0.59	0.41	0.41	6.01	2.11
BCW	2.41	-0.59	-0.59	-0.59	-0.59	-0.59	0.81	-0.29
BCW	0.41	1.41	1.41	2.41	3.41	1.41	2.21	1.11
BCW	-0.59	-0.59	-0.59	-0.59	-0.59	-0.59	1.61	0.31
BCW	1.41	5.41	3.41	1.41	3.41	1.41	1.31	6.01
BCW	5.91	-0.59	-0.59	-0.09	0.41	0.41	1.21	0.91
BCW	3.41	1.41	1.41	1.41	2.41	2.41	0.41	4.11
BCW	4.41	2.41	0.91	-0.59	7.41	-0.59	1.01	1.71
BCW	-0.59	1.41	0.41	-0.59	0.41	-0.59	0.31	0.01
BCW	0.41	-0.59	0.41	1.41	0.41	1.41	0.41	-0.19
BCW	-0.59	0.41	0.91	0.91	1.41	0.41	-0.29	0.21

Table A4.4.1. Longitudinal blurred vision data.

Variable vision

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	0.2	-0.3	-0.8	-0.7	-0.3	-0.8	0.6	-0.2
LDW	-0.8	0.4	0.7	2.4	-0.8	1.7	1	-0.3
LDW	3.2	6.2	4.2	6.7	3.2	4.2	5.6	5.3
LDW	0.7	3.2	-0.8	-0.8	-0.8	-0.8	-0.8	3.8
LDW	0.7	0.7	-0.6	0.1	0.9	5.4	0.4	0.1
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	3.57E-03
LDW	4.2	5.2	6.4	6.4	-0.8	-0.8	-0.8	-0.2
LDW	1.5	-0.8	-0.8	-0.8	-0.8	-0.8	5.6	-0.8
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
LDW	4.2	2.2	2.2	0.2	-0.8	0.2	-0.8	1.1
LCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.4	1.7
LCW	-0.8	-0.8	0.7	-0.3	-0.3	-0.2	1.5	1.1
LCW	-0.8	0.2	-0.8	-0.8	0.2	-0.8	-0.8	-0.8
LCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	2	-0.3
LCW	0.2	1.7	1.2	1.2	1.7	1.7	0.1	2.1
LCW	1.2	2.2	3.2	2.2	-0.8	-0.8	-0.2	1.3
LCW	-0.8	1.7	1.7	1.2	0.7	0.2	0.3	0.7
LCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
LCW	-0.8	0.2	-0.8	0.2	0.2	-0.8	-0.3	0.2
LCW	2.7	2.45	2.2	1.7	1.2	0.2	-0.6	0.1
LCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.3	-0.8
BDW	2.2	7.2	6.2	7.2	5.2	-0.8	-0.8	1.6
BDW	1.2	-0.8	0.2	1.2	-0.8	2.2	2.5	-0.8
BDW	-0.8	0.2	1.2	-0.8	0.2	0.2	0.8	-0.1
BDW	4.2	1.2	1.2	0.2	1.2	2.2	0.1	0.7
BDW	-0.8	1.2	0.2	-0.8	-0.8	-0.8	-0.8	-0.3
BDW	1.2	1.2	0.7	0.2	0.2	1.2	1.7	0.1
BDW	-0.8	-0.3	-0.55	-0.55	-0.8	0.2	-0.5	-0.6
BDW	3.2	1.2	1.7	2.2	1.2	-0.8	0.4	0.9
BCW	3.2	7.7	0.7	2.4	2.2	2.4	5.6	2.5
BCW	1.2	0.2	0.2	-0.3	-0.8	-0.8	0.4	1.3
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
BCW	3.2	0.2	0.2	-0.8	0.2	0.2	5.6	2.4
BCW	4.2	-0.8	-0.8	-0.8	-0.8	-0.8	0.8	-0.5
BCW	1.2	1.2	2.2	2.2	2.2	1.2	0.5	0.9
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
BCW	-0.8	3.2	1.7	0.2	2.2	1.2	-0.4	5.4
BCW	5.7	-0.8	-0.8	-0.8	-0.8	0.2	0.2	-0.2
BCW	-0.8	-0.8	-0.8	-0.8	1.2	-0.8	0.1	-0.6
BCW	4.2	0.2	-0.3	-0.8	-0.8	1.2	-0.7	-0.6
BCW	-0.8	3.2	1.2	-0.8	-0.8	-0.8	9	-0.8
BCW	-0.8	-0.8	-0.8	-0.8	0.2	-0.8	-0.8	-0.5
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	0.2	-0.5	3.57E-03

Table A4.4.2. Longitudinal variable vision data.

Glare

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.7
LDW	-0.8	-0.3	-0.3	-0.3	-0.8	0.2	-0.8	-0.3
LDW	-0.8	-0.8	0.2	0.2	-0.8	-0.8	-0.8	0.3
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	3.2
LDW	0.1	0.4	4.4	1.9	0.4	1.3	-0.6	-0.3
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	0.3
LDW	-0.8	0.9	1.5	2.4	-0.8	-0.8	-0.8	-0.8
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
LDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.4
LCW	-0.8	-0.8	-0.8	-0.8	0.2	-0.8	-0.8	2.3
LCW	-0.8	1.7	1.4	-0.4	3.57E-03	-0.5	-0.67	1.7
LCW	1.7	-0.8	0.7	-0.3	-0.8	0.2	-0.8	-0.4
LCW	-0.8	-0.8	2.2	2.2	-0.8	-0.8	2.2	-0.3
LCW	0.2	0.2	1.2	1.2	1.2	0.7	0.1	-0.1
LCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.3	1
LCW	2.2	0.7	0.2	1.7	0.2	0.2	0.3	0.4
LCW	2.2	-0.8	0.7	1.2	-0.8	-0.8	-0.8	-0.8
LCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
LCW	-0.8	0.7	2.2	1.2	0.2	-0.8	-0.6	0.4
LCW	-0.8	-0.8	-0.8	-0.8	-0.8	1.2	-0.3	-0.8
BDW	-0.8	4.2	4.2	4.2	4.2	-0.8	-0.8	-0.3
BDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
BDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	3.57E-03
BDW	1.2	2.2	0.2	0.2	0.2	-0.8	-0.7	-0.8
BDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.3
BDW	0.2	0.2	-0.3	-0.8	0.2	0.7	1.6	3.57E-03
BDW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.6	-0.8
BDW	4.2	1.2	1.2	1.2	1.2	-0.8	-0.8	-0.8
BCW	-0.8	3.2	-0.6	3.7	1.2	-0.8	0.7	-0.8
BCW	0.2	1.2	-0.8	-0.8	-0.8	-0.8	1.4	1.5
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	3.57E-03
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
BCW	1.2	2.2	1.2	1.2	-0.8	0.2	-0.6	-0.5
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
BCW	-0.8	1.2	0.7	0.2	-0.8	-0.8	1.1	1.9
BCW	1.7	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.2
BCW	4.2	1.2	3.2	3.2	2.2	7.2	2.7	5
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8
BCW	-0.8	2.2	0.7	-0.8	0.2	-0.8	9	-0.8
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.6
BCW	-0.8	-0.8	-0.8	-0.8	-0.8	-0.8	-0.5	-0.2

Table A4.4.3. Longitudinal glare data.

Photophobia

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.45
LDW	-0.45	-0.45	-0.95	-0.45	-0.95	-0.25	-0.95	-0.95
LDW	-0.95	-0.95	0.05	2.05	0.05	4.05	-0.95	2.15
LDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	0.65
LDW	-0.05	1.15	3.95	1.65	0.05	1.15	-0.35	-0.45
LDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.05
LDW	-0.95	2.05	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
LDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.55
LDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
LDW	-0.95	-0.95	-0.95	-0.95	-0.95	0.05	-0.95	-0.95
LCW	-0.95	0.25	-0.95	-0.95	-0.95	-0.95	-0.75	-0.25
LCW	1.05	0.75	-0.35	-0.75	-0.65	-0.55	-0.45	0.25
LCW	-0.95	-0.95	-0.95	0.05	-0.95	0.05	0.45	-0.95
LCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	2.45	-0.25
LCW	-0.95	0.05	0.05	0.05	0.55	0.55	0.15	0.05
LCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.85	-0.95
LCW	2.05	-0.95	0.05	1.05	0.55	0.05	0.25	0.25
LCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
LCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.65
LCW	-0.95	0.55	2.05	0.55	-0.95	0.05	-0.75	1.15
LCW	-0.95	-0.95	-0.95	-0.95	-0.95	1.05	-0.45	-0.95
BDW	-0.95	4.05	-0.95	4.05	4.05	-0.95	-0.95	-0.15
BDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.05	-0.95
BDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
BDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
BDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.45
BDW	-0.95	0.05	-0.45	-0.95	-0.95	0.05	-0.75	-0.45
BDW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.75	-0.95
BDW	3.05	1.05	1.05	1.05	-0.95	-0.95	0.15	-0.95
BCW	-0.95	6.25	-0.05	2.25	2.25	-0.15	-0.95	0.05
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	2.15
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	2.85
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.15
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
BCW	-0.95	0.05	0.05	-0.95	-0.95	0.05	-0.75	-0.55
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
BCW	-0.95	0.05	-0.45	-0.95	-0.95	0.05	1.05	1.85
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.75	-0.35
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	2.05	2.45	5.95
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	8.75	-0.75
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.65
BCW	-0.95	-0.95	-0.95	-0.95	-0.95	-0.95	-0.55	-0.15

Table A4.4.4. Longitudinal photophobia data.

Lens handling problems

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	2	2.5	0.5	0.1	0	0	0	0
LDW	0	1.5	0.5	5.6	0	0	1	0
LDW	1	0	0.5	2.5	3	3	0	0.7
LDW	3	5	7	1	0	1	2.8	2
LDW	9.6	2.7	1.2	3	1.2	3.5	0	0.5
LDW	2	2.5	2	2	1	1	2.2	1.7
LDW	0	0	0	0	0	0	0	0
LDW	3.4	1	3	1	1	0	0	0
LDW	0	0	0	0	0	0	0	0
LDW	6	3.5	3.5	1	2	0	0.4	2.1
LCW	0	0	0	0	0	1	0.3	4
LCW	1	0	0	0	0.2	0.7	0.5	1.9
LCW	5	0	0	0	0	0	1.4	0
LCW	3.5	3	3	3	0	0	1	1.2
LCW	0	1	1	0.5	1	1	0.4	2.8
LCW	0	4.5	3	4	0	2.5	2.4	3.4
LCW	7	2	1	2	1	0	1.2	0.4
LCW	3	1.5	0	0	3	2	4.6	2
LCW	2	1	1	1	1	1	1.6	1.1
LCW	3.5	3.25	3	1.5	0	2	0.7	3
LCW	0	0	0	0	1	2	2.7	2.3
BDW	0	0	5	5	5	0	0	0.9
BDW	0	0	0	0	0	6	0	0
BDW	1	1	1	1	0	0	3.6	0
BDW	0	0	0	1	0	0	0	0
BDW	4	2	1.5	1	1	0	0	0.5
BDW	0	1	1	1	0	1	0.2	0.4
BDW	0	0	0	0	0	0	0.1	0
BDW	5	4	4	4	0	0	0	0
BCW	0	2.5	0.5	2.5	3.7	1.5	0	0.5
BCW	2	1	0	0	0	0	0	3.6
BCW	0	0	0	0	0	0	0	0.3
BCW	1	0	0	0	0	0	0	0.4
BCW	3	0	0	0	0	0	0	0
BCW	2	2	3	1	1	1	1.3	2.5
BCW	7	1	0	0	1	3	2.8	0.4
BCW	5	2	2.5	3	2	1	0.4	2.7
BCW	5	0	0	0	0	0	1.3	1.3
BCW	7	2	2	4	5	6	4.9	0.2
BCW	9	2	2.5	3	7	0	4.2	0.2
BCW	0	8	5.5	3	3	0	2.9	0.2
BCW	1	5	2.5	0	0	0	1.3	0.4
BCW	0	0	0	0	0	0	0.2	0.8

Table A4.4.5. Longitudinal lens handling problems data.

Dryness

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	-1.28	-1.28	-1.28	-1.18	-1.28	-1.28	-0.48	-0.68
LDW	0.93	4.53	0.53	-0.78	-1.28	-1.28	-1.28	-0.58
LDW	6.42	0.72	4.73	4.73	1.73	4.73	0.53	5.03
LDW	5.92	0.72	0.72	-1.28	-1.28	3.73	2.52	4.33
LDW	5.23	3.52	-0.38	0.72	7.03	1.23	-0.38	6.33
LDW	3.73	3.23	3.73	2.73	3.73	3.73	2.33	4.92
LDW	2.73	2.73	0.23	2.93	-0.28	-0.28	5.13	-1.28
LDW	3.73	5.73	0.72	-1.28	0.72	6.73	0.72	5.92
LDW	1.23	-0.78	2.23	0.23	-0.78	-0.28	-1.28	0.63
LDW	0.72	0.72	0.72	0.72	-0.28	0.72	-0.68	-0.88
LCW	-1.28	-1.28	-1.28	-1.28	0.72	0.72	-0.28	5.03
LCW	-1.28	1.33	0.13	-0.78	-0.68	-0.68	2.13	0.42
LCW	-1.28	-1.28	0.72	-0.28	-0.28	0.72	2.33	3.43
LCW	-0.28	-1.28	0.72	1.73	1.73	1.73	4.13	-0.48
LCW	0.72	3.73	1.23	2.73	0.23	0.72	0.13	0.42
LCW	3.93	4.22	3.23	1.73	6.23	-0.28	1.73	1.43
LCW	3.73	4.73	3.73	3.23	0.72	-0.78	1.53	2.33
LCW	4.73	6.23	3.73	2.73	1.73	3.73	4.92	4.13
LCW	-1.28	-0.28	1.73	-0.28	1.73	-0.28	0.13	5.42
LCW	4.22	3.98	3.73	1.73	-0.28	0.72	3.33	2.33
LCW	3.73	3.73	3.73	3.73	3.73	2.73	0.42	2.02
BDW	2.73	6.73	4.73	6.73	3.73	-1.28	1.93	2.33
BDW	1.73	1.73	2.73	3.73	3.73	4.73	2.52	5.92
BDW	0.72	0.72	-0.28	-0.28	-0.28	-0.28	0.33	1.33
BDW	2.73	3.73	0.72	-0.28	1.73	1.73	1.13	3.02
BDW	-0.78	-1.28	0.23	1.73	0.72	-1.28	-1.28	-0.68
BDW	1.73	1.23	1.23	1.23	0.23	0.72	1.13	1.53
BDW	-0.78	-1.28	-0.78	-0.78	-0.28	2.73	3.33	-0.38
BDW	-0.28	0.72	-0.28	-1.28	-1.28	-1.28	-0.38	1.02
BCW	5.73	1.73	1.43	0.93	4.73	2.23	6.53	4.22
BCW	2.73	1.73	1.73	0.72	-0.28	-0.28	2.13	3.43
BCW	3.73	1.73	2.73	0.72	0.72	0.72	-0.58	0.63
BCW	-1.28	-1.28	-0.28	0.72	-0.28	1.73	2.93	1.43
BCW	-1.28	-1.28	-1.28	-1.28	-1.28	1.73	-1.08	-1.28
BCW	-0.28	0.72	1.73	0.72	0.72	1.73	1.73	-0.78
BCW	-0.28	0.72	0.72	0.72	1.73	0.72	1.23	1.63
BCW	-1.28	-0.28	0.23	0.72	-1.28	-1.28	0.93	6.23
BCW	4.22	-1.28	-0.28	-1.28	-1.28	-1.28	-0.78	-0.18
BCW	1.73	-0.28	0.72	0.72	2.73	6.73	6.83	5.73
BCW	-1.28	0.72	-0.28	-1.28	5.73	-1.28	8.72	5.92
BCW	0.72	0.72	0.72	0.72	-0.28	1.73	0.03	-0.88
BCW	-1.28	-1.28	-1.28	-1.28	-1.28	-1.28	-1.28	0.63
BCW	-1.28	-1.28	-0.28	-0.28	0.72	1.73	1.13	1.33

Table A4.4.6. Longitudinal dryness data.

Burning

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	-0.34	-0.34	-0.34	-0.34	0.16	0.66	0.36	0.26
LDW	-0.34	-0.34	-0.34	3.26	-0.34	-0.34	-0.34	-0.34
LDW	-0.34	-0.34	0.16	0.66	7.66	1.66	-0.34	0.56
LDW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	0.86	1.96
LDW	-0.34	-0.04	-0.24	0.36	8.36	2.66	0.56	7.96
LDW	-0.34	-0.34	-0.34	1.66	0.66	1.66	-0.34	1.06
LDW	0.66	-0.34	-0.34	-0.34	-0.34	-0.34	3.06	-0.34
LDW	-0.34	-0.34	-0.34	-0.34	-0.34	7.66	6.86	3.46
LDW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	0.46
LDW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	0.16
LCW	-0.34	-0.34	-0.34	-0.34	-0.34	2.66	0.66	3.76
LCW	-0.34	0.96	-0.04	-0.24	-0.14	-0.24	0.26	0.26
LCW	-0.34	-0.34	0.66	-0.34	-0.34	0.66	-0.34	-0.34
LCW	-0.34	-0.34	-0.34	1.66	0.66	-0.34	3.06	0.56
LCW	0.16	0.66	0.66	1.66	1.16	1.16	0.46	0.26
LCW	2.16	5.16	3.66	2.66	5.16	1.16	0.86	0.86
LCW	2.66	0.66	1.66	0.66	1.16	-0.34	1.06	0.76
LCW	-0.34	-0.34	1.66	-0.34	-0.34	1.66	3.16	6.06
LCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.14	1.76
LCW	1.76	2.21	2.66	1.16	-0.34	-0.34	0.96	0.36
LCW	-0.34	-0.34	-0.34	-0.34	-0.34	1.66	0.46	-0.34
BDW	-0.34	4.66	-0.34	4.66	4.66	-0.34	2.96	2.06
BDW	-0.34	5.66	4.66	3.66	6.66	6.66	1.06	1.16
BDW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34
BDW	1.66	3.66	-0.34	-0.34	-0.34	0.66	-0.34	-0.34
BDW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	0.16
BDW	-0.34	-0.34	0.16	0.66	1.16	1.16	-0.24	0.26
BDW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.14	-0.34
BDW	1.66	1.66	1.16	0.66	-0.34	-0.34	0.66	-0.34
BCW	-0.34	-0.34	1.66	-0.34	-0.34	1.16	4.26	2.36
BCW	0.66	-0.34	0.66	0.16	-0.34	-0.34	1.46	4.66
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.04
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	0.46
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.24	-0.14
BCW	-0.34	0.66	0.66	0.66	-0.34	1.66	0.46	0.36
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34
BCW	-0.34	0.66	0.66	0.66	0.66	0.66	2.06	7.16
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	1.36	1.86
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	6.66	1.86	2.36
BCW	4.66	4.66	3.66	2.66	6.66	1.66	9.66	0.06
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	9.66	-0.34
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.04
BCW	-0.34	-0.34	-0.34	-0.34	-0.34	-0.34	-0.04	0.66

Table A4.4.7. Longitudinal burning data.

Itching

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	-0.62	-0.62	-0.62	-0.62	-0.62	0.38	0.08	-0.62
LDW	6.88	2.88	1.88	8.28	1.88	-0.42	2.98	0.58
LDW	-0.62	-0.62	-0.12	0.38	3.38	-0.62	-0.62	0.18
LDW	4.38	1.38	-0.62	-0.62	-0.62	1.38	1.98	2.08
LDW	-0.62	0.68	-0.32	1.48	8.98	7.18	1.98	4.58
LDW	-0.62	-0.62	-0.62	-0.62	0.38	1.38	-0.62	3.38
LDW	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	9.38	-0.62
LDW	-0.62	-0.62	1.38	-0.62	-0.62	7.38	-0.62	6.88
LDW	1.88	-0.12	2.88	0.88	-0.12	0.38	-0.02	1.08
LDW	2.38	1.88	1.88	1.38	1.38	1.38	-0.62	-0.12
LCW	1.88	-0.62	0.38	1.38	4.38	6.88	0.68	7.68
LCW	1.38	-0.12	0.18	-0.02	-0.32	-0.22	-0.02	0.08
LCW	-0.62	-0.12	-0.62	0.38	0.38	1.38	-0.62	0.98
LCW	1.38	3.88	2.38	2.38	1.38	2.38	3.48	0.28
LCW	1.38	1.38	2.38	1.88	0.88	0.88	1.48	1.88
LCW	-0.62	0.88	-0.62	1.88	5.88	1.88	5.18	4.78
LCW	-0.62	1.38	1.88	1.38	0.38	0.38	0.98	0.48
LCW	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	2.78	-0.62
LCW	0.38	0.38	0.38	-0.62	1.38	0.38	0.78	2.48
LCW	1.38	2.88	4.38	2.88	1.38	1.38	0.08	0.98
LCW	1.38	2.38	2.38	3.38	2.38	2.38	0.98	1.28
BDW	2.38	6.38	6.38	7.38	4.38	-0.62	1.38	1.98
BDW	-0.62	4.38	3.88	3.38	7.38	3.38	4.78	0.18
BDW	1.38	0.38	0.38	-0.62	0.38	0.38	0.98	1.08
BDW	0.38	0.38	1.38	0.38	0.38	1.38	1.18	1.78
BDW	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.12
BDW	0.38	0.38	0.88	1.38	0.88	0.88	-0.42	-0.02
BDW	-0.12	-0.12	0.13	0.13	0.38	0.38	0.98	0.38
BDW	3.38	1.38	2.38	3.38	3.38	2.38	0.18	-0.62
BCW	4.38	2.88	0.88	1.28	4.58	2.18	4.98	3.98
BCW	4.38	2.38	1.38	0.88	0.38	1.38	3.38	6.48
BCW	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	0.88
BCW	-0.62	-0.62	-0.62	-0.62	1.38	2.38	4.18	5.68
BCW	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.32
BCW	3.38	2.38	3.38	2.38	1.38	1.38	1.38	7.68
BCW	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62
BCW	1.38	3.38	1.38	-0.62	-0.62	-0.62	1.08	6.88
BCW	5.38	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.02
BCW	-0.62	0.38	0.38	3.38	3.38	4.38	2.68	5.48
BCW	5.38	1.38	0.38	-0.62	6.38	-0.62	9.38	-0.22
BCW	0.38	-0.62	-0.62	-0.62	-0.62	-0.62	9.38	0.78
BCW	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.62	-0.32
BCW	0.38	-0.62	-0.12	-0.12	0.38	-0.62	1.88	1.18

Table A4.4.8. Longitudinal itching data.

Excess of secretion

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.59
LDW	0.81	0.81	-0.19	-0.19	0.51	0.81	1.31	0.51
LDW	-0.69	-0.69	-0.19	-0.69	-0.69	-0.69	-0.69	0.11
LDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	2.41
LDW	-0.69	-0.39	-0.39	-0.39	0.51	1.31	-0.69	1.71
LDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	0.51
LDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69
LDW	-0.69	-0.69	-0.69	-0.69	-0.69	0.31	-0.69	-0.29
LDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69
LDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.29
LCW	-0.69	-0.69	-0.69	-0.69	-0.69	4.31	-0.29	0.51
LCW	-0.69	1.61	-0.49	-0.49	-0.19	0.11	0.21	0.41
LCW	0.31	1.31	2.31	1.31	0.31	0.31	0.91	0.91
LCW	-0.69	-0.69	-0.69	2.31	1.31	-0.69	2.41	0.71
LCW	0.81	0.31	0.31	1.31	1.31	0.31	1.01	0.61
LCW	-0.69	-0.69	-0.69	-0.69	0.31	-0.69	-0.69	0.31
LCW	2.31	1.31	0.31	0.31	0.31	0.31	-0.09	0.31
LCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	0.41
LCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.09
LCW	-0.69	0.81	2.31	1.31	0.31	-0.69	-0.39	0.01
LCW	-0.69	0.31	0.31	1.31	-0.69	1.31	1.01	0.31
BDW	-0.69	-0.69	-0.69	-0.69	4.31	-0.69	2.31	-0.09
BDW	-0.69	4.31	1.81	-0.69	-0.69	-0.69	2.51	-0.39
BDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69
BDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69
BDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.19
BDW	-0.69	0.31	0.31	0.31	0.31	0.31	-0.59	-0.09
BDW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.49	-0.69
BDW	1.31	0.31	-0.19	-0.69	-0.69	-0.69	-0.69	-0.69
BCW	1.31	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69
BCW	0.31	-0.69	-0.69	-0.69	-0.69	-0.69	-0.49	4.41
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	4.21	-0.09
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.29
BCW	-0.69	0.31	0.31	0.31	1.31	1.31	-0.49	-0.29
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69
BCW	0.31	0.31	0.81	1.31	-0.69	0.31	-0.09	1.81
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.09	1.31
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	0.31	1.61	-0.69
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	0.41	-0.39
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	9.31	-0.69
BCW	-0.69	-0.69	-0.19	0.31	-0.69	-0.69	-0.69	-0.49
BCW	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	-0.69	0.21

Table A4.4.9. Longitudinal excess of secretion data.

Excess of tearing

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
LDW	-0.55	-0.05	0.95	1.95	-0.05	-0.25	3.05	0.65
LDW	-0.55	-0.55	-0.05	-0.55	-0.55	-0.55	-0.55	0.15
LDW	0.45	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	3.15
LDW	0.45	0.15	-0.45	0.05	-0.25	1.45	-0.55	1.25
LDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	0.75
LDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
LDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.15
LDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	0.15
LDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	2.15
LCW	-0.55	-0.55	-0.55	-0.55	0.45	1.45	-0.35	3.35
LCW	-0.55	0.65	-0.35	-0.25	-0.25	0.15	0.05	0.55
LCW	-0.55	0.45	2.95	-0.05	-0.55	0.45	-0.55	-0.55
LCW	0.45	-0.55	-0.55	-0.55	-0.55	-0.55	3.85	0.85
LCW	0.45	0.95	0.45	0.45	1.45	0.45	1.45	1.75
LCW	-0.55	-0.55	-0.55	-0.55	2.45	-0.55	2.65	2.05
LCW	1.45	1.45	0.45	0.45	0.45	1.45	0.05	0.25
LCW	-0.55	-0.55	-0.55	-0.55	1.45	1.45	0.95	1.05
LCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.35	-0.05
LCW	1.65	1.55	1.45	0.45	-0.55	-0.55	-0.35	0.25
LCW	-0.55	-0.55	-0.55	-0.55	2.45	1.45	1.15	-0.55
BDW	-0.55	-0.55	-0.55	-0.55	4.45	-0.55	2.45	-0.25
BDW	2.95	-0.55	-0.55	-0.55	-0.55	4.45	0.35	2.95
BDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
BDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
BDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.05
BDW	0.45	0.45	1.2	1.95	1.45	0.95	-0.05	0.55
BDW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.35	-0.55
BDW	-0.55	4.45	3.95	3.45	3.45	2.45	-0.35	-0.55
BCW	1.45	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
BCW	1.45	-0.55	-0.55	-0.55	-0.55	-0.55	-0.25	5.05
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	2.45	0.25
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
BCW	-0.55	0.45	0.45	0.45	-0.55	0.45	-0.25	-0.15
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	0.05	1.95
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	0.45	-0.05	0.95
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.45	-0.35
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	7.25	-0.05
BCW	-0.55	1.45	0.45	-0.55	-0.55	-0.55	6.35	-0.25
BCW	-0.55	1.45	0.45	-0.55	-0.55	-0.55	-0.55	-0.25
BCW	-0.55	-0.55	-0.55	-0.55	-0.55	-0.55	-0.25	0.35

Table A4.4.10. Longitudinal excess of tearing data.

Subjective judgement

Visual quality

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	8.5	9.5	9.5	9.8	9.5	9.5	9.4	8.8
LDW	10	9	9	9	9	9	8	9.1
LDW	7	8	7	7	8	7	1.9	4.8
LDW	8	10	7.5	10	10	10	8.3	8.5
LDW	9.2	9.8	9.2	9.8	8.3	9.2	9.4	9.5
LDW	10	9	10	10	10	10	10	9.9
LDW	7	7.4	7.2	6.4	8	9	10	10
LDW	8	9	10	8	10	8	6.6	10
LDW	10	10	10	10	10	10	10	10
LDW	7	7.5	7.5	8	10	8	9.5	8.5
LCW	5.5	9	9	9.1	7	7	5.1	6.5
LCW	9	9.5	9.5	9.8	9.5	9.6	9.2	8.8
LCW	5	8	7	8	7	7	7.4	8
LCW	9	8	7	8	8	8	7.1	7.7
LCW	6	6	6	5	7.25	8	8.5	7.1
LCW	8	7	8	8	8	9	7.6	8.6
LCW	7	6.5	7.5	8	7	9	7.5	8.7
LCW	8	8	7	7.5	7.5	7	7	6.9
LCW	8	8	8	9	9	9	6.6	6
LCW	7	6.5	6	7.5	9	10	9.2	9.1
LCW	9	8.5	8.5	8	9	8	9	8.2
BDW	8	8	8	8	8	10	9.2	5.8
BDW	9	9	9	9	10	7	3.8	7.9
BDW	9	10	9	10	10	9	9.4	8.3
BDW	7	7	8	8	8	7	9.2	8.9
BDW	7	7	7	7	7	7	7.4	6.6
BDW	9	9	9	9	9	9	9.6	8.7
BDW	10	9.5	9.25	9.25	9	9	8.2	8.4
BDW	8	7	8	9	9	9	8.5	8.7
BCW	7.5	6	8	5.7	8.5	8.5	7.5	7.9
BCW	8.5	10	7	7.5	8	9	5.5	5.6
BCW	10	10	9	10	10	10	9.8	9.5
BCW	6	9	9	10	9	10	7.6	9.2
BCW	9	10	10	10	10	10	6.8	10
BCW	8	7	8	8	8	8	7.7	8.4
BCW	9	10	10	10	10	10	9.4	9.4
BCW	8	8	8.5	9	9	8	8.4	8.7
BCW	7.5	10	9.5	9.5	9	9	8.2	8.9
BCW	8	10	8	8	8	7	7.8	9.3
BCW	10	9	9.5	10	10	10	10	9.3
BCW	9	8	8	8	8	9	9.2	9.1
BCW	10	10	10	10	10	10	10	9.7
BCW	10	10	10	10	10	10	9.8	9.6

Table A4.4.11. Longitudinal visual quality data.

Comfort

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	10	10	10	9.9	9.5	9.5	8.9	8.1
LDW	5	7	7	8	9	9	8	9
LDW	8.5	9.9	8	9.5	2	7	9	7.5
LDW	1	6	8	9	8	9	8.8	8.8
LDW	7.1	8.9	8.9	9.2	6.7	8.1	9.8	3.6
LDW	8	9	8	8	8	7	7.8	7.9
LDW	9	8.2	9.4	8.4	8.5	8.7	10	10
LDW	9	10	8	9	9	2	2.5	6.7
LDW	7.5	9.5	9	8.7	9.9	10	10	9.1
LDW	5	6	6	7	9	8	8.9	8.5
LCW	7	9.2	7.9	8.5	7	5	6	4.5
LCW	7	8.7	8.8	9.3	9.4	9.5	8.5	8.1
LCW	6	7	8	7	8	7	7.2	8
LCW	8	6	7	7	8	6	6.8	7.7
LCW	6	6	6	6	8	8	8	6.1
LCW	9	8	8	7	8	9	7.7	7
LCW	6	8	7.5	8	8	8.5	6.8	8.2
LCW	8	7	6	7	7	7	6.2	5.5
LCW	9	9	9	9	9	9	9	4.7
LCW	6	4	2	6	10	10	9.6	9.1
LCW	7.5	7.75	7.75	8	6.5	7	8.5	7.7
BDW	9	8	8	8	8	10	9.2	6
BDW	10	8	8.5	9	8	6	4.3	4.4
BDW	9	8	9	9	9	10	8.6	8.3
BDW	7	7	5	8	8	8	8.8	7.6
BDW	9.5	8	8.5	9	8	9	10	9.5
BDW	9.5	9.5	9.25	9	9	9.5	9.4	8.9
BDW	9	9.5	9.75	9.75	10	9	8.2	8.7
BDW	7	7	7	7	8	7	8.8	8.5
BCW	5	5.5	9.5	10	7	8.8	6.8	7.2
BCW	7	7	7	7.5	8	8	4.4	5.1
BCW	7	7	8	8	9	9	8.7	8.7
BCW	8	9.5	9	10	9	9	6.8	8
BCW	8	10	10	10	10	10	2.4	10
BCW	7	6	7	7	7	8	7.5	8.4
BCW	9	9	8	9	9	8	8.3	8.8
BCW	7	6	7.5	9	8	9	8.5	4.9
BCW	10	10	10	10	10	10	9.2	9.4
BCW	4	8	8	7	8	6	4.3	6.6
BCW	8	9	8.5	8	9	9	9	9.2
BCW	9	8	8.5	9	8	8	6.7	9.7
BCW	10	10	10	10	10	10	10	9.6
BCW	9	10	10	10	10	10	10	9.5

Table A4.4.12. Longitudinal comfort data.

Convenience

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	10	10	10	10	10	10	10	9.4
LDW	8	8	8	8	9	9	9.1	9.8
LDW	8	8	8	9.5	1	3	5.5	6.3
LDW	10	10	10	10	10	10	10	10
LDW	7.8	9.9	9.2	9.6	8.5	8.9	10	7.7
LDW	10	10	10	10	7	10	10	9.9
LDW	8	9	8.5	9.1	9.2	9.5	10	10
LDW	9	9	9	10	10	10	9.8	10
LDW	10	10	10	10	10	10	10	10
LDW	5	6	6	7	8	7	8.9	7.2
LCW	8.6	9.2	7.95	8.9	8	8	7.2	7.3
LCW	9.85	9.85	9.8	9.9	9.7	9.6	8.8	8.5
LCW	7.5	7	8	8	7	8	10	8
LCW	7.5	7	8	8	8	8	7.3	8.3
LCW	7.5	7	8	7	8.5	9	9.5	8.6
LCW	8	9	8	8	9	9.5	9.1	7.5
LCW	6	7	8	8	8	8.5	6.2	7.9
LCW	7.5	7.5	7	8	8	6.5	6.2	6.3
LCW	9	9	9	10	9	10	10	8.2
LCW	6.5	5.75	5	7.5	10	9	9.4	9
LCW	9	8.5	8.5	8	8	9	8.4	9.7
BDW	10	8	8	8	8	10	9.2	8.2
BDW	9	10	10	10	10	5	8.4	6.1
BDW	10	10	10	10	10	10	10	9.8
BDW	8	8	7	8	8	8	8.6	7.6
BDW	7	8	8.5	9	7	9	9	9.5
BDW	9.5	9.5	9.5	9.5	9	9.5	10	8.9
BDW	10	10	10	10	10	10	8.3	8.7
BDW	8	7	7.5	8	8	7	10	9.6
BCW	4	5.2	7.5	9	6	9.5	7.5	7.9
BCW	7	7	6	7	8	9	8.8	9
BCW	9	9	9	10	10	10	10	9.8
BCW	8	9	10	10	10	10	8	8.9
BCW	10	10	10	10	10	10	4.6	9.8
BCW	7	5	7	7	8	9	8.7	8.4
BCW	8	9	9	9	9	8	8.5	9.8
BCW	9	8	8.5	9	9	9	9.6	8.7
BCW	8	9.5	10	10	10	10	9.6	8.9
BCW	5	8	5	8	9	7	8.8	10
BCW	10	8	8.5	9	9	10	10	9.2
BCW	7	9	9	9	9	10	9.7	9.9
BCW	10	9	9	9	10	10	10	9.7
BCW	10	10	10	10	10	10	9.9	9.4

Table A4.4.13. Longitudinal convenience data.

Ocular health

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	10	10	10	10	9.5	10	9.4	9
LDW	8	8	8	7	9	8.5	7.7	8.8
LDW	9	9	8.5	9.5	9	9	9.5	7.9
LDW	5	9	9	8	8	9	9.4	8.3
LDW	8.1	8.1	8	9	6.7	8	8.8	3.7
LDW	10	9	8	9	6	6	6.8	6.5
LDW	7	7.9	7	7	7.6	8	10	10
LDW	10	10	10	10	10	5	6.2	7.8
LDW	9	10	10	10	10	10	10	10
LDW	8	8.5	8.5	9	10	9	9.6	10
LCW	9	9	9	9	8	1	6.4	7.3
LCW	9	9.2	9.9	9.9	9.3	9.8	8.8	8.4
LCW	7	7	8	7	8	7	10	8
LCW	6	8	8.5	7	8	7	5.6	6.5
LCW	6	6	7.5	7	7.5	8	9	5.5
LCW	10	6	8	8	7	8.5	4.2	4.2
LCW	6	8	7	8	7	8	6.2	8.4
LCW	8	7	7.5	7	7	7	5.8	5.1
LCW	10	10	9	9	9	10	10	8.1
LCW	7	4.5	2	5.5	9	9	9.4	7.8
LCW	9	8	8	7	7	8	8.4	7.6
BDW	9	8	8	8	8	10	9.2	6.1
BDW	9	9	8.5	8	10	7	4.4	5.8
BDW	10	10	10	10	10	10	10	9.7
BDW	4	7	6	8	8	9	8.5	7.5
BDW	8	8	8.5	9	8	9	10	9.4
BDW	9	9	9	9	9.5	9.5	9.2	8.3
BDW	9	10	10	10	10	10	8.4	8.4
BDW	5	7	7	7	8	7	8.4	9.3
BCW	5	5	8.3	7	6.2	7.2	8.5	6.1
BCW	8	6	7	7.5	8	9	6.6	8.2
BCW	9	9	9	8	9	9	10	9.8
BCW	9	9	10	10	8	10	6.6	7.7
BCW	10	10	10	10	10	10	3.3	9.9
BCW	8	8	8	8	8	8	8.2	8.3
BCW	9	10	10	10	9	9	7.7	9.6
BCW	9	7	7.5	8	8	8	7.3	6.5
BCW	6	10	10	10	10	10	9.5	8.7
BCW	10	10	10	10	10	8	4.4	4.6
BCW	10	9	9	9	9	9	10	9.3
BCW	9	10	10	10	10	9	9.9	8.9
BCW	9	8	8.5	9	8	9	10	9.7
BCW	10	10	10	10	10	10	9.8	9.5

Table A4.4.14. Longitudinal ocular health data.

Patient appearance

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	9.5	10	10	10	9.5	9	8.4	6.7
LDW	8	8	9	9	9	9	9.3	9.1
LDW	9	9	9	9.7	9	10	9.6	8
LDW	9	10	10	10	10	10	10	10
LDW	9.2	9.3	9.8	9.8	8.7	9.8	8.6	5.1
LDW	10	10	10	10	10	10	6.6	8.6
LDW	10	9.2	8	7.5	9.6	9.8	10	10
LDW	10	10	10	10	10	10	10	10
LDW	10	10	10	10	10	10	10	10
LDW	8	8.5	8.5	9	10	9	9.7	10
LCW	9	8.5	9	9	8	8	7.8	7.3
LCW	10	9.5	9.5	9.7	9.5	9.4	8.7	8
LCW	7	7	7	8	8	8	10	8.1
LCW	7	8	0	8	8	8	6.2	7.5
LCW	7	7.5	7.5	8	8	8	9	8.3
LCW	9	8	9	8	10	10	9.4	7.3
LCW	7	5	5	5	6	5	6.6	8.2
LCW	7	8	7.5	7.5	8	7.5	6.4	7.3
LCW	9	10	10	9	9	10	10	6.9
LCW	7.9	6.45	5	7	9	10	9.6	9.1
LCW	9	8.5	8.5	8	8	8	8.5	7.4
BDW	10	8	8	9	8	10	9.2	8.3
BDW	8	9	9	9	9	9	7.7	9.3
BDW	10	10	10	10	10	10	10	10
BDW	5	5	5	5	5	5	5.2	7.7
BDW	9	9	9	9	9	9	10	9.3
BDW	9	9	9.25	9.5	9.5	9.5	9.2	8.9
BDW	10	10	10	10	10	10	8.4	8.7
BDW	6	7	7	7	8	7	10	8.9
BCW	9	8	9.5	10	10	9.5	10	9.8
BCW	8	7	7	7.5	8	9	8.3	6.6
BCW	10	10	10	10	10	10	10	9.9
BCW	8	9	10	9	9	10	8.1	8.9
BCW	10	10	10	10	10	10	8.2	10
BCW	8	8	8	8	9	9	8.5	8.8
BCW	9	10	10	10	10	10	9.8	9.9
BCW	9	7	7.5	8	8	8	8.5	6.5
BCW	8	10	10	10	10	10	9.8	8.6
BCW	6	10	10	10	10	8	10	10
BCW	10	10	10	10	10	10	10	9.3
BCW	8	10	10	10	9	10	8	9.9
BCW	9	9	9	9	9	9	10	9.5
BCW	10	10	10	10	10	10	9.9	9.4

Table A4.4.15. Longitudinal patient appearance data.

Quality of life

GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	9.5	10	10	10	9.5	10	10	9.4
LDW	9	8	9	9	9	9	9.3	9.1
LDW	9	9.5	9	9.8	6	8	9.4	6.9
LDW	9	10	10	10	10	10	10	9.8
LDW	9.3	9	9	9.7	8.7	9.5	9.6	4.9
LDW	10	10	10	10	10	10	10	9.8
LDW	5	9	6	6.4	8.2	9.2	10	10
LDW	10	9	10	10	10	10	7.6	10
LDW	9	10	10	10	10	10	10	9.8
LDW	8	8	8	8	9	9	9	6.9
LCW	9	8.9	9	9	8	8	8.4	8.4
LCW	10	9.7	9.6	9.8	9.6	9.7	8.2	7.9
LCW	8	8	8	8	8	8	7.3	10
LCW	8	7	8	8	8	8	7	8.1
LCW	8	7.5	8	8	8	8.5	9.1	8.4
LCW	9	8	8	8	10	10	9.4	7.8
LCW	8	7	6	7	7.5	8	7.2	8.4
LCW	7	7	7	8	8	7.5	6	6.1
LCW	9	9	9	10	9	10	10	6.9
LCW	8	6	4	6.5	9	9	9.7	8.7
LCW	8	8	8	8	8	8	9.4	7.2
BDW	9	8	8	9	8	10	9.2	8.7
BDW	9	9	9	9	10	8	5.4	7
BDW	10	10	10	10	10	10	10	10
BDW	5	7	7	7	7	7	6.8	7.7
BDW	9	8.5	8.75	9	9	10	10	9.2
BDW	9	9.5	9.5	9.5	9.5	9	8.5	8.8
BDW	10	10	10	10	10	10	8.6	8.8
BDW	6	7	7	7	8	7	10	9.2
BCW	8	7.6	9.5	10	10	8.2	10	8.9
BCW	9	8	7	7.5	8	9	8.2	8.6
BCW	10	10	9	10	10	9	10	9.8
BCW	9	10	10	10	10	10	9.2	9.1
BCW	10	10	10	10	10	10	8.3	10
BCW	6	6	7	8	8	9	8.3	8.9
BCW	9	10	10	10	10	10	9.4	10
BCW	9	7	7.5	8	9	9	8.6	8.7
BCW	9	10	10	10	10	10	10	9.4
BCW	7	8	9	8	8	8	7.5	10
BCW	8	9	9.5	10	9	9	10	9.4
BCW	10	10	10	10	10	10	8	7
BCW	9	9	9	9	9	10	10	9.6
BCW	10	10	10	10	10	10	9.9	9.4

Table A4.4.16. Longitudinal quality of life data.

Overall satisfaction

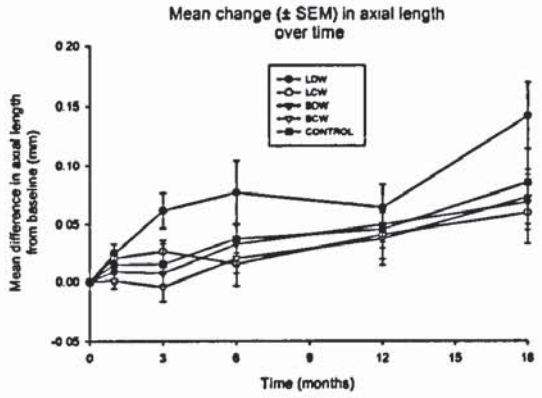
GROUP	1WK	2WK	3WK	4WK	12WK	24WK	48WK	72WK
LDW	10	9.8	10	10	9.5	9.5	8.8	9.1
LDW	7.5	8	8	8	9	9	7.4	9
LDW	8	9.8	8.5	9	3	5	7.8	6.1
LDW	6	8	10	9	10	10	8.8	8.8
LDW	9.4	9.5	9.7	9.8	7.1	8.5	9.4	5.9
LDW	8	9	8	9	8	8	8.9	8.1
LDW	8	8	8.2	8.1	8	8.9	10	9.8
LDW	10	9	9	10	10	8	7	8.9
LDW	9	9.7	9.7	9	10	10	10	9.7
LDW	7	7.5	7.5	8	9	8	9	8.1
LCW	9	9.3	9.2	9	8	5	6.1	5.2
LCW	9	9.2	9.4	9.7	9.7	9.7	8.7	8.6
LCW	8	7.5	7.5	8	8	8	10	9.1
LCW	8	7.5	7.5	7.5	8	8	6.8	7.7
LCW	7	7	7.5	7	8	8	9	7.2
LCW	9	8	8	8	8	9.5	7.9	5.9
LCW	7.5	7.5	7	7.5	8	8.5	6.6	8.2
LCW	8	7.5	8	8	7	7	6.9	5.9
LCW	9	9	9	9	9	9	8.9	6.8
LCW	8	6.5	5	7.5	10	9	9.2	8.1
LCW	8.5	8.25	8.25	8	8	8	9.3	7.8
BDW	9	8	8	9	9	10	9.2	8
BDW	10	8	9	10	10	8	5.2	6.2
BDW	10	9	9	10	10	10	9.4	9.8
BDW	7	7	6.5	7.5	7	7	7.4	8.3
BDW	8	8	8.25	8.5	8	9	7.6	9.3
BDW	9	9	9.25	9.5	9	9	9.5	9.4
BDW	10	10	10	10	10	10	8.8	8.7
BDW	7	7	7	7	7	7	8.8	8.4
BCW	7	6.2	7.3	8.7	6.5	7.8	5.4	8.2
BCW	8	6	7	7.5	8	8	6.2	7.8
BCW	10	8	9	8	9	9	9.6	9.3
BCW	9	9.8	10	10	10	10	8.5	9.5
BCW	9.5	10	10	10	10	10	4.7	10
BCW	7	7	8	8	8	8	7.4	8.6
BCW	9	10	10	10	10	9	9.2	9.8
BCW	9	6	7.5	9	9	9	8.6	4.9
BCW	8	10	10	10	10	10	9.4	9.4
BCW	7	9	8	8	9	7	7.8	7.2
BCW	9	9	9.5	10	9	9	8.4	9.2
BCW	8	8	8.5	9	8	9	9.3	8
BCW	9	9	9	9	10	9	10	9.5
BCW	10	10	10	10	10	10	9.9	9.6

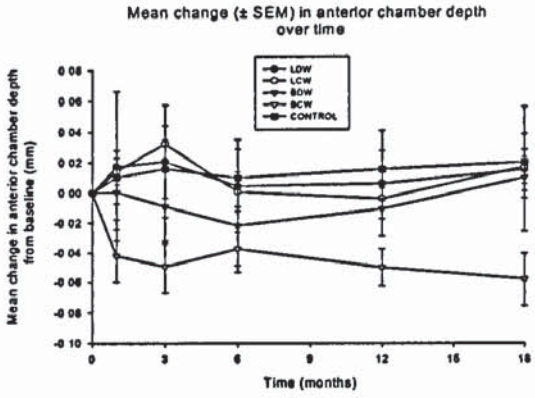
Table A4.4.17. Longitudinal overall satisfaction data.

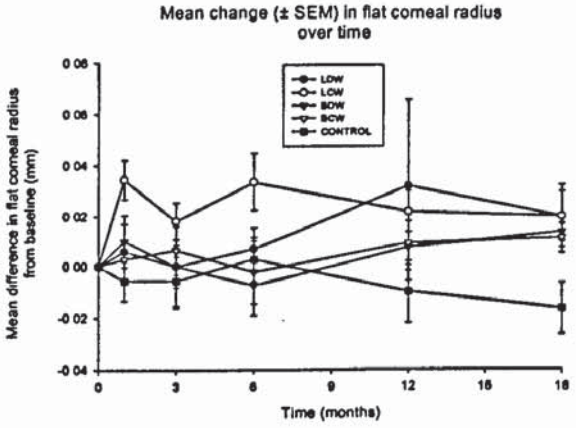
APPENDIX 5

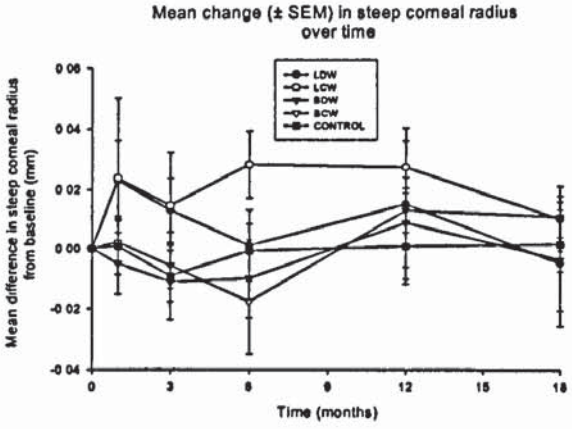
LONGITUDINAL DATA PLOTS

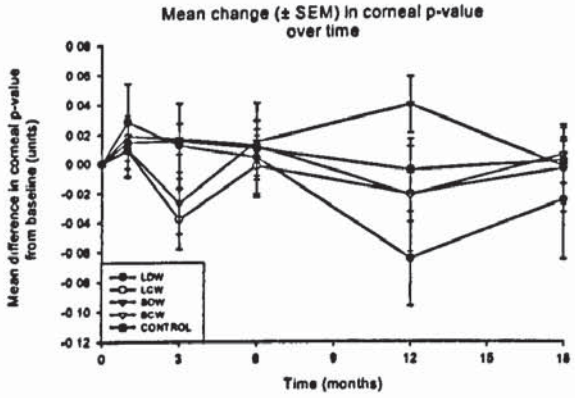
A5.1 Refractive and biometric plots: Mean change in refractive and biometric measures over time. Error bars indicate 1 SEM throughout.





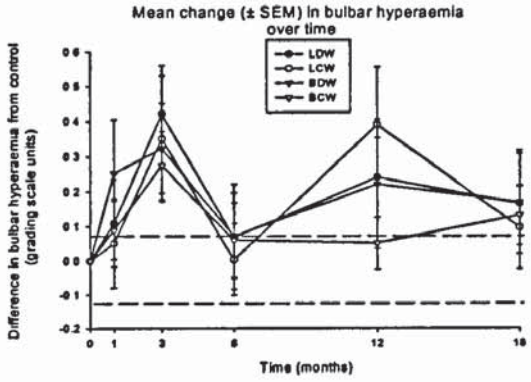


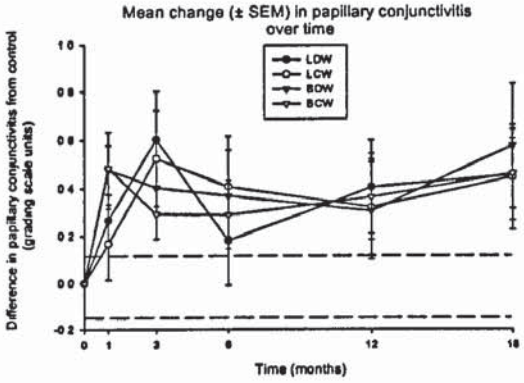




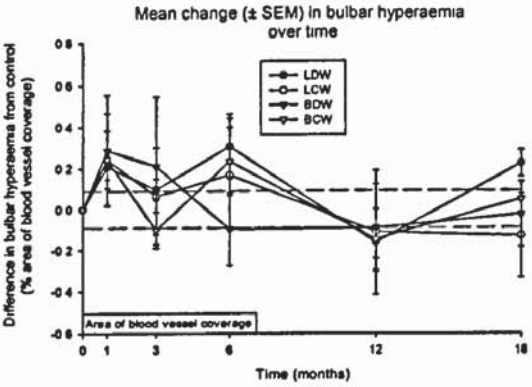
A5.2 Ocular physiology plots

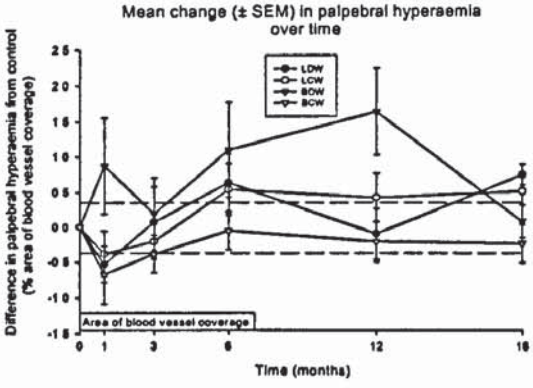
Subjective grading plots: Mean change in ocular physiology measures time. Error bars indicate 1 SEM throughout.





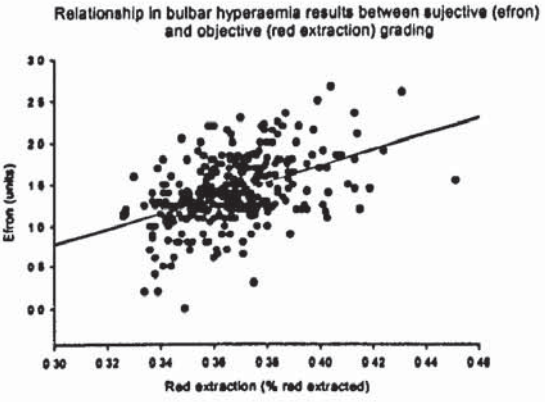
Objective grading plots: Mean change in ocular physiology measures time. Error bars indicate 1 SEM throughout.

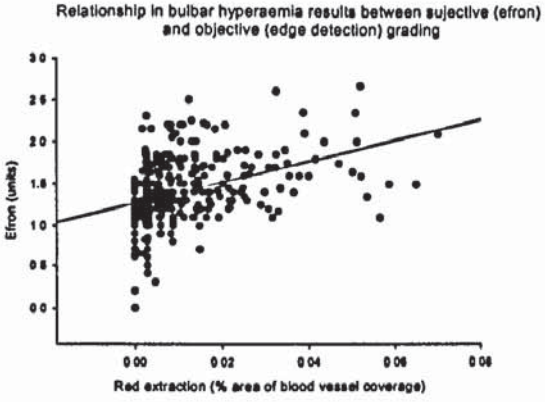


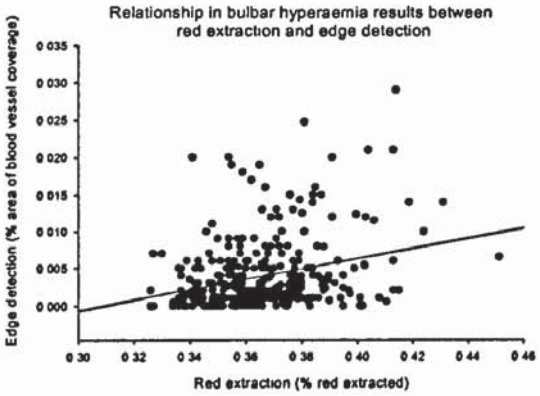


Relationship between subjective and objective grading plots: Correlation between subjective and objective measures.

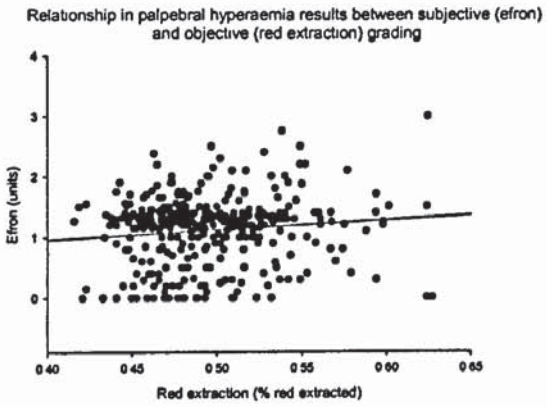
Bulbar hyperaemia

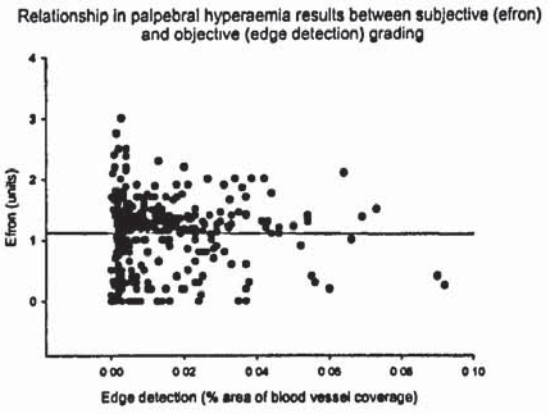


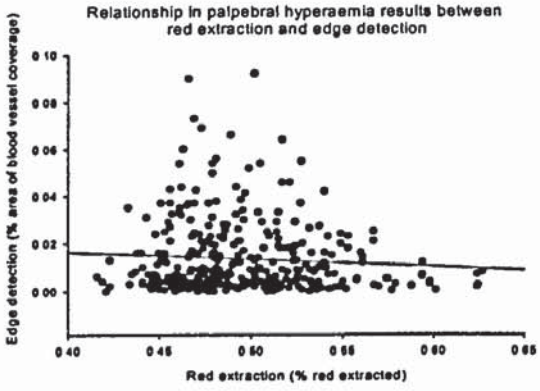




Palpebral hyperaemia

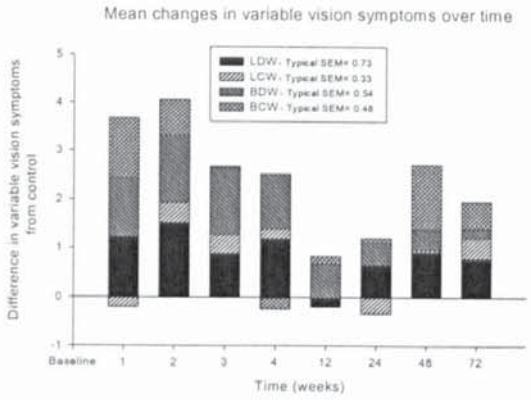


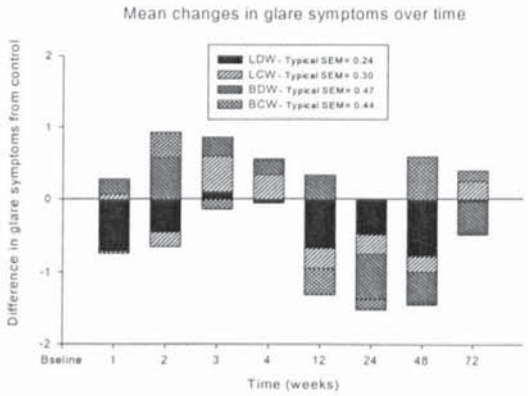


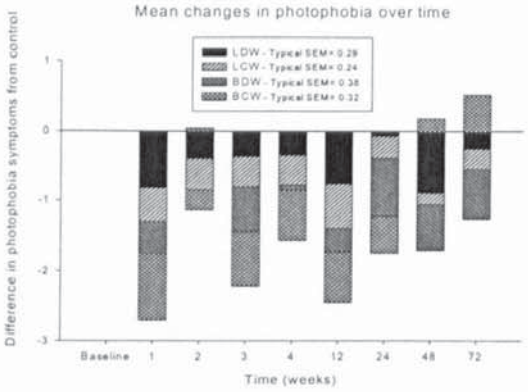


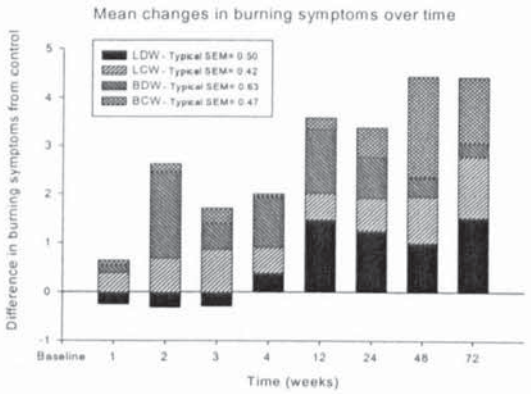
A5.3 Ocular symptommatology plots

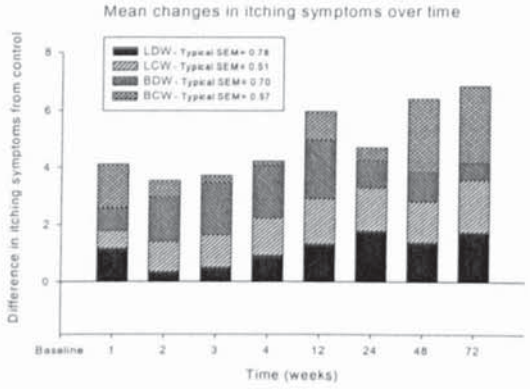
Subjective symptoms/complaints: Mean change in ocular symptoms over time.

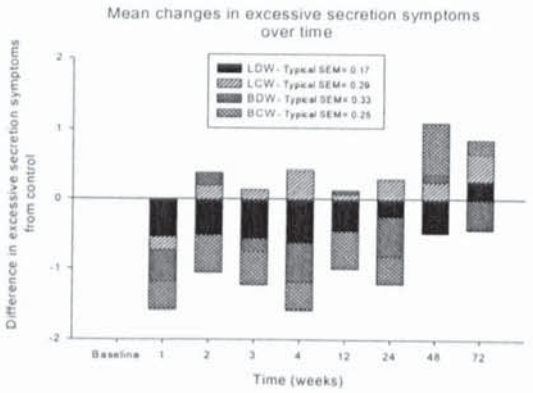


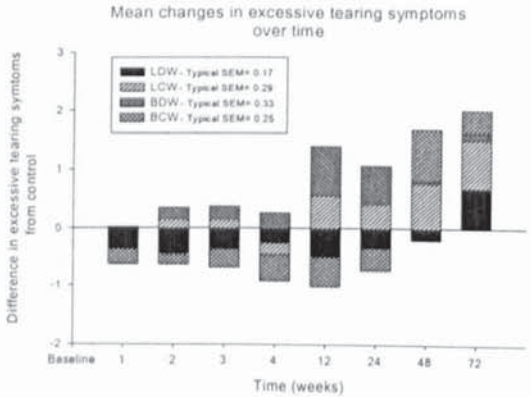




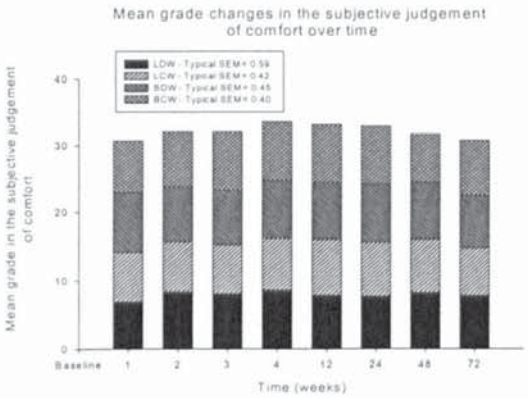


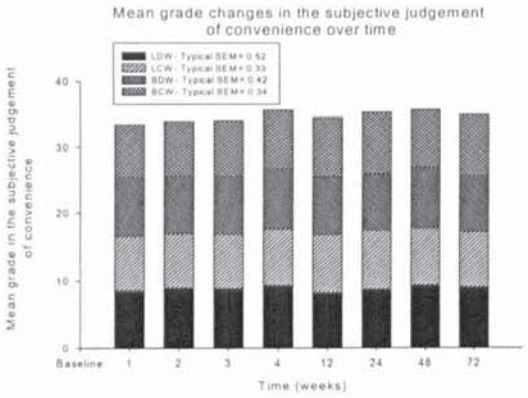


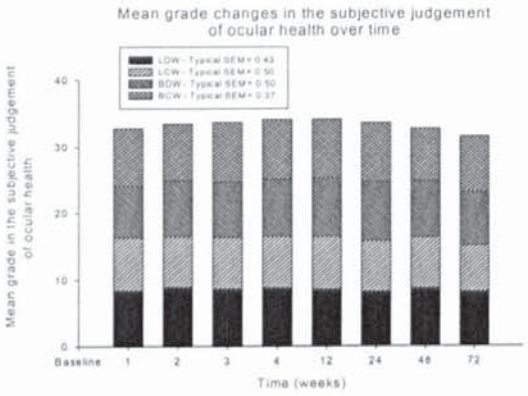


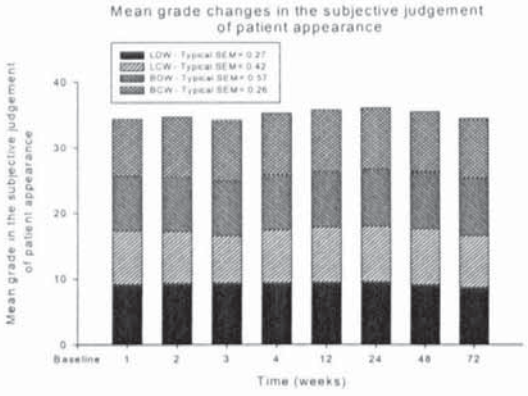


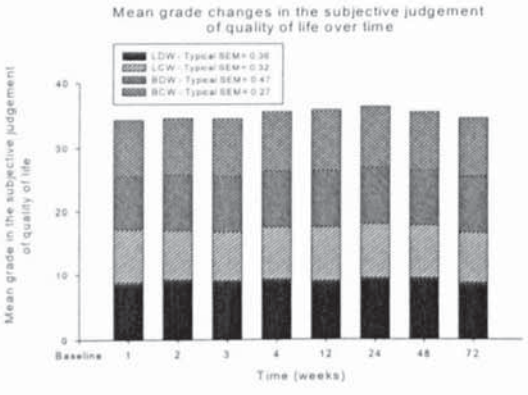
Subjective judgement: Mean grade changes in subjective judgements over time.











APPENDIX 6

SUBJECTIVE SYMPTOMS/COMPLAINTS AND JUDGEMENTS QUESTIONNAIRE

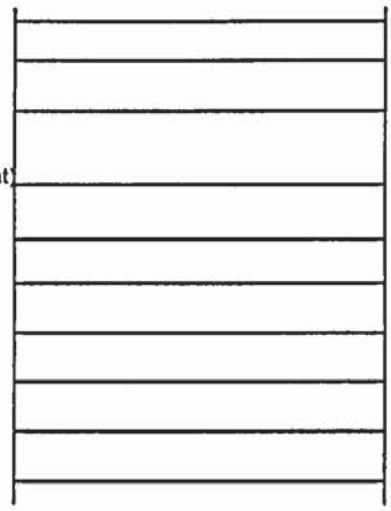
The following shows a duplicate of the visual analogue scales used to grade the subjects' subjective symptoms/complaints and judgements to contact lens wear.

PATIENTS' SUBJECTIVE JUDGMENT

Ref: **No. Visit:**

Do you suffer from any of the symptoms below? Please mark the position on the scale that most adequately describes the level at which you have experienced any of the following symptoms with contact lens wear. Parts of the scale are labelled but you are not restricted to only using those positions:

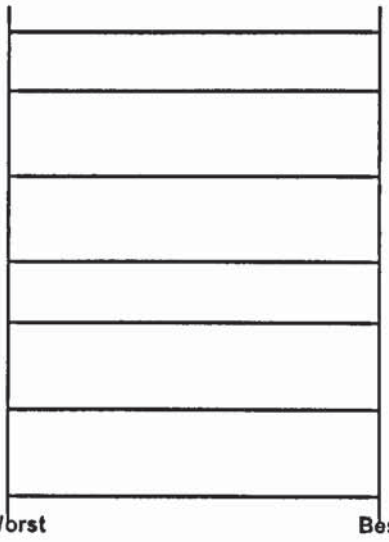
- Blurred vision
- Variable vision
- Glare
- Photophobia (i.e. sensitivity to light)
- Lens handling problems
- Dryness
- Burning
- Itching
- Excessive secretion
- Excessive tearing



No symptom **Symptom unbearable**

Please mark the position on the scale that most adequately describes the level at which you have experienced any of the following with contact lens wear. Parts of the scale are labelled but you are not restricted to only using those positions:

- Overall visual quality
- Comfort
- Convenience
- Eye health
- Eye appearance
- Effect of quality of life
- Overall satisfaction



Worst **Best**

SUPPORTING PUBLICATIONS

REFEREED PUBLICATIONS:

Santodomingo-Rubido, J., Gilmartin, B. and Wolffsohn, J. S. (2003). Drug-induced bilateral transient myopia with the sulphonamide sulfasalazine. *Ophthalmic and Physiological Optics* **23**, 567-570.

Santodomingo-Rubido, J., Mallen, E. A. H., Gilmartin, B. and Wolffsohn, J. S. (2002). Non-Invasive Measures of Ocular Biometry. *British Journal of Ophthalmology* **86**, 458-462.

REFEREED PUBLISHED ABSTRACTS FROM CONFERENCE PROCEEDINGS:

Santodomingo, J., Wolffsohn, J. S. and Gilmartin, B. (2003). Continuous and daily silicone hydrogel contact lens wear: ocular physiology and clinical tear film changes. Presented at the British Contact Lens Association Conference. June 2003, Brighton, UK.

Mann, A., **Santodomingo, J.**, Peach, H., Franklin, V., Wolffsohn, J and Tighe, B. (2003). Continuous and daily silicone hydrogel contact lens wear: biochemical markers. Poster presented in the British Contact Lens Association Conference. June 2003, Brighton, UK*.

Santodomingo-Rubido, J., Mallen, E. A. H., Gilmartin, B. and Wolffsohn, J. S. (2002). Non-Invasive Measures of Ocular Biometry. Poster presented at the 17th International Conference of Optics, Optometry and Contactology. March 2002, Madrid, Spain.

Santodomingo, J., Wolffsohn, J. S., Gilmartin, B., Mann, A., Peach, H. and Tighe, B. (2002). Tear Film Clinical and Biological Effects of Continuous Wear. *Contact Lens and Anterior Eye* **25**, 210. Poster presented at the British Contact Lens Association Conference. May 2002, Birmingham, UK.

Wolffsohn, J. S., **Santodomingo-Rubido, J.**, Mann, A., Peach, H., Franklin, V., Tighe, B. and Gilmartin, B. (2002). Tear film clinical and biological effects of continuous contact lens wear. *Journal for Research in Experimental and Clinical Ophthalmology* **34**, S1.

Wolffsohn, J. S., **Santodomingo, J.**, Mann, A., Peach, H., Franklin, V., Tighe, B., Gilmartin, B. (2002). Tear film clinical and biological effects of continuous contact lens wear. Poster presented at the European Association for Vision and Eye Research Conference. October 2002, Alicante, Spain.

*Awarded best poster in the British Contact Lens Association Conference. June 2003, Brighton, UK

CONTINUOUS AND DAILY SILICONE HYDROGEL CONTACT LENS WEAR: OCULAR PHYSIOLOGY AND CLINICAL TEAR FILM CHANGES

Santodomingo-Rubido, Jacinto
Wolffsohn, James S
Gilmartin, B

Background: Research on the use of silicone-hydrogel contact lenses for continuous wear has been extensive over the past few years. An ongoing study is examining both ocular physiology and clinical tear film changes in neophyte contact lens wearers wearing silicone-hydrogels contact lenses over time.
Methods: Fifty-one young non-contact lens wearing subjects were fitted with silicone-hydrogel lenses and randomly allocated between wearing one of the two types of materials currently on the market (Balafilcon A or Lotrafilcon A) on an either daily or continuous wear basis for 30 days. An additional control group of fourteen age-matched non-contact lenses wearers were examined. Objective grading of bulbar and palpebral hyperaemia and tear meniscus height and subjective measurement of non-invasive tear break-up time was carried out before and 1, 3, 6 and 12 months after fitting.
Results: Bulbar hyperaemia significantly increased in all the groups over time ($p<0.0001$). No statistically significant differences were found in palpebral hyperaemia between groups ($p>0.05$). However, some differences were found in palpebral hyperaemia over time ($p<0.05$). Both tear meniscus height and non-invasive break-up time did not significantly change over time or between groups ($p>0.05$).
Conclusions: Very few changes in terms of ocular physiology and tear film characteristics were found between materials and modalities of wear in neophyte contact lens wearers. However, these changes might be important indicators of the possible cumulative effects of long-term wear.

TEAR FILM CLINICAL AND BIOLOGICAL EFFECTS OF CONTINUOUS WEAR

Santodomingo, Jacinto
Wolffsohn, James
Mann, Aisling
Peach, Helena
Franklin, Valerie
Tighe, Brian

Research on the use of silicone-hydrogel contact lenses for continuous wear has been extensive over the past few years. The material is very different to conventional hydrogels and features, such as the high modulus of elasticity, the increased DK/t and the different wetting properties, of current generation silicone-hydrogel lenses result in significantly different tear tribology. This study is unique in examining both clinical and biological aspects of the tear film in neonate contact lens wearers wearing silicone-hydrogels contact lenses.

Sixty young non-contact lens wearing subjects were fitted with silicone-hydrogel lenses and randomly allocated between wearing one of the two types of materials currently on the market and on an either daily or continuous wear basis for 30 days. An additional group of 14 age-matched non-contact lenses wearers were examined. Non-invasive clinical measures of the tear film, such as tear break-up time, tear prism height and Tearscope lipid layer assessment, together with biological factors, such as lipids and kinin, were quantified by a masked researcher before and weekly after fitting for one month.

Subjects will be followed through at three, six, twelve and eighteen months. This poster presents the methodology behind the study and the results of the first month of tear film analysis.

CONTINUOUS AND DAILY SILICONE HYDROGEL CONTACT LENS WEAR: BIOCHEMICAL MARKERS

Mann, Aisling
Santodomingo-Rubido, Jacinto
Peach, Helena
Franklin, Valerie
Wolffsohn, James
Tighe, Brian

The aim of this study was to investigate the effects of silicone hydrogel lens wear on tear protein composition and deposition. It is well established that many immunoresponsive proteins are present in the tears. Therefore, it is reasonable to assume that these and other constituents of the tear film may provide predictive diagnostic markers which will provide knowledge about the aetiology of contact lens complications and highlight clinical contra-indications to contact lens wear. In addition, we observed the changes that occur on introducing the biomaterial to the human body for the first time (patients were neophytes with respect to ocular biomaterials) and the changes that occurred with time. This study combined clinically observed parameters with those taken under laboratory conditions and provided us with a unique and comprehensive perspective on patient tolerance and the biocompatibility of contact lenses over an eighteen month wear history. The differences between two formulations of silicone-hydrogel material (which vary in characteristics such as water content and surface coating) were examined and the differences between daily and extended wear (both during the day and night) were observed. Seven marker proteins were analysed: IgA, IgG, lactoferrin, albumin, IgE, kallikrein and kininogen, the latter two are members of the kinin family with potent pro-inflammatory function. The clinical parameters and results are presented in the accompanying poster; this poster presents the results obtained up until six months wear for all patients (n=47). The results presented compare the deposition profiles observed after 1 and 6 months wear and demonstrate distinct changes in concurrence with the clinical parameters performed. Although none of these proteins could be regarded as being specific to one particular disease or adverse response, our findings in this study would suggest that their assessment may prove useful in the quantification of distinct events in contact lens wear.