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REPRODUCIBILITY OF MEASUREMENTS OF PRE-CONTACT LENS TEAR FILM KINETICS UNDER NORMAL AND ADVERSE ENVIRONMENTAL CONDITIONS

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ABSTRACT

Objectives: To evaluate the reproducibility of tear film kinetics (TFK) measurements during the full interblink period in habitual wearers of delefilcon A daily disposable contact lenses under different environmental conditions.

Methods: Two independent studies were performed, one involving 90 eyes measurements in 49 subjects and the second involving 58 eyes measurements in 32 subjects, after 3 hours of conventional wear in normal environmental conditions (NEC) and an additional 3 hours of computer use under adverse environmental conditions (AEC), defined as 20% relative humidity (RH). Digital videos were obtained by non-invasive Tearscope illumination, followed by a parallel-group post-hoc comparative analysis by masked investigators of the videos obtained during the two studies. Parameters analyzed included non-invasive break-up time (NIBUT); dehydration speed (DS) between the initial break and the spontaneous blink, and minimum protected area (MPA) of the lens surface by the tear film.

Results: After 3 hours of wear in normal environmental conditions, the overall population (n=148) had a mean NIBUT of 7.1 ± 7.0 sec, a mean DS of 0.28 ± 0.66 mm^2/sec, and a mean MPA of 93.4 ± 16.6%. After an additional 3 hours in AEC, mean NIBUT was 8.4 ± 9.8 mm^2/sec, mean DS was 0.26 ± 0.75 mm^2/sec, and MPA was 95.2 ± 14.0%. The TFK characteristics in the two studies were similar for each environmental condition: after 3 hours of conventional wear, the mean [95% CI] differences between the two studies were −0.9 [−3.2, +1.4] sec for NIBUT, 0.00 [−0.22, +0.22] mm^2/s for DS, and 2.0 [−3.5, +7.4] % for MPA; after an additional 3 hours of wear in 20% RH, the mean [95% CI] differences between the two studies were −1.3 [−4.5, +1.9] sec for NIBUT, −0.03 [−0.28, +0.22] mm^2/s for DS and −0.3 [−4.9, +4.3] % for MPA.

Conclusions: This analysis showed that the measurement of pre-contact lens TFK carried out in two different studies involving habitual wearers of delefilcon A having worn their contact lenses for an initial 3 hours under NEC and a further 3 hours under low (20%) hygrometry (AEC) produced similar on-eye wettability,

including a long NIBUT, slow DS following the initial break, and wide MPA at the next blink. The results establish the reproducibility of the measurement of pre-contact lens TFK using the Tearscope; by quantifying the measurement variability, the data makes it possible to carry out precise sample size calculations in future studies involving pre-contact lens TFK measurements to quantify on-eye wettability under both normal and adverse environmental low (20% RH) hygrometric conditions.

Keywords*: Tear film kinetics. repeatability, reproducibility, delefilcon A, adverse environmental conditions (AEC)*

INTRODUCTION

Tear film break-up time, or the interval between a complete blink and the appearance of the first break in the tear film, is considered a clinical marker of tear film stability.[1] Various non-invasive techniques have been used to measure tear film break-up time in contact lens wearers, including interferometry, the Tearscope, and videokeratoscopy.[1] The drawback of limiting the assessment of tear film stability during the interblink period when measuring non-invasive break-up time (NIBUT) is that it only provides information of wettability on that period. These assessments cannot determine the nature and severity of the break from that time until the next spontaneous blink. Knowing the status of the contact lens front surface at the time of the blink is essential, as it determines the influence of the friction of the eyelid that occurs during the blink, a factor associated with contact lens comfort.[2,3] The advent of high-resolution video recording has led to capturing the pre-contact lens tear film illuminated by the Tearscope over the full interblink period and quantifying the tear film characteristics over the whole period via post hoc analysis.[3] A similar approach has been implemented via the analysis of distortion of videokeratoscope concentric rings to quantify the tear film changes during the interblink period.[1]

A key characteristic of any measurement technique is its validity. TFOS DEWS II Tear Film sub-committee acknowledged this to be an issue when measuring tear film stability.[4] In summarizing issues regarding the measurement of the tear film break-up time with fluorescein the committee stated that it has an "inherent variability." Even when considering the non-invasive measurement of the tear film break-up time, it stated that the techniques had "reasonable agreement that they operate with a coefficient of variation of around 10%".

The committee quoted the "coefficient of variation" as an indicator of NIBUT measurement validity. The coefficient of variation is obtained by dividing the population standard deviation by the population mean, which indicates the between-people variability within the population but not the validity of the measurement. Basic clinical metrology principles identify repeatability and reproducibility as the key measurements validating parameters.[5] Repeatability refers to the variation in repeated measurements obtained over a short time under identical conditions, while reproducibility refers to measurements made under different conditions, such as different operators, conducted over an extended time. Finally, repeatability is often reported as the standard deviation of the difference between the two sets of measurements in clinical studies. This approach overestimates by approximately a factor of two repeatability, as repeatability standard reporting in metrology is 95% confidence interval.

To test the reproducibility of the method, we needed a stable system. We, therefore, selected delefilcon A (DAILIES TOTAL1, Alcon Laboratories, Fort Worth, TX) silicone hydrogel contact lenses, which have highly repeatable on-eye performance. Delefilcon A is an advanced generation silicone hydrogel polymer formulated with phosphatidylcholine,[6,7] a component of natural tears that plays a key role in the maintenance of the tear film.[8] These lenses, first made commercially available in 2013, contain 33% water distributed in a core-to-surface water gradient over a 1-2 micron transition zone ranging from 33% at the core to ~80% at the front and back surfaces.[6,7]

The objective of this study was to evaluate the reproducibility of tear film kinetics (TFK) measurements during the full interblink period in habitual wearers

of delefilcon A daily disposable contact lenses under different environmental conditions.

METHODS

Study population

The intention to treat the population of this study consisted of habitual wearers of delefilcon A soft contact lenses. Study 1 involved 90 eyes with valid measurements in 49 subjects, and Study 2 involved 58 eyes with valid measurements in 32 subjects. Thus, a total of 81 subjects were included in this study. All subjects were aged ≥18 years and had worn delefilcon A contact lenses for at least 2 months. Subjects were required to have vision correctable to 6/7.5 or 0.1 logMAR or better in each eye at a distance with the study contact lenses at the time of screening and to be willing to wear their contact lenses every day or at least for a minimum of 5 days per week for 6 hours per day during the study period. Participants had to discontinue artificial tears and rewetting drops on the days of study visits. Subjects with any ocular anterior segment infection, inflammation, abnormality, or disease were excluded, or who used any systemic or ocular medications for which contact lens wear could be contraindicated. Subjects could not have participated in any other clinical study within 30 days before enrollment. The Ethics Committees approved the protocols of the two separate studies under the UK IRAS centralized ethics committee system, and all subjects provided written informed consent prior to testing.

Study design

The current analysis is a post-hoc parallel-group comparison of the measurements of pre-contact lens TFK obtained in two separate clinical studies, carried out approximately one year apart, following the same protocol and measurement conditions to determine measurement reproducibility.

The clinical protocol for the two studies required each subject to have worn delefilcon A contact lenses for 10 ± 3 days before the day of the study visit. After each wearing period, contact lens wettability was assessed twice using the Tearscope (Keeler, Windsor, UK), once after three hours of wear under normal environmental conditions (NEC) and again after a further three hours of wear while using a computer in a setting of 20% relative humidity (RH), representing an AEC or dry environment typical of an air-conditioned office.

Maintenance of 20% RH

The 20% RH was maintained using an environmental ocular goggle device designed and built by OCULAR TECHNOLOGY GROUP-*International* using modified welding googles and a portable instrument that can maintain relative humidity between 0% and 80%. The instrument comprises a portable attaché case containing the battery-operated system that produces constant airflow at the required speed and humidity and a pair of goggles that creates the constant controlled environment around the eyes.

Tearscope analysis

TFK analysis was based on digital videos of the tear film over the total interblink period for each subject. The tear film was visualized using the Tearscope diffuse lighting system attached to a Topcon DC4 slit lamp (Topcon, Newbury, UK) set at x25 magnification; recordings were captured with the Topcon DV3 digital camera.[1] The video recordings were masked and randomized before analysis by trained personnel. The parameters analyzed included NIBUT, defined as the time elapsed (seconds) between eye opening after a blink and the appearance of the first dark spot (break in the tear film) within the tear film (**Figure 1A)**; minimum protected area (MPA), defined as the percent (%) of the lens surface covered by the tear film that occurs immediately before the next blink (**Figure 1B**); and dehydration speed (DS), defined as the speed of increase of uncovered area of the lens after the first break in the tear film (i.e., the area in **Figure 1B** minus the area in **Figure 1A**) divided by time and reported as mm^2/sec. NIBUT was measured for three successive interblink periods, and the TFK analyzed for the interblink period corresponding to the median NIBUT.

Statistical analyses

Data were analyzed using SAS 9.2 statistical software (SAS Institute, Cary, NC). Two data points were recorded; after an initial 3 hours of wear under normal environmental conditions and after a further

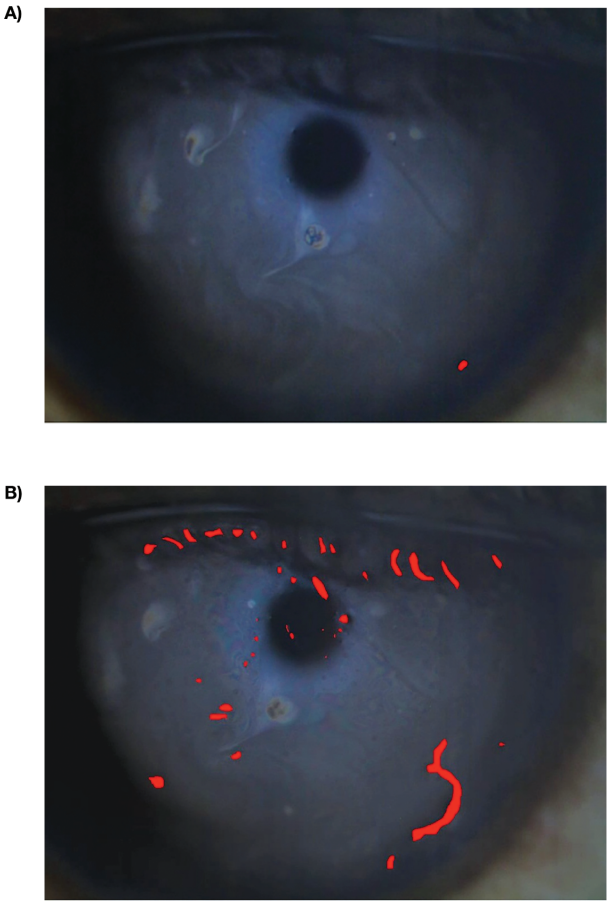

Figure 1. Examples of exposed areas, as assessed by the Tearscope, (A) at first break and (B) immediately before the blink.

3 hours of wear and exposure to 20% RH. Descriptive statistics for categorical data are reported as the number of subjects (n) and the frequency (%), and for continuous data as mean, standard deviation (SD), median, minimum, maximum, and 95% confidence interval (CI). Measurement reproducibility, as per accepted metrology standards, is reported by the 95% confidence level of the mean difference.

RESULTS

Subject disposition

The study population consisted of 81 wearers of delefilcon A lenses from two studies, 49 from Study 1 and 32 from Study 2. The study's overall population demographic characteristics are shown in **Table 1**, and baseline ocular characteristics are shown in **Table 2**.

Overall the subjects included 35% men (33% Study 1, 38% Study 2) and 65% women (67% Study 1, 63% Study 2), and the mean age was 34.8±11.8 years (35.1±13.1 Study 1 and 34.3±9.5 Study 2), range 19 to 74 years. Baseline refractive errors were -3.76 ± 1.87D spherical (–3.55 ± 1.88 Study 1, −4.07 ± 1.85 Study 2), cylinder −0.36 ± 0.26DC (–0.38 ± 0.26 Study 1, −0.33 ± 0.27 Study 2) and best corrected decimal Snellen visual acuity 1.23 ± 0.21 (1.23 ± 0.21 Study 1, 1.23 ± 0.22 Study 2). There were no significant differences in mean baseline characteristics between the habitual wearers of delefilcon A contact lenses in the two studies (p>0.05).

TFK characteristics in normal vs. adverse environments: Studies 1 and 2 Combined

NIBUT

After wearing their habitual delefilcon A lenses for 10 ± 3 days, the mean ± SD NIBUT after the initial 3 hours of conventional wear on the day of the visit was 7.1 ± 7.0 seconds. Following exposure to 20% RH for an additional 3 hours (total, 6 hours of wear), the mean ± SD NIBUT was 8.4 ± 9.8 seconds (**Figure 2**). Thus, the mean [95% CI] difference for

Table 1. Demographic Characteristics of Wearers of Delefilcon A Lenses Intention-To-Treat Population

	Study 1	Study 2	Total
Number	49	32	81
Age, yr			
Mean ± SD	35.1 ± 13.14	34.3 ± 9.49	34.8±11.84
Median	32.0	32.0	32.0
Range	19–74	19–56	19–74
Sex, n (%)			
Male	16 (32.7)	12 (37.5)	28 (34.6)
Female	33 (67.3)	20 (62.5)	53 (65.4)

Table 2. Baseline Ocular Characteristics of Wearers of Delefilcon A Lenses Intention-To-Treat Population

	Study 1	Study 2	Total
Sphere (D)			
Number of eyes	98	64	162
Mean ± SD	−3.55 ± 1.88	−4.07 ± 1.85	−3.76 ± 1.87
Median (range)	−3.25 (−9.25 to −0.25)	−3.75 (−8.50 to −1.00)	−3.5 (−9.25 to −0.25)
Cylinder (D)			
Number of eyes	98	64	162
Mean ± SD	−0.38 ± 0.26	−0.33 ± 0.27	−0.36 ± 0.26
Median (range)	−0.38 (−0.75 to 0.00)	−0.25 (−0.75 to 0.00)	−0.32 (−0.75 to 0.00)
BCVA (Decimal) (OD & OS)			
Number of eyes	98	64	162
Mean ± SD	1.23 ± 0.21	1.23 ± 0.22	1.23 ± 0.21
Median (range)	1.25 (1.0 to 1.6)	1.25 (0.9 to 1.6)	1.25 (1.0 to 1.6)

NIBUT between the two environments was −1.3 [−4.5, +1.9] seconds.

Dehydration speed (DS)

Mean ± SD DS following the initial 3 hours of conventional delefilcon A lens wear was 0.28 ± 0.66 mm^2/seconds. After exposure to 20% RH for an additional 3 hours (6 hours of wear), the mean ± SD DS was 0.26 ± 0.75 mm^2/seconds (**Figure 3**). The mean [95% CI] difference for DS between the two environments was −0.03 [−0.28, 0.22] mm^2/seconds.

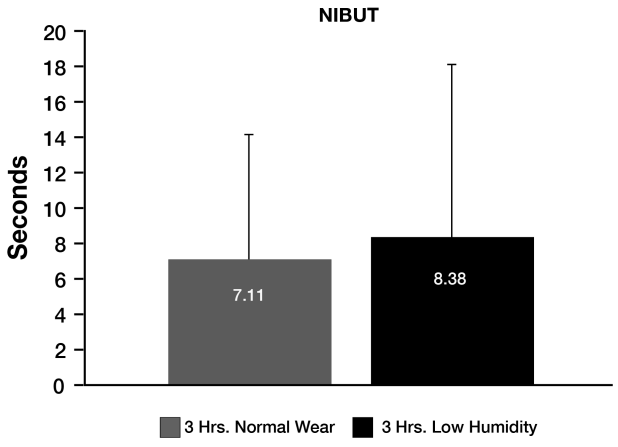

Figure 2. Mean ± SD non-invasive break-up time (NIBUT) for habitual delefilcon A wearers after 3 hours of normal wear and 3 hours of exposure to 20% relative humidity.

MInimum protected area (MPA)

After wearing their habitual delefilcon A lenses for the initial 3 hours, the mean ± SD % MPA was 93.4 ± 16.6%; after 3 hours at 20% RH (total, 6 hours of wear), the mean ± SD % MPA was 95.2 ± 14.0% (**Figure 4**). The mean [95% CI] difference for MPA between the two environments was −0.32 [−4.94 to 4.31] %.

TFK characteristics after the initial 3 hours of delefilcon A lens wear were indicative of good on-eye wettability, as evidenced by long pre-contact lens NIBUT, slow dehydration after the initial break, and very high tear film coverage at the time of spontaneous blink. Further, TFK characteristics were unchanged after an

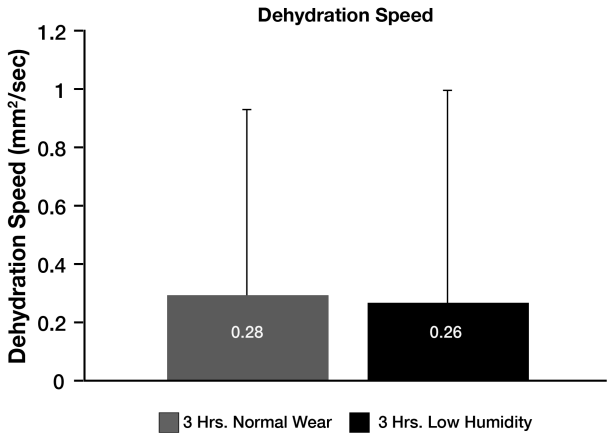

Figure 3. Mean ± SD dehydration speed for habitual delefilcon A wearers after 3 hours of normal wear and 3 hours of exposure to 20% relative humidity.

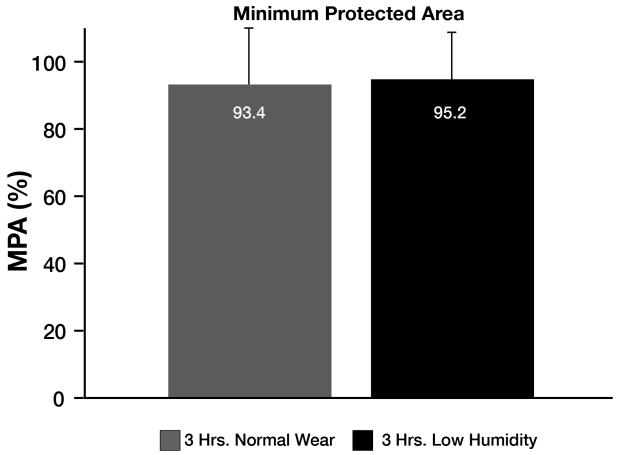

Figure 4. Mean ± SD percent minimum protected area (MPA) for habitual delefilcon A wearers after 3 hours of normal wear and 3 hours of exposure to 20% relative humidity.

additional 3 hours of intensive computer work in a low-humidity environment (i.e., AEC), indicating that good on-eye wettability was maintained under low-humidity conditions while performing computer activities.

TFK Reproducibility in Study 1 vs. Study 2

Normal environment: 3 hours lens wear

After 3 hours of conventional wear, the mean [95% CI] differences between the two studies were −0.9 [-3.2, +1.4] seconds for NIBUT, 0.00 [−0.22, +0.22] mm^2/s for DS, and 2.0 [−3.5, +7.4] % for MPA (**Figure 5)**. Hence, TFK characteristics after the first 3 hours of wear were similar for the two studies, as demonstrated by the small mean differences recorded and two-sided 95% CI for all the parameters.

Adverse environment: 3 hours in 20% RH

After an additional 3 hours of wear in reduced RH of 20%, the mean [95% CI] differences between the two studies were −1.3 [-4.5, +1.9] seconds for NIBUT, −0.03 [−0.28, +0.22] mm^2/s for DS and −0.3 [−4.9, +4.3] % for MPA (**Figure 6**). Therefore, TFK characteristics after 3 hours of wear of this lens material while carrying out computer activities in a low-humidity environment (AEC) remained similar for the two studies as demonstrated by the small mean differences recorded and two-sided 95% CI for all parameters.

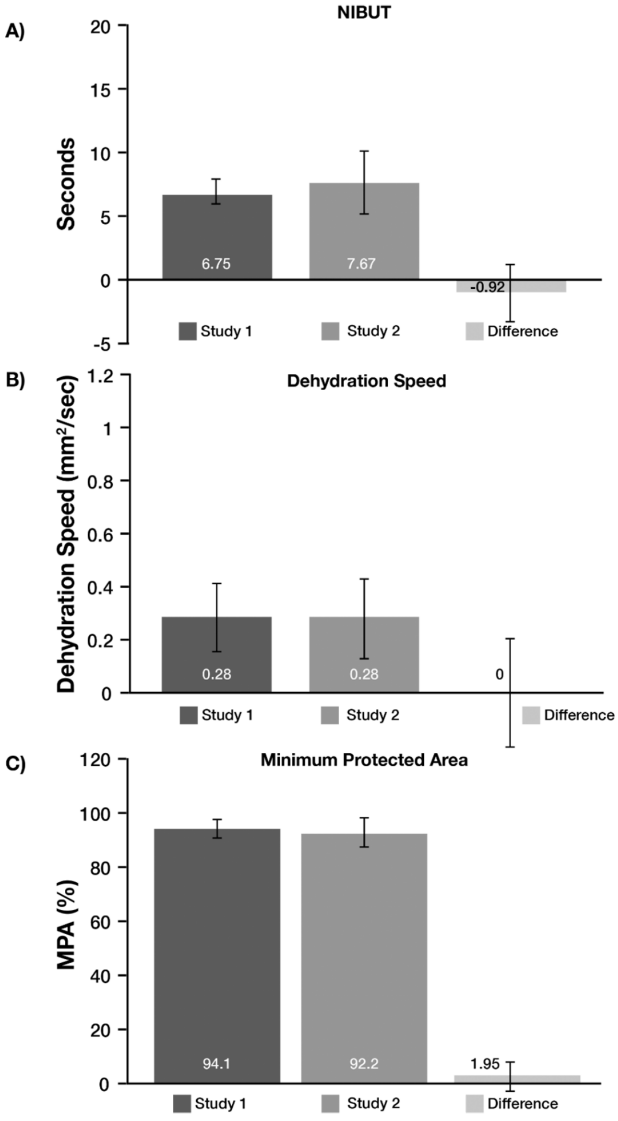

Figure 5. Mean [95% CI] (A) non-invasive break-up time (NIBUT), (B) dehydration speed, and (C) minimum protected area in a normal environment for Study 1 and Study 2 and the difference between Studies 1 and 2

DISCUSSION

The main objective of the analysis was to evaluate the reproducibility of TFK measurements during the entire interblink period in habitual wearers of delefilcon A daily disposable contact lenses under different environmental conditions. The data obtained showed that these measurements were highly reproducible, with

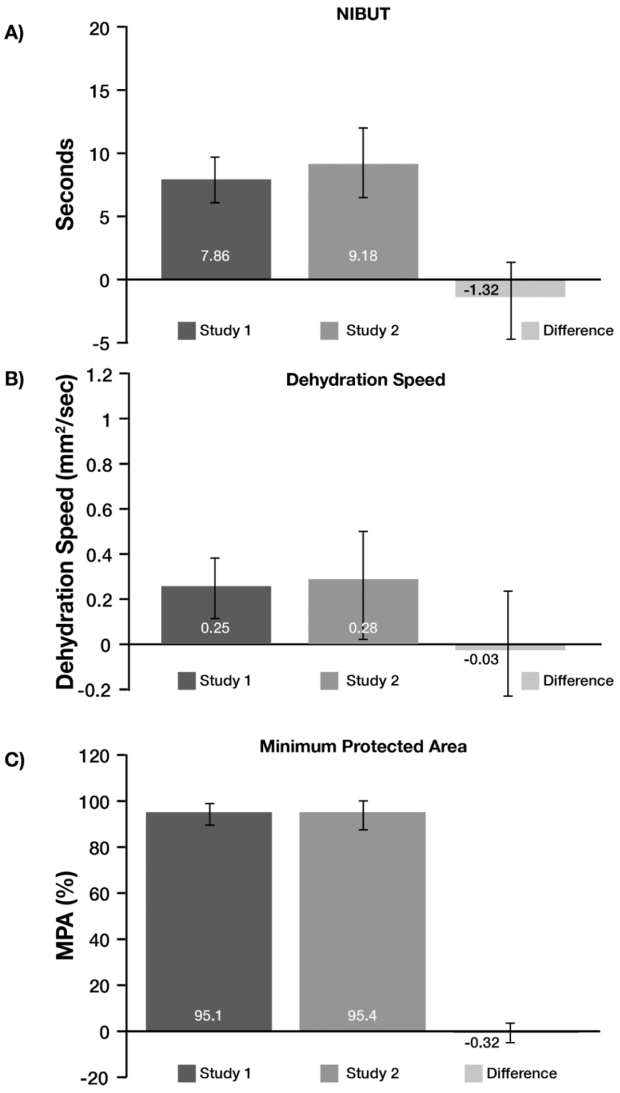

Figure 6. Mean [95% CI] (A) non-invasive break-up time (NIBUT), (B) dehydration speed, and (C) minimum protected area (MPA) at 20% relative humidity for Study 1 and Study 2 and the difference between Studies 1 and 2.

mean [95% CI] differences between the two studies of −0.9 [−3.2, +1.4] seconds for NIBUT, 0.00 [−0.22, +0.22] mm^2/s for DS, and 2.0 [−3.5, +7.4] % for MPA. Moreover, the Tearscope video recording method was reliable for quantifying pre-contact lens TFK and could therefore be used to assess contact lens on-eye wettability in clinical studies. These data, therefore, meet the objective of this study and support the hypothesis tested.

Analysis of TFK parameters in contact lens wearers allows the quantification of tear film dynamics over the entire interblink period.[3] These TFK parameters included NIBUT coverage of the contact lens surface by the tear film; lens surface coverage by tears at the time of the blink (MPA), when the eyelid interacts with the contact lens; and the speed at which the tear film destabilizes once the blink has occurred (DS). This is indicative of surface resistance to dehydration in vivo and analogous to measuring the receding angle of the contact lens surface in vivo. The studies utilized this methodology to evaluate contact lens wearers under normal environmental conditions and following prolonged and intensive computer use under the controlled low-humidity conditions encountered in air-conditioned offices.[9,10]

The large body of data collected approximately one year apart in two studies of similar protocols enables conclusions as to on-eye wettability of delefilcon A contact lenses. The overall data showed that on-eye wettability, as determined by detailed TFK analysis, was normal after the first 3 hours of wear and remained normal after an additional 3 hours of wear under low-humidity conditions while carrying out controlled, intensive computer tasks. These findings support the recommendations that delefilcon A contact lenses be prescribed for subjects involved with intensive device use and subjects exposed to adverse hygrometric environments for sustained periods. Additionally, this analysis also showed that delefilcon A TFK were normal and consistent across studies, indicating that good on-eye wettability was a constant for the material, confirming results of previous studies involving delefilcon A.[11-14]

To our knowledge, this report is the first to determine that measurements of pre-contact lens tear film characteristics were reproducible. First, these characteristics had been identified in the TFOS DEWS II Tear Film workshop report as essential parameters to quantify to judge the validity of a measurement method. Second, this report comparing two separate clinical studies established that the measurement of pre-contact lens TFK using the Tearscope is reproducible and, therefore, valid and of clinical application. Third, the measurements obtained to determine the standard deviation of the difference for this methodology

provides the information required to calculate sample sizes for future studies using this same technique. Indeed, the comparison of NIBUT, DS, and MPA obtained in the two separate studies showed their similarity, confirming the reliability of this technique.

CONCLUSION

In conclusion, the TFK measurements produced repeatable results in two clinical studies characterizing contact lens on-eye wettability under normal and low-humidity conditions. The results reported enable precise sample size determination in future studies using the Tearscope method to measure pre-contact lens tear film stability. Delefilcon A contact lenses performed consistently in two individual clinical studies carried out approximately one year apart. Delefilcon A TFK was unchanged under challenging indoor environmental conditions while performing intensive computer visual tasks. Delefilcon A contact lenses are suitable for contact lens wearers involved in intensive usage of computers and digital devices.

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