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Novel *in vitro* method to determine *pre-lens* tear break-up time of hydrogel and silicone hydrogel contact lenses

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ABSTRACT

Purpose: To develop an *in vitro* model to determine pre-lens non-invasive break-up time (NIBUT) and to subsequently use this method to compare the NIBUT over contemporary daily disposable (DD) contact lenses (CL).
Methods: Three silicone hydrogel (SH) and two conventional hydrogel (CH) DD CLs were incubated in an artificial tear solution (ATS). A model blink cell (MBC) was utilised to mimic intermittent air exposure. CLs were repeatedly submerged for 3 seconds (s) and exposed to air for 10 s over periods of 2, 6, 12, and 16 hours (h). NIBUTs (n = 4) were determined out of the blister pack (T_0) and at the end of each incubation period.
Results: Overall, nesofilcon A showed the longest NIBUTs ($p < 0.001$). At T_0, CHs revealed significantly longer NIBUTs ($p \leq 0.001$) than SHs. After 2 h, nesofilcon A showed the longest NIBUT, however, this was only statistically significant compared with delefilcon A ($p \leq 0.001$). After 6 h, nesofilcon A NIBUT was significantly longer than all other CLs ($p \leq 0.001$). Etafilcon A showed a significantly longer NIBUT ($p \leq 0.001$) after 12 h and delefilcon A had the longest NIBUT ($p \leq 0.001$) after 16 h. Statistically significant ($p \leq 0.05$) changes of NIBUT within the lens materials varied between time points. After 16 h, all CLs showed significant reductions in NIBUTs ($p \leq 0.001$) in comparison to T_0.
Conclusion: NIBUT values reduced gradually over time and varying levels of deposition impacted measured pre-lens NIBUTs. While NIBUT of CH materials are longer immediately out of the blister pack, after tear film exposure, the NIBUTs obtained using this methodology became very similar.

1. Introduction

Contact lenses (CL) are a very convenient and common device to correct vision and are available in a wide variety of materials [1,2]. Most wearers use soft lenses, which are typically replaced after time periods between 1 day and 4 weeks [3]. Although CLs are effective at correcting vision, they remain plagued by issues associated with end of day dryness and discomfort [4–7], which may lead to cessation of CL wear or “contact lens dropout” [4,6,8–10].

One way to improve the performance of CLs (and potentially reduce dropouts) is to increase the replacement frequency of CLs [11]. The ultimate for this concept is to replace lenses every day, and daily disposable (DD) CLs were introduced in the mid-1990′s [12–15] and continue to increase in popularity [16–18]. Their use has been associated with a decrease in CL-related inflammation [19] and microbial keratitis [20], improved overall comfort and visual acuity [21], and reduced tear film deposits [14,21–24].

The pre-corneal tear film coats the ocular surface to prevent dehydration, nourish the cornea, and provide a smooth layer for clear vision [25–27]. To carry out all of these functions, the integrity and stability of the tear film is important and if its stability over the lens surface is poor, then CL-related complications may arise [28–31]. The tear film is a complex structure composed of a wide variety of mucins, proteins, lipids, and salts that are organised in a certain order [7]. When CLs are placed onto the ocular surface they disrupt the tear film by splitting it into a pre- and post-lens layer [7] and by accumulating proteins [32,33] and lipids [11,34–37]. These processes result in decreased tear film stability compared with that seen without a lens in place [27,30,31].

Tear film stability is commonly measured through the determination of the tear break-up time (TBUT), which measures the thinning/instability of the tear film layer [27,38] and can be tested invasively or non-invasively (NIBUT) [27,39]. To measure the stability invasively, a small amount of sodium fluorescein is added to the tear film on the ocular surface to permit its visualization. [38] However, this method changes the physiological integrity of tears and leads to a reduced TBUT compared with non-invasive measures [40–42]. By projecting various grids or patterns onto the tear film overlying the cornea, it is possible to measure TBUT non-invasively [43,44]. Most methods to determine

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NIBUT utilise a topographer that projects uniform placido ring mires onto the ocular surface and any changes in the structure of these mires depict a break-up of the tear film. [27,43,44] Average BUTs in normal eyes are often > 20 seconds (s), where < 10 s is considered abnormal and ≤ 5 s is often associated with dry eye symptoms, [40,45], whereas during CL wear BUTs generally lie between 3–10 s [7,27,46–51]. Generally, TBUT and NIBUT measurements are carried out *in vivo* to determine the performance of a CL and its effect on tear film stability. However, the two methods are not limited to *in-vivo* use and could potentially help to predict the on-eye performance of CLs, when applied *in-vitro*. This would help during the development of novel CL materials or surface coatings to aid in wetting and could be a valuable addition to the early screening of surfaces, providing faster pass/fail criteria prior to more expensive and time-consuming in-eye evaluation.

To-date, very little data exist on the NIBUTs associated with DD lens materials. Given their increasing popularity this study sought to develop an *in vitro* model to determine *pre-lens* NIBUTs and to subsequently use this method to compare NIBUTs between various contemporary DD CLs.

2. Material & methods

2.1. Contact lenses and pre-treatment

Three silicone hydrogel (SH) lenses [delefilcon A (Alcon), somofilcon A (CooperVision), narafilcon A (Johnson & Johnson)], and two commercially available conventional hydrogel (CH) DD CLs [etafilcon A (Johnson & Johnson), nesofilcon A (Bausch + Lomb)] were evaluated in this study. All lenses had a dioptric power of −3.00 and base curve of 8.5 or 8.6 mm and were obtained from the manufacturer in the original commercial packaging.

Table 1 details the properties of the CLs examined.

2.2. Artificial tear solution

The composition of the artificial tear solution (ATS) used has been previously reported [52]. In short, the solution contains various lipids (oleic acid methyl ester, cholesterol, triolein, phosphatidylcholine, cholesteryl oleate, and oleic acid), various salts, urea, glucose, proteins (lysozyme and hen egg albumin), and mucin, the concentrations of which were based on those in normal human tears [52].

2.3. Model blink cell

A model blink cell (MBC) was utilised to incubate the CLs in the ATS. The MBC used in this study is an updated version to that which has been previously described, [53] which enabled the incubation of up to 48 CLs at a time. Specifically, it is composed of a polytetrafluoroethylene (PTFE/Teflon™) trough that is divided into 4 chambers that can each be filled with 250 mL of the ATS test solution. Each CL is placed on a Teflon button (Fig. 1A) that is positioned on a Teflon plate, which is attached to a motor that raises and lowers the plate in and out of the test solution. In order to further secure the CLs and prevent them from floating off the Teflon buttons, each lens is held in place with a clip. A gap of 100 µm between the button and clip-on allows the CLs to float freely and prevents the mounted CLs from getting damaged. Furthermore, the mechanics are set up within an environmental chamber (Fig. 1B) that enables the regulation of humidity and temperature during lens incubation.

2.4. Topographer

To measure the NIBUTs, a corneal topographer (CA-100, Topcon Canada) was utilised to illuminate the upper CL surfaces and project a uniform Placido ring structure onto them (Figs. 2 & 3). An additional video camera (Canon-XA10; Fig. 3) was used to capture the changes of the Placido ring appearance by recording the LCD on the topographer.

2.5. Experimental outline

The experiment was conducted one lens type at a time. At the start of the experiment, four lenses of each type were taken out of the blister pack, placed onto a Teflon button in the MBC, and immersed into the ATS once before the initial (T_0) NIBUT was measured. Thereafter, the CLs were submerged in the ATS for 3 s and exposed to air for 10 s, to mimic intermittent air exposure. The environment in the MBC chamber was set at a humidity of 50 ± 5% and a temperature of 34 ± 4 °C. After 2, 6, 12, and 16 h of incubation each lens was raised into focus of the topographer and the BUTs were determined. After each measurement was taken, the lenses continued to cycle in and out of the ATS until the 16 h time-point.

2.6. Data analysis

NIBUTs were determined by analysing the recorded videos manually by comparing the video sequences frame by frame until a

Table 1
Properties of the contact lenses used in the study.

	DAILIES TOTAL1®	clariti™ 1day	1-DAY ACUVUE® TruEye®	1-DAY ACUVUE MOIST	Biotrue 1Day
United States adopted name (USAN)	delefilcon A	somofilcon A	narafilcon A	etafilcon A	nesolfilcon A
Manufacturer	Alcon	CooperVision	Johnson & Johnson	Johnson & Johnson	Bausch + Lomb
Water content (%)	33% (surface > 80%)	56%	46%	58%	78%
FDA group	V	V	V	IV	II
Centre thickness (mm)	0.09	0.07	0.09	0.08	0.05
Oxygen permeability ($x10^{-11}$)	140	60	100	28	42
Oxygen transmissibility ($x10^{-9}$)	156	86	118	25.5	42
Surface treatment	None. Higher water content at the surface than in the polymer bulk	None	Internal wetting agent	None	None
Published contents of blister pack solution	Polymeric wetting agents	Buffered saline	MC	PVP	Borate buffered saline
Principal monomers	Not disclosed	Not disclosed	MPMDSM, DMA, HEMA, siloxane macromer, TEGDMA, PVP	HEMA, PVP, MA	HEMA, NVP

HEMA, hydroxyethyl methacrylate; MA, methacrylic acid; PVP, polyvinyl pyrrolidone; NVP, N-vinylpyrrolidone; DMA, N,*N*-dimethylacrylamide; HEMA, hydroxyethyl methacrylate; MPDMS, monofuncional polydimethylsiloxane; PVP, polyvinyl pyrrolidone; TEGDMA, tetraethyleneglycol dimethacrylate; MC, methyl cellulose.

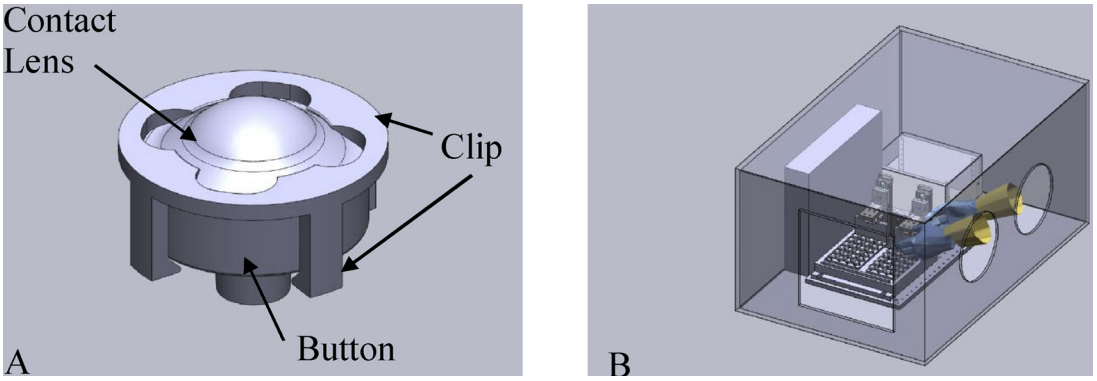

Fig. 1. Teflon button for holding lenses (A) and Model Blink cell controlled environmental chamber (B).

significant change in the structure of the mires occurred. To achieve this, the innermost 6 to 8 concentric rings reflected from a CL were analysed, compared the initial Placido ring structure, once it came out of solution, and measured the time until the first distortion (gaps or distortions as shown in Fig. 4B) of the Placido mires occurred (n = 4; Fig. 4). Artefacts and distortions (due to lens deposition and/or dehydration) on the lens surfaces were not considered as a break-up, if they were already visible when the lens came out of solution. The observer who recorded the first disruption in the mires was masked as to the lens material and time of ATS exposure during this process.

After assessing the NIBUTs of every lens material, data analysis was conducted using repeated measures-analysis of variance (RM-ANOVA) and univariate analysis to test for any significance within each time-point and lens material, using SPSS Statistics 23. An alpha level of $p < 0.05$ was considered significant. Individual differences were analysed using a Tukey post-hoc analysis.

3. Results

The results of the study are reported in Tables 2 and 3 and Fig. 5. Table 2 illustrates that the NIBUT measurements depended significantly on the duration of incubation, the type of CL material, as well as the interaction between these factors ($p < 0.001$). When a general comparison was made between all tested CL types (all time-points pooled), CH lens materials showed significantly greater NIBUTs than SH lenses ($p \leq 0.001$), but no significant difference between the two CH CLs themselves ($p = 0.276$) or between the SH lens materials ($p \geq 0.912$). Nesofilcon A had the longest average NIBUT of all tested CLs, with this difference being significant ($p \leq 0.001$) over the SH materials only.

As shown in Table 3, at T_0, the two CH lenses revealed significantly longer NIBUTs ($p \leq 0.001$) than all three SH materials, but no significant difference was found between the two CH lens materials ($p = 0.262$) or the SHs ($p \geq 0.984$). After 2 h of lens incubation, delefilcon A showed the shortest NIBUT ($p \leq 0.037$) in comparison to all other CLs and etafilcon A presented the longest NIBUT; however, this was only statistically significant compared with delefilcon A ($p \leq 0.001$). After 6 h, the NIBUT of etafilcon A was significantly longer than all other examined CLs ($p \leq 0.001$). After 12 h of incubation, the CH nesofilcon A showed a statistically superior NIBUT over all other tested CLs ($p \leq 0.001$). With a NIBUT of 3.6 ± 0.3 s, delefilcon A had the longest break-up time after 16 h of incubation and this difference was significant ($p \leq 0.001$).

Statistically significant ($p \leq 0.05$) changes of NIBUT within the lens materials varied between time-points. Overall, NIBUT decreased significantly ($p \leq 0.002$) between T_0 and 2 h for all CLs, except for somofilcon A ($p = 0.728$) - which showed no relevant change - and narafilcon B, which marginally increased. NIBUT between T_0 and 6, 12, and 16 h was significantly lower for all CLs ($p \leq 0.001$). For delefilcon A, the reduction in NIBUTs was statistically significant ($p \leq 0.001$) among most of the time-points, except between 2 h – 6 h and 12 h – 16 h ($p = 0.638$ and $p = 0.299$, respectively). For somofilcon A lenses, statistically significant difference in NIBUT decrease were found amongst all time-points ($p \leq 0.002$), except between T_0 – 2 h and 12 h – 16 h ($p = 0.782$ and $p = 0.328$, respectively). As mentioned above, narafilcon B revealed an increase of NIBUT after 2h of incubation, whereas, all other time-points showed a continuous decrease in NIBUT. All differences between the time-points within narafilcon B were statistically significant ($p \leq 0.001$). For etafilcon A, statistically significant differences ($p \leq 0.045$) in NIBUT were found between all time-points. Nesofilcon A showed significant reduction differences ($p \leq 0.001$) amongst some time-points, except between 2 h – 6 h and 12 h – 16 h.

4. Discussion

The purpose of this study was to develop an *in vitro* model which could be used to determine pre-lens NIBUT values and to subsequently use this concept to compare the NIBUT of contemporary CH and SH DD materials over a period of 16 h. The *in vitro* model used a methodology in which lenses were incubated in an ATS that mimicked the composition of the tear film and during their incubation were intermittently exposed to the air, in an attempt to better mimic *in vivo* CL wear [53]. In

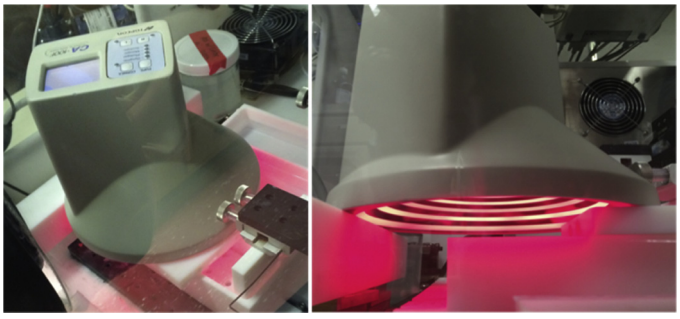

Fig. 2. Experimental set up of the topographer over the MBC.

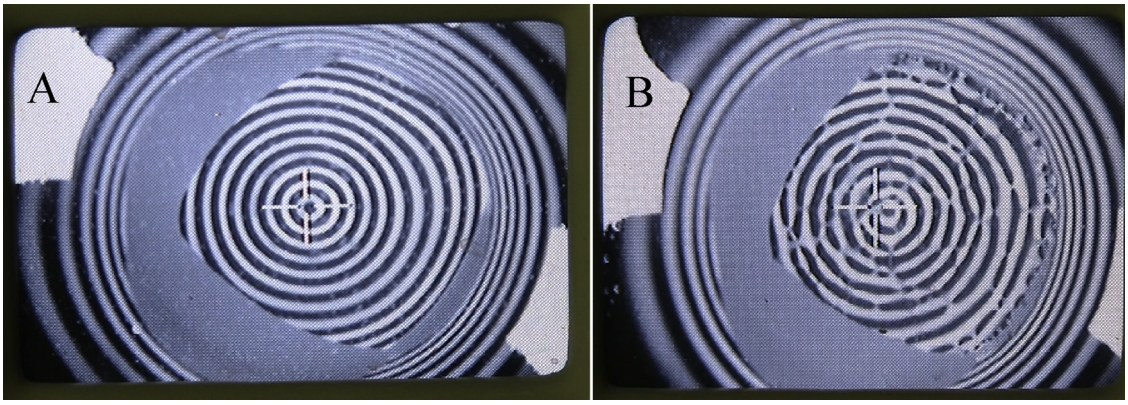

Fig. 3. Placido ring image over a "fresh" contact lens (A) and a dried-up lens surface (B). The smooth rings in A compared with the irregular rings in B indicate the difference between a confluent and a broken tear layer.

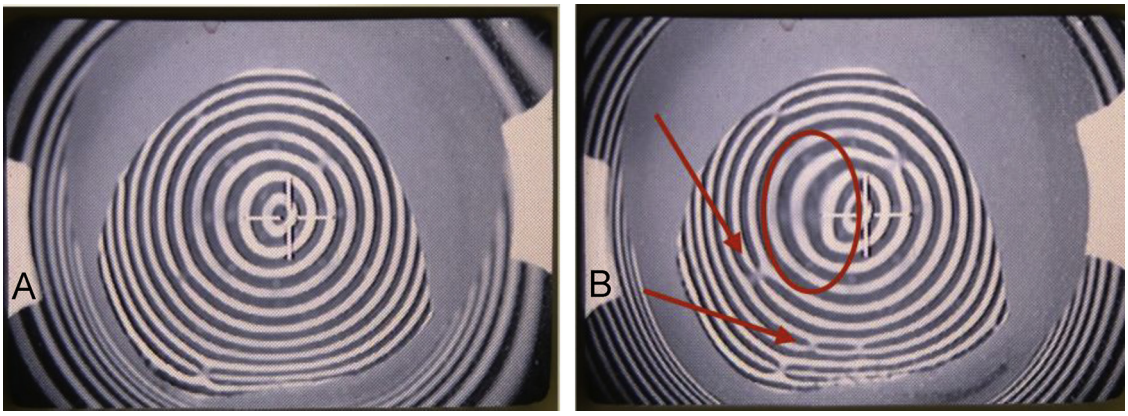

Fig. 4. *In vitro* placido ring images retrieved from the experiment; T_0 (A) and first break-up (13 s) over lens material (B).

general, NIBUTs for CH were longer than those for SH materials, particularly when immediately removed from the blister pack, and that the NIBUTs for all materials reduced over time.

Close inspection of Fig. 5 shows graphically how the NIBUTs reduced with increasing exposure to the ATS over time. Of interest, is that the NIBUT reduced for all materials, such that after 16 h the differences in NIBUT were relatively small, as compared with the T_0 times, in which the CH materials had clearly longer NIBUT. It would appear that over time, exposure to the ATS and the MBC doping procedure was a great "leveller", with this process reducing any major differences in NIBUT between all 5 materials.

One possible reason for the differences in NIBUTs could be related

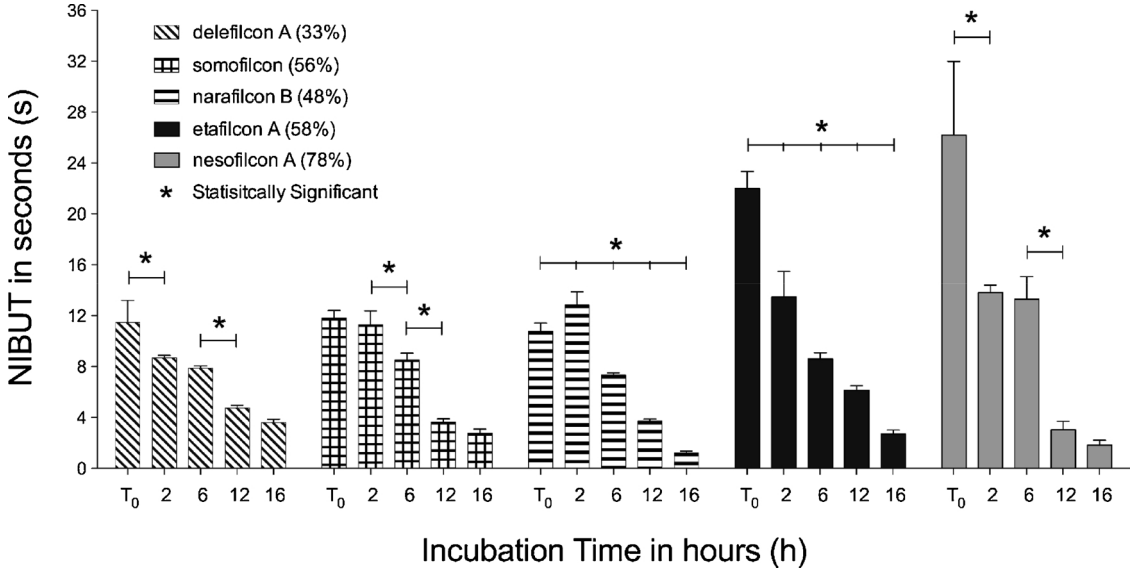

Fig. 5. Histogram representing the NIBUT for the five daily disposable materials for up to 16 h after incubation in a model blink cell. Statistically significant differences (*) are indicated for $p \leq 0.05$.

Table 2
Repeated-measures analysis of variance statistical results for NIBUTs over various DD contact lens materials.

Repeated-measures analysis of variance statistical results for NIBUTs across time					
Variable	Sum of squares	Degrees of freedom	Mean square	*F*	*p*
Duration of incubation	2608.087	4	651.022	343.941	< 0.001
CL material	351.111	4	87.778	34.435	< 0.001
Incubation time * CL material	665.989	16	41.624	21.991	< 0.001
Error	113.57	60	1.893		

Table 3
NIBUT over contact lenses in seconds (mean ± SD).

USAN	delefilcon A	somofilcon A	narafilcon B	etafilcon A	nesofilcon A
T_0	11.4 ± 1.8	11.8 ± 0.6	10.8 ± 0.6	22.0 ± 1.3	26.2 ± 5.8
2 h	8.7 ± 0.2	11.3 ± 1.1	12.9 ± 1.0	13.5 ± 2.0	13.8 ± 0.6
6 h	7.9 ± 0.2	8.5 ± 0.5	7.3 ± 0.2	8.6 ± 0.5	13.3 ± 1.8
12 h	4.8 ± 0.2	3.6 ± 0.3	0.2	6.1 ± 0.4	3.0 ± 0.7
16 h	3.6 ± 0.3	2.8 ± 0.3	1.2 ± 0.1	2.7 ± 0.3	1.8 ± 0.4

to any surface modifications and/or blister packing solution (BPS) additives that are usually applied to commercially available CLs to enhance surface wettability and lens comfort [54–61]. Although none of the lenses in this study were surface treated, several did incorporate wettability enhancing features. Delefilcon A have a composition that creates a “water-gradient” and so while the silicone bulk material has a water content of only 33%, this increases to > 80% at the lens surface [62–65]. To minimise lens dehydration, friction and prevent deposits on narafilcon A CLs, the manufacturer incorporated the internal wetting agent poly(vinyl-pyrrolidone) (PVP) [66,67]. Somofilcon A-based lenses do not contain any surface treatment or internal wetting agent [68]. In addition, narafilcon A and etafilcon A lens materials contain BPS additives to enhance lens wettability and possibly tear film stability (Table 1). These various surface and/or solution modifications, might explain some of the differences in NIBUTs of this study. Although nesofilcon A does not contain any published wetting agents in its monomer composition or BPS, it showed the highest NIBUTs within the first 6 h, which is possibly attributable to its high initial WC of 78%. Whereas, for etafilcon A, the high T_0 NIBUT might be a combined effect between BPS additives (PVP) and its relatively high WC (58%) compared with the bulk WC of the SH materials. The differences in NIBUTs between the SH lens materials are minimal, suggesting that monomer composition and BPS additives have minimal impact on NIBUTs determined using this methodology.

The most likely reason for this reduction in NIBUT relates to deposition of the lenses with components of the ATS. Previous work has shown that, on average, CH materials tend to preferentially deposit proteins (particularly group IV materials such as etafilcon A, which has a strong attraction for lysozyme) [33,69–75] and SH materials tend to preferentially deposit lipids [34–36,57,75–77]. This deposition holds true even for those materials replaced on a DD basis such as those examined in this study [23,71,74,77–79]. It is likely that progressive deposition over the course of the day, regardless of its type, resulted in a gradual reduction in surface wettability, measured by a reduction in NIBUT. To-date, there are no studies that have attempted to directly link levels of increasing deposition with reducing NIBUT, and the suggestion that increasing deposition led to the reduction in NIBUT remains a hypothesis only. However, several studies have shown that deposition is cumulative [23,32,37,71,73,74,78–88], that pre-lens NIBUT is often lower after a period of wear [48,89] (although not always) [90] and that comfort reduces both over the day and across the replacement period [11].

It is of interest to compare these *in vitro* results with previously published *in vivo* values for T_0 NIBUTs. The results of this study for the SH materials are nearly two times longer than previously published results, with Varikooty et al [51] and Kojima et al [49] reporting in eye pre-lens NIBUT values of 5–8 s. For the CH CLs, the same relative difference is observed, with T_0 NIBUTs in this study being over 20 s, whereas *in vivo* data reported for CH materials are typically half this or lower [58]. These differences may exist for a variety of reasons. One difference between the herein presented *in vitro* setup and the in-eye situation relates to the large amount of ATS the lenses were exposed to (250 mL), compared to the physiological levels of tears that are available at any given time (3 mL/24 h) [91–93]. This may impact the data in two ways. Firstly, the volume of tears sorbed to the lenses in the *in vitro* test may result in reduced dehydration during the time that the lenses are exposed to the air, as excess fluid may accumulate on the lens surface. Previous work has shown that deposition is influenced by the degree to which lenses dehydrate [53]. Thus, different levels of deposition between the lenses in this *in vitro* analysis may occur compared with that seen in eye, which could impact the subsequent NIBUT determined. Secondly, the excess amount of ATS would provide greater amounts of protein and lipid to be available to deposit on the lens materials than that seen in eye, again potentially impacting the NIBUT recorded. Previous work has shown that greater amounts of available lipid results in more lipid deposition [37] and that the amounts of proteins and lipids (and their relative concentrations) can impact lens deposition, particularly on SH materials [35,94]. The deposition of lipid or denatured protein on lens materials may increase the hydrophobic nature of the lens surfaces, reducing the NIBUT. Another aspect that may help explain these differences relates to the mounting of the lenses during the deposition process. The CLs in this experiment are mounted horizontally within the MBC rather than vertically, as they are when worn. This exerts a different force on the tear spreading over the lens surface, which may affect the observed NIBUTs and drying patterns. In addition, the MBC does not take the mechanical contribution of the blink of the eyelids into account. The eyelids, and the lid margins in particular, are thought to play a major role in the spread of the tear film [95,96]. The lids help to redistribute and re-establish the formation of the tear film layers as the lids open. The meibum lipids that are expressed and secreted by the lids as someone blinks play a crucial role in stabilising the tear film and preventing tear film evaporation, which affects the measured BUTs [27,30,93,97,98]. In the MBC model, the lipids are fully incorporated and solubilised in the ATS, creating a homogeneous mixture, and will therefore not form an outermost layer that could retard the dehydration of the tear film, which may lead to faster NIBUTs than *in vivo* data shows [46,47,50].

As far as can be established from the literature, this is the only study that has measured NIBUT during simulated CL wear, over a day, with CH and SH DD materials. Comparison with other work needs to be done in the light of the differences in measurement conditions therefore. One previous study examined pre-lens NIBUT over two CH materials after 5 h [48] and found that the NIBUT only reduced for wearers who were symptomatic, with asymptomatic wearers showing no such reduction in wettability. Varikooty et al [51] tested tear breakup after 8 h of SH CL wear and recorded times between 5.8 s (delefilcon A) and 4 s (narafilcon B) over CLs. In this study, NIBUT measurements after 6 h–12 h are in line with these results, suggesting that the described *in vitro* method for these time periods are comparable to *in vivo* studies.

Furthermore, fluorescein TBUT (FTBUT) measurements have been shown to be relatively variable due to the introduction of fluorescein altering the tear film composition, thus, disturbing its natural stability and break-up behaviour [38,99]. Results of a recent paper show that FTBUT are shorter and more compressed than NIBUT in a group of individuals [42], with NIBUT being thus considered to be more representative of a natural tear film. NIBUT measurements are the recommended method for tear film stability assessment in the recent TFOS DEWS II report [38]. Therefore, using a non-invasive measuring technique, both *in vivo and in vitro,* enables the determination of more natural and reliable tear film stability values that are more specific and sensitive than FTBUT measurements.

A limitation of the herein presented methodology, however, is that the pre-lens NIBUTs were determined manually, which could result in subjective bias when analysing when the first break up occurred. However, the observers were masked and thus any observations would be biased equally across all lenses equally. An additional drawback might be the grey area that appeared at the midperiphery of the lens images (Fig. 4), which was a consistent artefact on all CLs and the effect of pooled test solution that is attributed to the Teflon button and lens clip design used in the MBC (Fig. 1A). To ensure consistency during NIBUT analysis, the grey area was excluded and focus pertained on the innermost 6–8 concentric ring reflections on the lens surfaces. To resolve these limitations for future studies, the Teflon button/clip design require to be optimised to lessen pooling of the test solution and, ideally, all videos would be examined using automated software that would recognise any type of distortion and this process is being undertaken [100].

In conclusion, a system was developed that measures pre-lens NIBUTs over CLs *in vitro* that exposes the lens materials to an ATS that mimics the composition of the tear film and incorporates the lens surface drying that occurs during the inter-blink period. This system was able to obtain *in vitro* data that, after 6 h of tear film exposure, is comparable to *in* vivo data. While NIBUT of CH materials are longer than that obtained with SH materials immediately out of the blister pack, it appears that after tear film exposure the NIBUTs obtained between CH and SH DD materials are very similar. Further work is warranted in which the pre-lens NIBUT is determined over the course of the day to determine if a progressive reduction does occur and, if so, whether such a difference is mitigated by the materials being worn.

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