Autoreferat of the dissertation

In vitro and *in vivo* Contact Lens Dewetting Investigations using *Placido* Ring based Videokeratoscopy

submitted by
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The PhD thesis consist of 135 pages, 67 figures, 15 tables and 270 references and deals with the application of *Placido* ring based videokeratoscopy for the evaluation of the pre-contact lens surface. Originally *António Plácido da Costa* developed a concentric ring pattern, consisting of black and white rings to evaluate its image reflection from a human cornea to screen for corneal curvature abnormalities.[1] Modern applications of the so called *Placido* disc allow to view to the reflected rings over time, which enables an investigator to assess surface changes. The evaluation of the pre-contact lens surface is clinically important as this surface impacts vision and comfort. [2–5] These factors are among others crucial for the contact lens wearer and can be lead to a drop out of contact lens wear if insufficient.[6–9]

A wettable contact lens surface is essential for a clinical application. The ability of the lens surface to maintain its wetted status or to get re-wetted is challenged by, but not only by the interface to the air, to mechanical lid interactions, to possible cumulated deposits like proteins or lipids.[7; 10–12]

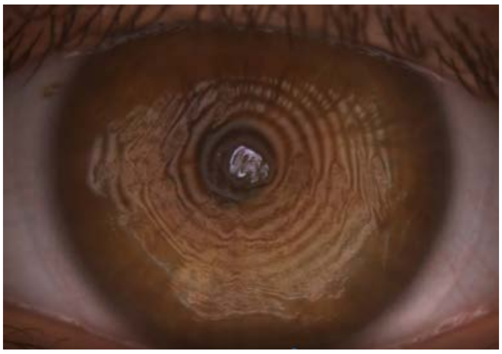

Figure 1 Dewetted contact lens surface visible by *Placido* ring based videokeratoscopy

In order to assess how long can a liquid thin film be present on a polymer surface, the investigational options provided by the *Placido* ring based videokeratoscopy have been used to explore its application in an *in vitro* and *in vivo* field. The PhD work focuses on these two key areas. It describes how the *Placido* ring based videokeratoscopy can be applied *in vitro* and *in vivo* by experimental laboratory studies on the one hand side and by clinical studies on the other side. These scientific projects have been published [13; 14; 4; 15; 16] and are listed chronologically, which shows a certain development process for the creation of measurement endpoints.

The three presented *in vivo* studies, which all complied with ethical principles, show the progress from a purely subjective evaluation of the reflected *Placido* rings from the contact lens surface to a more sophisticated way using an analysis software. In the first in vivo study the time to first distortion was assessed on the one hand side and for the evaluation of the dewetting process a grid with five segments was combined with pictures, which have been extracted from videos of the interblink period at the time points of 5, 10, 15, 20 and 25 seconds post blink. The reflected *Placido* ring structure was graded according to an experimental grading scale ranging from zero (fully wetted) to 3 (strong Placido ring distortion in more than 33 % of the graded area).

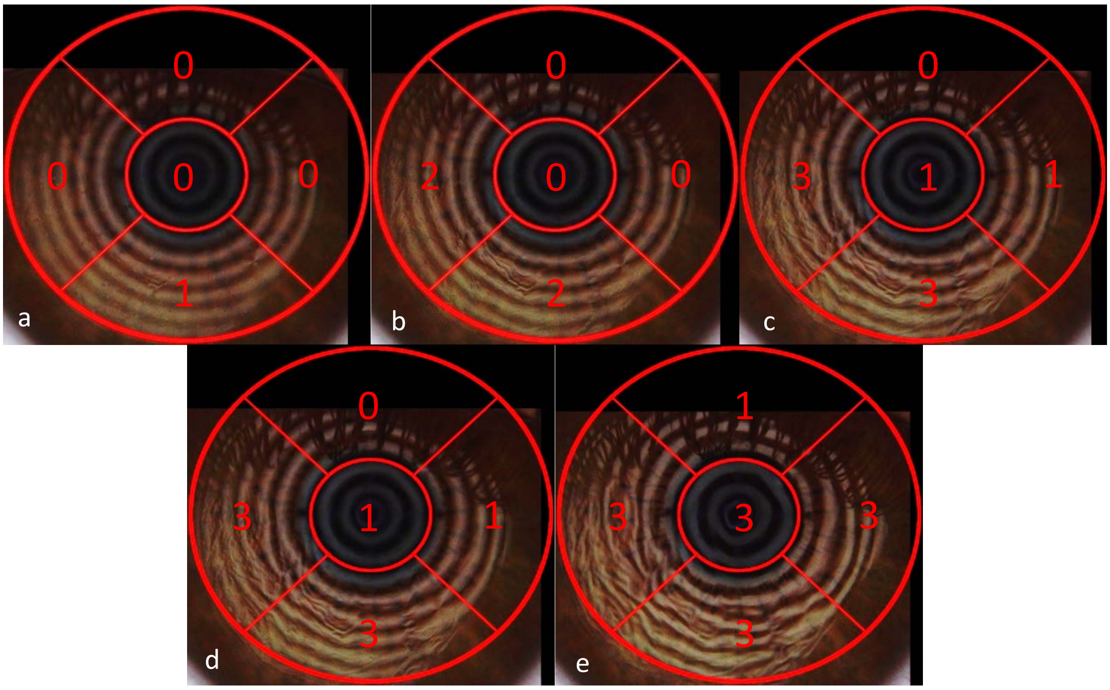

Figure 2 Example for a subjective grading of the fixed-images of the five time points after blink (a: after 5 seconds, b: after 10 seconds, c: after 15 seconds, d: after 20 seconds and e: after 25 seconds)

This procedure needed manual preparation of the pictures, training of the investigators and a time consuming grading process. However, the procedure was able to describe the dewetting process of soft contact lens within the interblink period. The data shows increasing grades over the time points 5, 10, 15, 20 and 25 seconds post blink, which shows a decreasing quality of the pre-lens tear film. Although there was no overall statistical significant difference, the gradings were statistically significant different in the meta-analysis for a pairwise comparison. This indicates that the subjective grading method allows a differentiation of the pre-lens tear film dewetting using the *Placido* ring based videokeratoscopy.

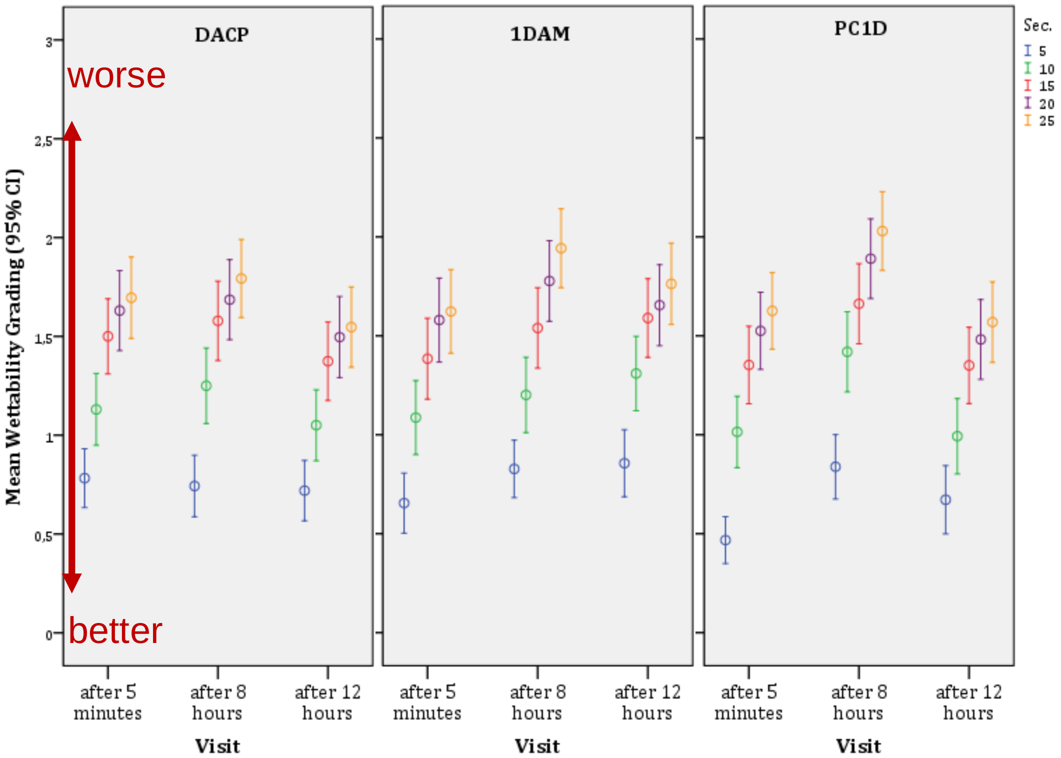

Figure 3 Mean wettability grading of Dailies Aqua Comfort Plus (DACP9, 1 Day Acuvue Moist (1DAM) and Proclear 1 Day (PC1D) during all visits regarding to the time points [s]

In the second *in vivo* study used a more time efficient analysis approach. This approach was software based. That means that an evaluation grid, which was much finer in comparison to study one, was digitally projected onto the reflected *Placido* rings by the video capturing software, called NIK-BUT mode, which is provided with the Keratograph 5M´s tear film scan software.

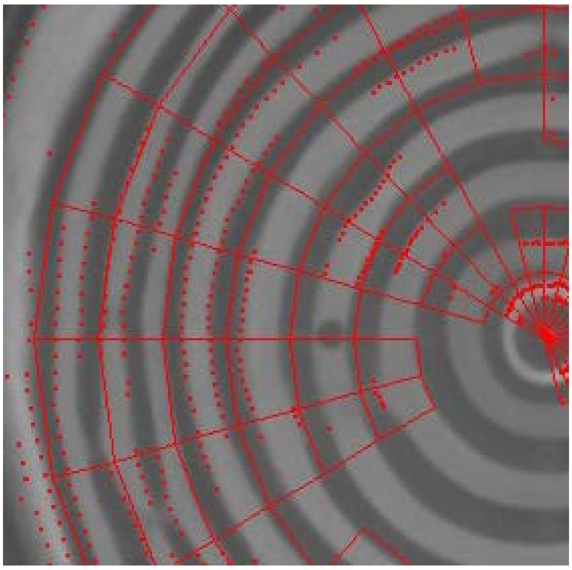

Figure 4 Objectively analyzed *Placido* ring reflections

This software is self-detecting changes in the reflected *Placido* ring image looking for changes of the ring edges and grey level alterations. Challenges for this objective approach are the pupil play during the measurement, floating mucin structures in the tear film after the lid opening and shadows on the reflected *Placido* rings caused by the eyelashes. In order to avoid a lot of artefacts, the detection was desensitized for the areas close to the lids, where more shadows are present. This compromises the fully objective evaluation and a trained investigator had the opportunity to edit the objectively predetermined data points. This was needed in the majority of measurements, but was by far less time consuming in comparison to study one. The use of the analysis software allowed the development of new study endpoints. So it was possible to determine the dewetting time up to a specific share of dewetted segments of the analysis grid. The slope of the increase, of time related dewetted segments, represents the dewetting speed, which can also function as analysis endpoint. Using a self-programmed interface for transferring the data from the manufacturer´s data base to an analysis software offers fast approach to calculate specific endpoints.

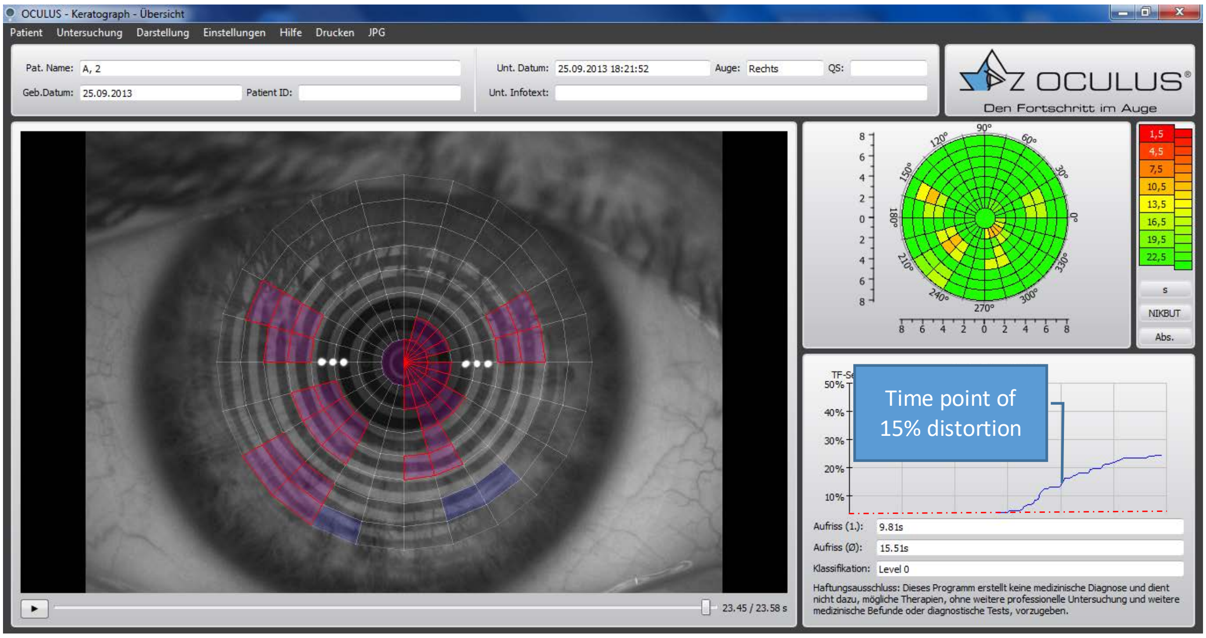

Figure 5 Display of a pre-lens tear film stability measurement results showing automatically detected segments in red and investigator added findings highlighted as blue segments

The third introduced *in vivo* study required comprehensive prework to determine hardware and software development due to the aim to measure contact lens dewetting and visual acuity simultaneously. The pre-work and published information indicate a relationship of pre-lens wettability and visual quality. This third study was the first published study, which used a technique that allowed the evaluation of these two endpoints at the same time. A hardware modification was necessary, which included the addition of a high resolution micro screen and an adjustable optical system to change the target distance. The modified experimental Keratograph K5M, allowed to present the subject with differently sized *Landolt* rings in different directions during the simultaneously conducted dewetting assessment.

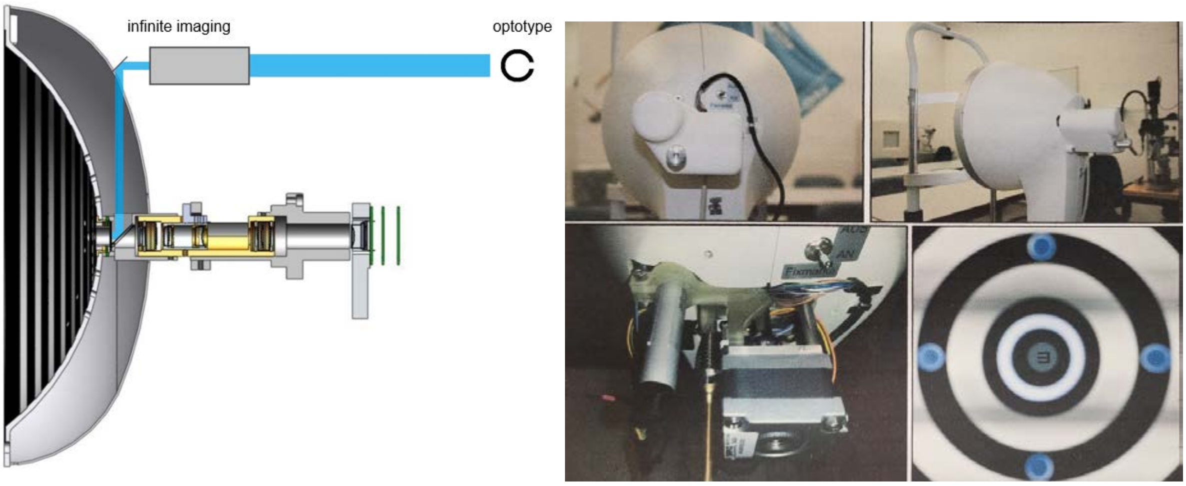

Figure 6 Concept of the realized Keratograph 5M modification (left), experimental prototype (right)

The results show the elapsing time to reach a reduction of the visual acuity is increasing with increasing size of the optotype. It could be confirmed that there is a connection between the pre-lens dewetting and the visual performance of the contact lens wearer. In addition, it could be shown that for increasing relative visual demand, smaller dewetting areas and, in connection with this, shorter dewetting times are required until a drop in visual performance occurs. Furthermore, it could be shown that there is a trend but there are no significant differences between subject groups with stable pre-corneal tear film and instable pre-corneal tear film with respect to the contact lens anterior surfaces leading to a decrease in visual acuity and the associated dewetting time.

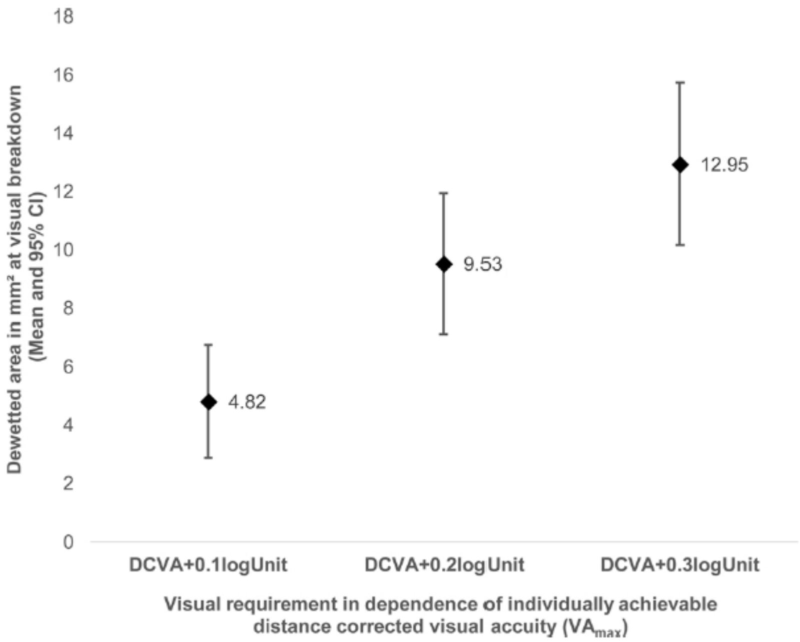

Figure 7 Visualized correlation of dewetted contact lens surface to relative visual acuity level

The impact of the dewetting location was analyzed as well. The data shows that the periphery of the contact lens has an influence on the visual performance of the contact lens wearer during dewetting. This can be concluded, because there were some measurements with peripheral dewetting and no central dewetting, which lead to the drop of the visual acuity level. In addition, based on the three-dimensional area calculation in mm^2 of the individual segments, it became possible to compare segments of different sizes with each other. It may also allow comparing better the dewetted area, captured with different techniques.

The *Placido* ring based videokeratoscopy method can also be applied *in vitro*, which was introduced in chapter 5. Besides investigating *in vitro* wettability,[17–19] researchers explored the sustainability of a wetted lens surface over time. This topic is of special interest, because a liquid film on a solid substrate does not behave consistently.[20] The phenomenon is caused by the thermodynamics of the surface free energy minimization and kinetically mediated by the hydrodynamics of the liquid.[21] The so-called surface dewetting considers the existing kinetic effect over time, which the traditionally used sessile drop or captive bubble methods do not take into account.

Figure 8 Measurement device without housing (left) and a soft contact lens on the stage below the *Placido* disc (right): 1 = horizontally mounted Keratograph 5M (climate housing not shown); 2 = adjustable x-y-z-platform; 3 = measurement stage; 4 = contact lens; 5 = white illuminated ring mires

Contact lenses may interact with different solutions ranging from the natural tear film over saline solution, tap water, rewetting drops, blister solution or lens care solutions. In a first *in vitro* study a group of different soft contact lenses were presoaked in their specific blister solution, saline solution or artificial tear solution. The data shows that all lens materials dewetted faster, when presoaked in saline solution. This indicated that wetting enhancing agents, which are present in most blister solutions and the artificial tear solution are beneficial in terms of slowing the dewetting process. This can be concluded by the smaller AUC values achieved with blister and artificial tear solution in comparison to saline solution. Other endpoints like the dewetting time to reach 25% and 50% dewetted segments are showing that as well, especially when comparing the ATS results with saline solution results.

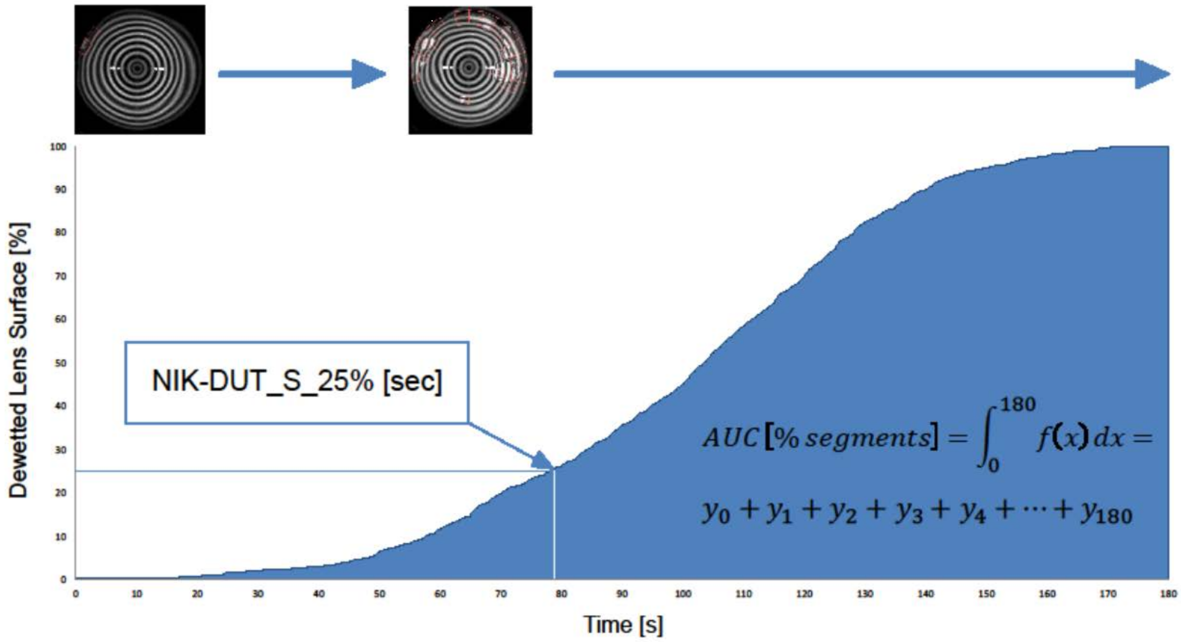

Figure 9 Visualization of endpoint in relation to the in vitro dewetting process

However, a direct conclusion to the in vivo field can´t be made. The reason is that the *in vivo* pre-lens tear film is much thinner than the *in vitro* thin film. This results in a long measurement time of 180 seconds to observe full dewetting in the majority of cases. In order to attempt to combine *in vivo* aspects with in vitro measurements the criteria of the dewetted area of 4,82mm^2, which leads to a drop of the visual acuity as shown in the third in vivo study was introduced in a second in vitro study.

Dewetting is influenced by several factors, including evaporation, surface structure, temperature, humidity and gravity. Three primary factors, i.e. the adhesive forces, the cohesive forces and the surface tension, have a decisive influence on the de-wetting process. It was possible to show that the constituents of the phospholipid-containing test solution interacted during the storage period as a result of the movement of these constituents over the lens surface. This can be seen from the fact that, despite renewed equilibration in saline solution, a significantly faster dewetting of the contact lens was measured after being stored in the phospholipid-containing solution. This was the case with all contact lens materials examined and is reflected by the primary target variable. The AUC value increased more than 50% in the group of hydrogel materials and silicone hydrogel materials. On average, the time required to reach 4,82 mm^2 of dewetted surface was 68 s in the case of the hydrogel materials and 69 s in the case of the silicon hydrogel materials, which, after being kept in the phospholipid-containing solution, was shortened to 15 s and 31 s respectively. It can be assumed that constituents of the phospholipid-containing solution accumulate on the surface. Since no subsequent investigations have been carried out in this respect, this, however, cannot be proven. Since the phospholipid-containing eye drops dilute in the lacrimal fluid after application, the amount of phospholipid which interacts directly with the contact lens surface is likely to be significantly lower in an *in vivo* situation. Changes in the contact lens surface relevant to visual acuity occur only after more than 10 s after the blinking. It was demonstrated that phospholipids lead to faster dewetting when interacting with a contact lens material for a prolonged period of time. As the de wetting area of 4,82 mm^2 is reached by contact lens wearers after a typical interblink period during visual tasks requiring a certain level of attention, it is unlikely to expect a drop of the visual acuity by one log level.

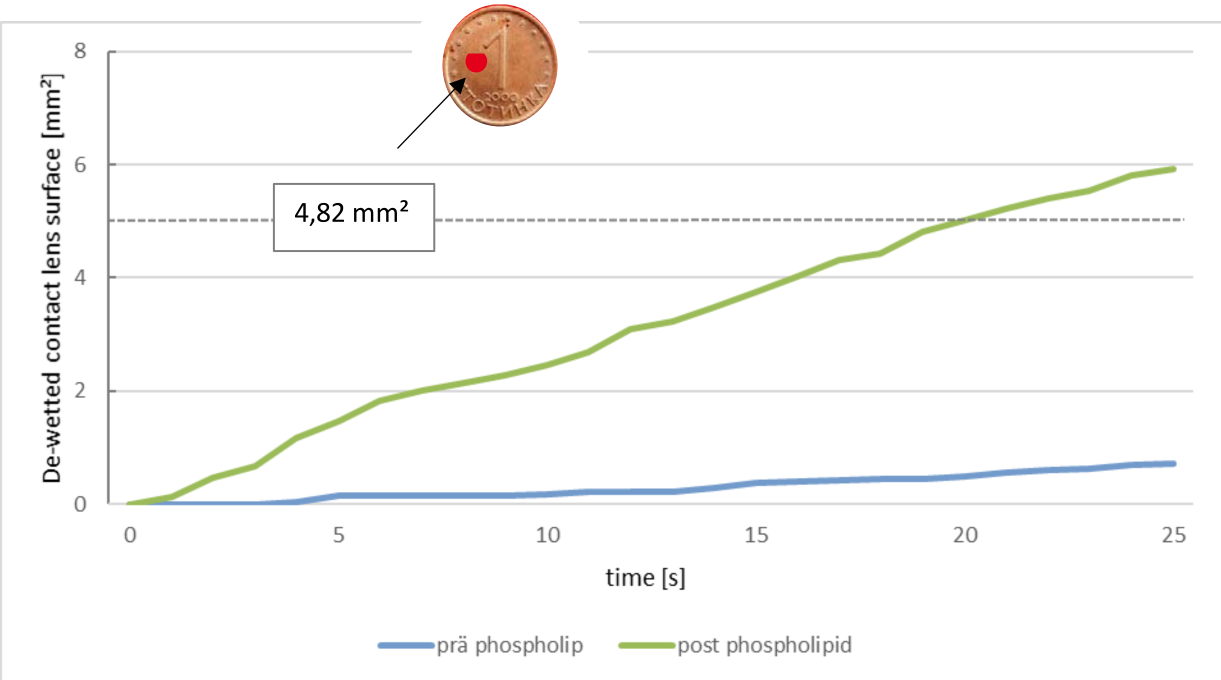

Figure 10 Visualization of clinical considerations for the *in vitro* dewetting process

The PhD thesis summarized method depending limitations as well. These limitations are connected with the used instrument itself, with the used analysis software and are connected with environmental conditions during the measurement and as well with visual tasks conducted before the measurement.

Placido ring based videokeratoscopes are today available globally and offered in a variety of versions including bigger *Placido* discs and smaller *Placido* cones. The devices are widely used for measuring the corneal curvature and modern versions allow the assessment of the pre-corneal or pre-lens surface. The PhD work is limited to one device, the Keratograph 5M, which allows a non-contact measurement. Several conducted studies show the successful use in the in vitro and in vivo field. It can be concluded that ex vivo studies may be realized as well.

Future further development of the Oculus NIK-BUT measurement mode, as part of the Keratograph 5M´s software, would be needed to allow the regular contact specialist in the practice, an objective dewetting measurement. This may allow the practitioners to find the best matching soft contact lens material for their customers.

Contributions

The PhD work “*In vitro* and *in vivo* Contact Lens Dewetting Investigations using *Placido* Ring based Videokeratoscopy“ adds following new information in the field of contact lens investigations:

C1 The typical usage of *Placido* rings focuses on the corneal curvature evaluation and starting at 2009 the determination of the non-invasive corneal tear film break up time. This PhD work extends these applications by the *in vivo* pre-contact lens dewetting evaluation and the *in vitro* contact lens dewetting analysis. It furthermore summarizes existing knowledge in the field of contact lens dewetting and presents new research.

C2 In order to use the *Placido* ring based videokeratoscopy in the contact lens related *in vivo* and *in vitro* field new analysis strategies needed to be developed. An initial attempt introduces a new subjective analysis approach. In further steps, which are described in the PhD work, a new objective way is described as well.

C3 Multiple studies were conducted to explore new endpoints, which allow the differentiation of a contact lens dewetting status at a specific time point. This includes the subjective classification, which ranges from grade 0 to grade 3 and the objective quantification of dewetting by adding an analysis grid with 192 segments. The usage of this grid allows the assessment of the dewetting process by cumulating the dewetted segments in a time dependent manner to achieve a time related dewetting graph. This approach provides information about the dynamic process. Developed dewetting endpoints based on this graph are the area under curve, the speed of dewetting up to a certain dewetting level or the dewetting slope. The *Placido* ring based videokeratoscopy method gives also information about the time point of dewetting and the localization where the dewetting starts.

C4 Unique hardware modifications are presented in this PhD work, which allow the simultaneous evaluation of the visual acuity and the contact lens dewetting. This introduced invention enabled the determination of a clinical relevant dewetted area, which is linked to the decrease of the visual acuity by one, two and three log levels.

C5 Many conducted contact lens wettability studies lack in their ability to link the *in vitro* and the *in vivo* world. This PhD work demonstrated investigational set ups, which allow their usage in the lab but also under clinical conditions. Some developed endpoints are usable in the *in vitro* and the *in vivo* field, which might be used in the future to make better predictions for *in vivo* outcomes based on *in vitro* data.

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