TITLE PAGE

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Physical properties and interaction with the ocular surface of water-gradient contact lenses

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Water-gradient contact lenses

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MANUSCRIPT

Abstract

# Since the introduction of silicone-hydrogel (SHy) contact lenses (CLs), many SHy materials have been produced, including water-gradient (WG) CLs with a SHy core and a thin hydrogel outer layer (e.g., delefilcon A, verofilcon A, and lehfilcon A). Their properties have been investigated in various studies assessing both the chemical-physical characteristics and the comfort, but the overall picture is not always consistent. In this study, WG technology is reviewed by looking at basic physical properties both *in vitro* and *in vivo* and at the interaction with the human ocular surface. Surface and bulk dehydration, surface wetting and dewetting, shear stress, interaction with tear components and with other environmental compounds, and comfort are discussed.

# Keywords

# Contact lens; water-gradient; dehydration; wettability; shear force

# 1. Introduction

Fifteen years after the introduction of silicone-hydrogel contact lenses (SHy-CLs) in 1999,1 delefilcon A was released, and described by the manufacturer as based on a water gradient (WG) technology. This CL is made of a SHy core of low (33%) equilibrium water content (EWC) surrounded by an interpenetrating anchoring zone of 1-2 micrometers2 and a hydrogel (Hy) coating of 5-6 micrometers,3 with an EWC of 80%. Few years ago, an outer thin layer with a porous morphology was observed also for filcon V (SHy),4,5 although these CLs are not classified as WG-CLs. Recently, two other WG-CLs were released: verofilcon A (SHy) and lehfilcon A (SHy), with a core EWC higher than delefilcon A (SHy) (51% and 55%, respectively) (Table 1).6,7

Verofilcon A (SHy) and lehfilcon A (SHy) have seen only a limited characterization, probably due to their recent release on the market, while the properties of delefilcon A (SHy) CLs have been in-depth investigated in various studies. Nonetheless, the final picture is not always consistent. In this review, the current literature on WG-CLs is commented by looking at basic physical properties such as dehydration, surface wetting and dewetting, shear stress, interaction with tears and other compounds, and, finally, by summarizing results concerning comfort.

# 2. Dehydration

Dehydration has a potential impact on CL dimensional changes, gas transmission, ocular surface desiccation, dryness sensation, and CL discomfort. A measure *in vitro* of the dehydration properties is usually achieved by gravimetric methods. The weight of a hydrated CL is measured by digital microbalances, which can perform extremely fine measuring (with a resolution in the order of 10-3 mg): a change of weight is linked to a change of water content in the CL. Some authors proposed refractometry methods to measure EWC.8–10 Different types of refractometers are available based on the deviation of light at the interface between the sample of interest (liquid or solid) and a reference material or based on the principle of totally internal reflection of light. The method allows characterizing the surface layers of a sample in contact with the reference material. Both gravimetric and refractometry methods allow studying CL dehydration process either *in vitro* on unworn CLs11,12 or *ex vivo* when a CL is removed from the eye.8,13 Concerning refractometry, there could be issues with its accuracy and reliability, depending on the instrument used.9,10

The gravimetric method has very good accuracy, but it is quite time consuming. One way to study *in-vitro* dehydration by the gravimetric method is through the rate (Eq. 1),11 where weight T(n) is the sample weight at time n and weight T(n-1) is the sample weight at time (n-1) with intervals of 1 minute:

$Dehydration rate = \left[\frac{weight\_{T(n)} - weight\_{T(n-1)}}{weight\_{T(n)}}\right]$ [1]

During *in-vitro* experiments, different dehydration phases can typically be identified through the dehydration rate curve as a function of time. 11 The initial phase is characterized by a relatively high and uniform dehydration rate before a progressive rate decrease occurs. Its duration is limited (up to a few tens of minutes depending on the CL material), and it is associated with the evaporation of the water on the surface and of the outer layer.11,12 Thisinitial phase is representative of the *in-vivo* initial dehydration, when the CL is placed in the eye. In this phase, conventional Hy-CLs are associated with greater dehydration rates11,14 than the first commercialized SHy-CLs, both *in vivo* (as reported in a study limited to balafilcon A (SHy))13and *in vitro* (five SHy-CLs were studied: lotrafilcon A, lotrafilcon B, balafilcon A, senofilcon A, and galyfilcon A)11. This difference can be attributed to the relatively low EWC of the first SHys (lotrafilcon A, lotrafilcon B, balafilcon A), while Hy- and SHy-CLs with similar EWC display similar dehydration.11

Concerning WG-CLs, Schafer et al. compared three CLs before and after 15 minutes of wear by refractometry analyses.8 For delefilcon A (SHy), a refractive index of 1.34 was reported for unworn CLs, which increased to 1.43 after wear.8 The authors concluded that the surface of delefilcon A (SHy) dehydrates quickly, causing the CL to behave like its low-EWC bulk after a few-minute wear. A different behavior of delefilcon A (SHy) compared to other materials emerged also in another study, which assessed dehydration before and after nine-day wear by refractometry analyses.15 Surprisingly, delefilcon A (SHy) showed an increase in its EWC. It should be noted that the authors reported a refractive index for unworn CLs of 1.43,15 while Schafer et al. reported 1.34.8 Considering that the surface layer with 80% hydration should have a refractive index very similar to that of water, the initial value reported by Insua Pereira and Lira15 could have been overestimated, perhaps due to the rapid dehydration. Walther et al.16 studied dehydration gravimetrically and delefilcon A (SHy) showed the lowest rate of dehydration compared to other seven daily disposable CLs (Hy: hilafilcon A, nelfilcon A, omafilcon, A, etafilcon A; SHy: narafilcon A, narafilcon B and filcon II 3). However, the water loss was evaluated over 20 minutes and both the superficial and the bulk water likely contributed to the dehydration rate. The relatively low bulk EWC of delefilcon A (SHy) may have determined the lower dehydration over 20 minutes compared to other materials. These results confirm the dependence of the dehydration rate on the initial EWC, but do not describe what happens to the water of the surface layer as soon as the CL is inserted into the eye from the blister.

Chan et al. compared the initial and final EWCs, using a gravimetric method (Eq. 2) after one and sixteen hours of incubation in an *in-vitro* blink model with artificial tear solution (ATS) at ocular temperature.17 Relative dehydration was evaluated, defined as:

$Relative dehydration = \left[\frac{initial EWC - final EWC}{initial EWC}\right]$ [2]

The formula to calculate initial (or final) EWC took the form of Eq. 3:

$EWC = \left[\frac{wet weight - dry weight}{wet weight}\right]$ [3]

where wet weight was achieved weighting the CL just after blister removal (or after *in-vitro* incubation), and the dry weight was the weight after heating the CL at 105°C for 1 hour and then cooling it down in a desiccator for 30 minutes. After one hour, delefilcon A (SHy) showed the lowest relative dehydration (~10%), slightly lower than senofilcon A (SHy), comfilcon A (SHy) and omafilcon A (Hy), and largely lower than etafilcon A (Hy). Even after 16 hours, delefilcon A (SHy) showed one of the lowest relative dehydrations (~5%). Also Eftimov et al.18 considered a blinking model and investigated the evaporative loss of water. SHy-CLs with wetting agents incorporated in their core (SHy: narafilcon A, senofilcon A) were highly susceptible to extended desiccation, while delefilcon A (SHy) resisted 8 hours of desiccation/rehydration cycles. Also in this case, the results do not describe separately what happens to the EWC of the thin outer layer. Dehydration can be assessed *in vivo* indirectly by evaluating the staining and two different studies reported a low rate of dehydration-induced staining in people wearing delefilcon A (SHy).19,20

Overall, two key aspects have been discussed (limited to delefilcon A (SHy), the only WG-CL for which dehydration studies are available): (i) dehydration of the outer layer over the very first minutes of wear, and (ii) the longer-term dehydration phase. Only a few studies assessed them separately. Schafer et al. used refractometry, and found quick dehydration of the WG-CLs outer layer.8 Preliminary data on surface dehydration were also obtained by Molock et al.,21 and delefilcon A (SHy) displayed the lowest relative surface dehydration. The authors concluded that the high EWC of the surface layer may not correspond to higher dehydration and this appeared in contradiction with Schafer et al.8 but Molock et al. did not report details of the experimental methods, hindering the results comparison.21 More studies are available on the longer-term dehydration behavior of delefilcon A (SHy) CLs, which appears generally equal or better than many other Hy- and SHy-CLs, with lower rate of dehydration and lower *in-vivo* dehydration-induced staining. The only exception was found by Woods et al. with higher relative dehydration found gravimetrically for delefilcon A (SHy) compared to omafilcon A (Hy) and stenfilcon A (SHy) over 12 hours of wear.22

# 3. Surface wetting and dewetting

CL wettability can be assessed *in vitro* by measuring the contact angle (CA).23 Advancing CA describes the initial *in-vivo* tear spreading on the CL (wetting), whereas receding CA depicts the pre-lens tear film stability, when the tear film retracts (dewetting).23 The advancing and receding water CAs of SHy-CLs were compared by Eftimov et al.24 Concerning advancing CAs, delefilcon A (SHy) displayed a better wettability, attributed to its low silicon surface content and to the high surface hydration.

Also Menzies and Jones reported a better wettability of delefilcon A (SHy) compared to all the other CLs, except for nelfilcon A (a Hy-CL with 69% EWC).25 Concerning dewetting, delefilcon A (SHy) displayed one of the lowest receding CAs among the investigated materials. Interestingly, the differences highlighted by the receding CAs were much lower than the ones found with advancing CAs.24,25 Other authors studied *in-vitro* surface dewetting by different techniques inspired by *in-vivo* processes. For example, Havuz and Gokmen used a 15 mm chrome coated artificial cornea model and captured 24 frames per second with a videokeratoscope device to evaluate surface dewetting.26 Subbaraman et al. recorded videos of the fluid draining from the surface of a CL submerged in a saline solution and then raised out of the fluid at a controlled rate.27 The results are variable. Depending on the material, Havuz and Gokmen found that the dewetting starts between 26 s (for delefilcon A (SHy)) and 99 s (for fanfilcon A (SHy)). The low dewetting time of delefilcon A (SHy) could be ascribed to the rapid dehydration of the surface, which transforms the CL properties into those of a low-EWC SHy-CL.

A worse value for delefilcon A CLs was also reported by Walther et al.,28 who compared them to two conventional Hy-CLs (nesofilcon A and etafilcon A) and two SHy-CLs (somofilcon A and narafilcon A). However, these authors also discussed the dependence on exposure time and possible deposition during the *in-vitro* experiment in an ATS. Out of the blister pack (T0), conventional Hy-CLs revealed significantly longer non-invasive tear break up times (NITBUTs) than SHy-CLs, while delefilcon A had the longest NITBUT at the end of an incubation period of 16 hours (although all CLs showed significant reductions in NITBUTs in comparison to T0). On the contrary, Subbaraman et al. found that the dewetting time of WG-CLs was more than four times longer than etafilcon A (Hy), somofilcon A (SHy), and stenfilcon A (SHy) CLs.27 It must be noted that Havuz and Gokmen26 and Walther et al.28 investigated the dewetting properties of delefilcon A (SHy), while Subbaraman et al.27 analyzed verofilcon A CLs (SHy).

Concerning *in-vivo* methods, lateral shearing interferometry was used to analyze the pre-lens tear film surface quality and compare nelfilcon A (Hy) and delefilcon A (SHy) after six hours of wear.29 This technique analyzes the shape of a wavefront after reflection from the central area (approximately 4×4 mm) of a CL during wear. The reflected wavefront creates fringe pattern images that are recorded and analyzed by numerical methods to deduce information on tear film surface and its dynamic changes. Relatively to the bare eye condition, both CLs resulted in a reduction of the film surface quality, but a smaller change was induced by the WG-CL. Another study compared subjects fitted with different CLs, with delefilcon A (SHy) displaying longer pre-lens NITBUT.30 Varikooty et al. considered symptomatic and asymptomatic CLs wearers.20 The mean NITBUT was ~1 s longer with delefilcon A (SHy) than with somofilcon A (SHy) and narafilcon A (SHy), and the wettability was graded marginally better. No substantial differences were found between asymptomatic and symptomatic CL wearers. Dumbleton et al. presented a comparison study of different CLs after six hours of wear, including 3 hours of conventional wear and 3 hours at 20% relative humidity.31 Delefilcon A WG-CL performed better than stenfilcon A (SHy) and narafilcon A (SHy), displaying a better coverage (i.e., a reduced value of the exposed lens area at blink) and the fastest tear film spread before break. Similar results were reported by Guillon et al.32 Also in this paper, the authors concluded that delefilcon A (SHy) CL performed better than stenfilcon A (SHy) and narafilcon A (SHy) after six hours of wear including three hours of computer use at 20% relative humidity.32

To evaluate tear film stability, Itokawa et al.33 measured NITBUT and tear interference patterns on the CLs before and after 15 minutes of wear. The grade of the tear interference patterns on delefilcon A CLs was significantly smaller (i.e., better) than those on etafilcon A (Hy) and polymacon (Hy). The authors also measured the ocular surface temperature, a parameter that was considered useful to evaluate tear film stability during CL wear. In this case, they found that the variation of temperature was smaller with delefilcon A (SHy) than etafilcon A (Hy) and polymacon (Hy) CLs.

All the mentioned comparative studies carried out *in vivo*20,29–33 reported better wetting/dewetting performance of WG-CLs compared to other materials. Indeed, lower tear film evaporation (i.e., higher NITBUT values) with delefilcon A (SHy) was found in different studies and WG-CLs have shown the ability to overcome potential CL-wear issues, such as reduced tear film evaporation, tear reservoir, and lipid layer thickness that can negatively influence subjective comfort. An exception was nesofilcon A (Hy), which was found to show a lower effect than delefilcon A CLs (SHy) on the pre-lens NITBUT both after twenty minutes on the first day of wear and after eight hours of wear on the seventh day.34 The same authors also investigated stenfilcon A (SHy) CLs and found similar results for delefilcon A (SHy). Overall, the presence of any CL produced a reduction of NITBUT, but with different extents.

In summary, based on the comparison between *in-vitro* and *in-vivo* results, the interaction with tear components is expected to be a key element. *In vitro*, in fact, the surface layer of WG-CLs seems to lose its hydration quickly and there is no clear evidence that the *in-vitro* dewetting properties are better than the ones of other materials. Nonetheless, the scenario changes when considering most of the results of *in-vivo* investigations, better clinical performances being typically reported for WG-CLs.

# 4. Shear stress

Tribology deals with the interaction between surfaces in relative motion. The shear force depends on the sliding velocity and two regimes have been described for the eye.35 At relatively high sliding velocities (hydrodynamic regime), the two sliding surfaces (lid wipers and cornea) are separated by the tear film and the viscosity of tears governs the sliding resistance.35–37 At lower speed (boundary regime), the sliding surfaces are in close contact within the limits of their surface roughness4,38 and the coefficient of friction (CoF) is represented by the ratio between shear force and normal applied force. The hydrodynamic phase is dominant in the tribology of the bare healthy eye in normal conditions.35

CL wear may induce viscosity alterations, causing higher shear stress at high sliding velocity.36 Additionally, CL wear reduces film thickness by splitting it, resulting in the contact between sliding surfaces. This would cause the system to fall back into the boundary regime even at high speed. For this reason, interest in friction and how to reduce it have progressively grown. An approach is based on wetting/lubricating agents or on high water content surfaces. For example, Rudy et al. discussed the strong correlation between surface treatments and CLs mechanical behavior, finding that delefilcon A (SHy) exhibited a CoF five times lower than the value of plasma surface treated balafilcon A (SHy).39

Tribology experiments by Dunn et al.40 report WG-CLs CoF to be below 0.02. For comparison, the CoF of a healthy cornea is 0.001-0.01041,42 and the CoF of 24 types of CLs was found by Roba et al.43 to vary from 0.011 to 0.562. On average, reusable CLs had higher CoFs and lower EWCs than daily disposable CLs.43 However, the correlation between CoF and EWC was unclear, perhaps due to the influence of other CL characteristics (e.g., CL composition, presence of poly(vinylpyrrolidone) (PVP) and/or surface treatments). The sliding speed in the experiments by Roba et al.43 and by Dunn et al.,40 was of the same order of magnitude (0.1 and 0.2 mm/s, respectively) as well as the applied normal force (from 0.25 to 5 mN, and from 0.1 to over 2 mN, respectively). The main difference between these experiments is the use of a mucin-coated glass as a counter surface with a lubricant based on packing solution containing lysozyme and serum by Roba et al.43, while Dunn et al.40 used a borosilicate glass probe sliding on the WG-CL surface with the CL submerged in borate-buffered saline. Friction experiments on delefilcon A (SHy) CLs were also carried out by atomic force microscopy.39,44 Also in this case, measurements were conducted in a salt solution in the absence of the typical tear components and the CLs were soaked in buffered saline prior to analysis.39,44 In general, it is advisable to include the presence of mucins during tribology experiments to mimic *in-vivo* conditions.45

Sterner et al. investigated the effect of lubricant composition and *in-vitro* aging on the CoF of different CLs, including delefilcon A (SHy).46 In this case, a mucin-coated glass disk was used and the CLs were tested before and after exposure to an *in-vitro* aging process, consisting of continuous immersion (20 s) and withdrawal (20 s) from a tear-like fluid for 18 hours. After *in-vitro* aging, CLs containing PVP showed unaltered CoF, whereas delefilcon A (SHy) and other CLs displayed a significant increase in CoF, suggesting that the presence of a persistent wetting agent is an advantage in maintaining a low CoF during prolonged wear. Dunn et al. also discussed the possibility of collapse of the surface gel layer of delefilcon A (SHy).40 These authors reported a CoF for WG-CLs of 0.02 by applying a contact pressure of a few kPa, i.e. in the order of magnitude of the contact pressure of the eyelid in healthy eyes.47,48 However, at contact pressures higher than 10–20 kPa, the gel was found to collapse and dehydrate, and friction increased.40 The authors concluded that the ability of the soft surface layer to provide lubricity is dependent on its ability to support the applied pressure without dehydrating. To mimic friction *in vivo*, Hart et al.49 measured both the shear force and the cellular response to friction when sliding CLs against monolayers of living human corneal epithelial cells. The shear stress varied from 16 ± 2 Pa for WG-CLs (delefilcon A (SHy) and verofilcon A (SHy)) to 86 ± 12 Pa (stenfilcon A (SHy)), and cell damage increased with increasing shear stress and increasing sliding duration. Compared to other CLs, WG-CLs caused less cell damage. The authors concluded that surface gel layers with a large polymer mesh size and high EWC represent an effective approach to lower contact pressure, shear stress and cell damage.

In summary, *in-vitro* tribology measurements are representative of the so-called boundary regime that occurs at the slowest sliding speeds of the eyelid during blinking. Despite some differences between the experimental conditions of the works reported in the literature (mainly the use of tear-like fluids or saline solutions and the presence or absence of mucins deposited on the sliding probe), the CoF of delefilcon A (SHy) CLs is reported to be relatively low. Based on the available data, it can be inferred that a surface gel layer with high EWC represents an effective approach to lower contact pressure and shear stress, as well as the presence of wetting agents on the surface. However, the efficacy is dependent on its ability to support the applied pressure without dehydrating and on the persistency during wear of the lubricant agents.

# 5. Interaction with different compounds

CL surface charge strongly affects protein deposition and its extent. Due to electrostatic interactions, positively charged proteins deposit onto the surface of anionic CLs, whereas negatively charged proteins deposit on cationic CLs. Generally, neutral SHy-CLs have low protein and high lipid deposition.1,50

Recent studies focused on the deposition of lysozyme, which is a positively charged and abundant protein of the tear film,51,52 evidencing that CL materials are affected by increasing lysozyme deposition with increasing incubation time.53,54 Chan et al. measured lysozyme activity in an *in-vitro* blink-simulation model and in a static vial deposition model on three Hy- (etafilcon A, omafilcon A, nelfilcon A) and three SHy-CLs (delefilcon A, senofilcon A, somofilcon A) by employing an ATS containing lysozyme and other tear components.53 Phan et al. studied the same CLs with a blink-simulation model and employed fluorescently tagged lysozyme.54 Both studies reported the highest deposition at all time points for etafilcon A (Hy), both in terms of total amount54 and of active protein.53 Delefilcon A (SHy) displayed an overall deposition of fluorescent lysozyme similar to other Hy- and SHy-CLs.54 Notably, except for etafilcon A (Hy), it showed the highest amount of active protein among all CLs.53

Subbaraman et al. investigated the relationship between protein deposition and clinical symptoms for etafilcon A (Hy) wear: interestingly, poor correlation was reported between subjective symptoms and protein deposition, whereas stronger correlations was found between active lysozyme and comfort, suggesting that investigation of the total protein deposition must be integrated with information on the conformational state.55 Future studies should investigate the denaturation percentage also for other tear proteins,51,52,56 for example by exploiting the peculiar fluorescence emission originating from complex formation of lactoferrin with terbium at its the iron-binding sites.57

Recent studies analyzed the uptake of lipids, such as cholesterol.58,59 A first study was performed employing radioactive cholesterol,59 whereas a following study employed a fluorescent tag.58 Also in this case, delefilcon A (SHy) displayed a behavior similar to other SHy-CLs.58,59 As for protein deposition, the difference might be in lipid modification (i.e., oxidation) and not in total amount, highlighting the need for further investigation. Regarding the sorption localization, both labeled cholesterol and lysozyme permeated through the entire thickness of delefilcon A (SHy), despite the layered structure.54,58

As discussed previously, hydration, wetting/dewetting properties, and shear stress during wear of WG-CLs are expected to be strongly affected by the morphology and composition of the outer layer, which depends on its interaction with tears. For example, tear mucins can adhere to the CLs *in vivo* and form a layer, which is desirable as long as CL-adherent mucins maintain their properties and do not trap debris or pathogens.60,61 Some differences in the formation of the mucin layer were found between different CLs, probably due to interactions between the polar groups of the CL and the mucins.60,62 This aspect deserves to be studied in detail and further investigations are required, in particular on WG-CLs.

Also environmental agents can adhere to the CL surface,63–66 causing foreign body reaction and exacerbating allergic conjunctivitis.67 Among them, pollen is made up of positively charged particles. Mimura et al. exposed twelve different CLs to a saline solution containing pollen and reported a higher portion of adhesion area for Hy materials compared to SHy-CLs.67 Delefilcon A (SHy) showed SHy-CLs characteristics, displaying the lowest value among the investigated materials.67

Cosmetics products can also interact with CLs. Generally, SHy-CLs are more prone to absorb cosmetics, being more lipophilic. For example, cosmetic cleansing oil for makeup removal, which contains surfactants and mineral oils, affects SHy-CLs. Tsukiyama et al. soaked different CLs in cleansing oil and rinsed them with multipurpose solution prior to stereomicroscope analysis.68 Lipophilic ingredients penetrate SHy-CLs, causing swelling and staining. On the other hand, delefilcon A (SHy) and lotrafilcon A (SHy), which is a plasma coated SHy-CL, hardly absorbed the oils.68 Zeri et al. focused on the interaction between CLs and mascara by employing scanning electron microscopy and energy-dispersive X-ray spectroscopy on CLs exposed *in vitro* to mascara, and CLs worn for 8 hours by mascara wearers. The results showed an affinity for mascara more than two times higher in delefilcon A (SHy) than filcon V SHy-CLs.69

In conclusion, the outer layer of delefilcon A (SHy) CLs, which are the only WG-CLs considered for the investigation of interactions so far, affects the deposition of proteins onto the lens surface without masking completely the properties of the SHy bulk, as suggested by the interaction with lipophilic molecules. Nonetheless, pollen, which is positively charged as lysozyme, displayed a very weak interaction with delefilcon A (SHy), highlighting that other factors else than charge may play a fundamental role. In this case, the particle size was extremely different, with pollen having an average size of about 20 µm67 and lysozyme having a hydrodynamic radius of about 2 nm.70

# 6. Effect of wear and wear duration on comfort and quality of vision

Although the measure of comfort/discomfort is challenging to achieve and discomfort is a multidimensional concept,71 several studies have sought to characterize changes of WG-CLs parameters during wear, with most of the available works covering delefilcon A (SHy) (few studies assessed verofilcon A (SHy) *in vivo* and no study includes lehfilcon A (SHy)).

Subjective comfort has been often assessed by visual analogue scales, asking participants to rate comfort on scales between 0 and 10 (or 0 and 100). Wolffsohn et al. did not find any difference in terms of comfort between delefilcon A (SHy), filcon II 3 (SHy), and narafilcon A (SHy).72 Also Diec et al. found no difference between three SHy- (delefilcon A, somofilcon A, narafilcon A) and two Hy-CLs (omafilcon A, nelfilcon A).73 Contrarily, other authors reported a better comfort with delefilcon A (SHy) in comparison with nelfilcon A (Hy).29,74 In a further study, Varitooky et al. found the highest comfort with delefilcon A (SHy) and narafilcon A (SHy) and the lowest with somofilcon A (SHy).75 Insua Pereira and Lira15 compared different CLs, with delefilcon A (SHy) and narafilcon A (SHy) having slightly higher comfort ratings. Overall, it can be deduced that delefilcon A (SHy) comfort was typically equal to or better than other CLs.

Several studies aimed to assess variations of WG-CLs properties over wearing time. These studies consistently reported high subjective comfort at insertion and over the first hours of wear, with a small reduction at prolonged wear.15,73,75 Varikooty et al. evaluated subjective comfort in patients fitted with delefilcon A (SHy) on their second day of use (visual analogue scale 0-100).75 Participants were grouped in symptomatic and asymptomatic, according to the frequency and severity of dryness symptoms with their usual CLs. Overall, delefilcon A (SHy) was rated slightly higher than other CLs and, although a slight reduction of comfort, ratings remained relatively high even after 12 hours (Figure 1).75 In a similar study, Wolffsohn et al. extended the wearing time to 16 hours, and recorded comfort over the 7th and last day of use.30 Consistently with other studies, there was a significant reduction of comfort over time (0-10 scale), with mean values (± standard deviation) of 8.3±1.6, 7.9±1.6, and 7.4±1.6 at 8, 12, and 16 hours of wear, respectively (Figure 1). The majority of the aforementioned studies trialed daily CLs in delefilcon A (SHy) for no longer than 1-2 weeks, and only a few studies provide an evaluation of comfort over a longer term,73,76 with values remaining stable over 3 to 12 months at the same time point of the day.

Another parameter examined was the quality of vision.75,77,78 High and low contrast visual acuities were found to be within normative values for healthy eyes and did not show clinically meaningful changes over 12 and 16 hours of wear.75 These results were consistent with findings on ocular aberrations, which were not affected by wearing time in a study comparing measures 20 minutes and 8 hours after CL insertion.77 As for the subjective comfort, quality of vision also appeared to remain consistent over longer term, with values on a visual analogue scale (1-10) showing no changes at two weeks (8.0 ± 1.9), one month (8.1±1.2), and two months (8.4±1.1).73

Overall, available literature indicates that delefilcon A (SHy) is associated with high quality of vision and high comfort ratings, which are retained even after extremely long wearing times. However, while taking these results together, there are characteristics and limitations of the available studies that must be considered in weighting the conclusions. For example, some of the studies included only current CL wearers.15,72,75 Overall, this could result in a selection bias, where users with greater tolerability are preferentially studied, leading to the overestimation of certain CL-related parameters. Additionally, retrieved studies are generally limited to young myopes (most average ages well below 30 years), with presbyopic, astigmatic, and hyperopic patients remaining poorly represented. As such, the aforementioned findings may not be transferable to all groups of CL wearers. Lastly, “end of day” data are often difficult to interpret as these measures may have been collected after an inconsistent number of hours of wear.34,73,75

# 7. Conclusions

Many SHy-CLs are available on the market, including lenses with a SHy core and a Hy outer layer with very high hydration (>80%), such as delelfilcon A (SHy), verofilcon A (SHy), and lehfilcon A (SHy). Among them, most of the results reported in the literature concern delefilcon A (SHy).

*In-vitro* analyses suggest a possible surface dehydration after insertion.11 Since dehydration starts with an evaporative process on the CL anterior surface, the dehydration of the outer layer deserves to be discussed in detail, especially for WG-CLs.11,12 Two aspects have been discussed in this review: (i) the very first minutes of wear and (ii) the longer-term dehydration phase. In the first phase, the surface of delefilcon A (SHy) dehydrated very quickly in a study based on refractometry (a method which allows characterizing the surface layer of a sample), starting from a surface refractive index (1.34), compatible with its high EWC (>80%), and reaching 1.43 after 15 minutes of wear.8 Since the first phase of evaporation is expected to last only a few minutes, in some experiments the second dehydration phase may have masked the initial one.15,16 Indeed, in the second phase, delefilcon A (SHy) shows a lower dehydration rate, behaving as a low EWC SHy-CL.16,17

The hydration state of the surface layer also plays a role in wetting and dewetting. WG-CLs are typically better than other SHy-CLs concerning *in-vitro* surface wettability when measuring the advancing water CA, which describes the initial spreading of the tear film on the CL surface (wetting).24 However, concerning the tear film stability when the pre-lens tear film retracts (dewetting), these differences between different materials resulted less pronounced, as observed *in vitro* by analyzing the receding CA24,25 and by *in-vitro* techniques inspired by *in-vivo* processes.26,27 This could be ascribed to the rapid dehydration of the outer layer, which causes WG-CL properties to quickly transform into those of a low EWC SHy-CL, showing low dewetting time. Nonetheless, if the field is extended to other WG-CLs, the results are controversial: for example, some authors27 reported a dewetting time four times longer for verofilcon A (SHy) than for other CLs.

*In-vitro* and *in-vivo* results are not entirely consistent. For example, delefilcon A (SHy) displays a low rate of dehydration-induced staining.19,20 Overall, despite some contradictory results, the *in-vivo* NITBUT on the lens surface20,28,30 and the tear interference pattern29 on the CLs were found to be better with WG-CLs than with other materials.

Relatively low CoFs are typically reported for WG-CLs,39,40 but lubricity is dependent on the surface layer ability to support the applied pressure without dehydrating. In this respect, some authors concluded that the possible collapse and dehydration of the surface layer could increase CoFs,40 whereas the presence of a persistent wetting agent is able to maintain a low CoF even after prolonged wear.46

Hydration, as well as deposits on the CL surface and tear film quality, is influenced also by the interaction between the surface layer and the tear components. In this case, the outer layer of delefilcon A (SHy) affects the deposition of proteins onto the lens surface.53,54 Nonetheless, these CLs often display a conventional SHy-CL behavior, as suggested by the interaction with lipophilic molecules.58,59,69

Finally, in terms of comfort, delefilcon A (SHy) typically performs equal72,73 to or better15,29,74,75 than the other CLs. Even considering prolonged wear, high subjective comfort was reported both after insertion and over the first hours of wear, with a small reduction with increasing wearing time.15,73,75

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**Legends**

**Table 1**. Properties of the WG-CLs discussed in this review.

**Figure 1**: Comfort with delefilcon A (rated between 0 and 10 or 0 and 100) reported in different studies as a function of time from insertion.15,30,75 For the studies from Wolffsohn et al.30 and Varikooty et al.75, data points represent mean subjective comfort and error bars ±1.96 standard deviation. Insua Pereira and Lira15 did not provide the standard deviation in the paper, and error bars show minimum and maximum rates.