

# The Impact of Comfort Eluting Agents and Replacement Frequency on Enhancing Contact Lens Performance

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**Abstract:** This review explores the development and clinical implications of soft contact lenses designed to elute comfort agents, emphasizing their role in enhancing user experience and ocular health. As discomfort remains one of the primary reasons for discontinuation of lens wear, this concept aims to address this challenge by gradually releasing these agents over their period of use. This review also explores the effectiveness, safety, and user satisfaction associated with frequent replacement schedules of these lenses. Clinical trials demonstrate that lenses with eluting comfort agents significantly reduce dryness and irritation, leading to improved wear-time and overall comfort. The findings suggest that frequent replacement not only enhances lens hygiene but also maximizes the therapeutic benefits of the eluted agents, promoting a healthier ocular environment. The implications for practice highlight a shift towards more patient-centered approaches in contact lens design and management, aiming to improve adherence and satisfaction among users. This research paves the way for future innovations in contact lens technology, focusing on personalized solutions that cater to individual comfort needs.

**Keywords:** comfort, contact lens, replacement frequency, wettability

## Introduction

Since their conception in the early 1960s, soft contact lenses (CL) have become a highly successful biomedical device, with an estimated 150 million wearers worldwide.<sup>1</sup> However, this success has involved overcoming numerous challenges, many of which continue to persist today. The first generation of CLs was crafted from the hydrogel material polyhydroxyethyl methacrylate (PHEMA)<sup>2</sup> and commercialised in the early 1970's. These lenses were well tolerated for daily wear, but due to their relatively low oxygen permeability, extended or continuous overnight use resulted in a variety of hypoxia-related complications.<sup>3–5</sup> The late-1990s saw the commercialisation of the first silicone hydrogel (SiHy) CL materials, which provided superior oxygen transmissibility and resolved many of the issues associated with hypoxia for extended and continuous wear.<sup>6–9</sup> However, the first-generation SiHy materials were more hydrophobic than hydrogel materials due to the large amount of siloxane-based monomers incorporated, resulting in increased lipid deposition,<sup>10</sup> and relatively poor in vitro wettability.<sup>11</sup> Increased lipid deposition on CLs has been shown to increase the likelihood of tear film breakup and promote dewetting of CL surfaces.<sup>12,13</sup> Companies have used a variety of surface modifications or the incorporation of internal wetting agents to mask the underlying hydrophobic components of the CL material from the tear film.<sup>14–17</sup>

When a clinician is selecting an appropriate CL for a patient, in addition to choosing between hydrogel or SiHy-based materials, they must choose an appropriate frequency of replacement. The mid-1980's saw the introduction of frequent replacement lenses, with most lenses being replaced every two or four weeks. These lenses exhibited significant clinical advantages over soft lenses that had traditionally been replaced annually or longer, especially with respect to comfort,

vision, deposition, number of unscheduled visits and overall complications.<sup>18–21</sup> However, reusable CLs still exhibited complications due to poor compliance with cleaning, frequency of replacement and poor case hygiene.<sup>22,23</sup> Some of these issues were addressed with the introduction of the daily disposable CL modality in the mid 1990s.<sup>24–26</sup> Although they are relatively more expensive, daily disposable replacement schedules offer greater convenience, exhibit fewer adverse events and have improved compliance compared to lenses which need to be regularly cleaned and reconditioned.<sup>23–30</sup> Indeed, the current market trend favors the use of daily disposables.<sup>31</sup> However, this shift has raised growing concerns about waste generation and environmental sustainability and incurs an increased cost for the wearer.

The evolution of CL materials remains dynamic, as the industry continues to develop materials with superior performance to previous generations.<sup>16,17</sup> However, this evolutionary progress has resulted in an immense catalogue of CLs available today. This multitude of choices can be both beneficial but also challenging for clinicians, as selecting the optimal lens type for a particular patient is not always straightforward.

The success of CL wear is heavily influenced by lens performance on the eye, particularly with respect to comfort,<sup>32,33</sup> which is the primary reason for discontinuing CL wear in long term wearers.<sup>33–35</sup> However, understanding CL comfort is a complex matter influenced by numerous factors, including lens fit, design, modulus, wettability, friction, lubricity, water content, oxygen permeability, ocular responses, tear film interactions, lens deposition, and the uptake and release of components from multipurpose solutions (MPS) for reusable lenses, as well as demographic factors.<sup>23,32,34,36–40</sup> Several comprehensive reviews have been published addressing CL discomfort,<sup>23,32,34,37–39,41–46</sup> but there is still no consensus regarding the exact mechanisms that drive CL discomfort and the factors needed to alleviate this.

There are two factors worthy of consideration that have received relatively little discussion. The first relates to the possibility of incorporating wetting agents into CL materials that are released slowly and that act as “comfort agents”. Some commercial lenses already incorporate wetting agents into the blister packaging solution to enhance initial comfort,<sup>47</sup> while others incorporate these agents directly into the lens material during their manufacture.<sup>39</sup> The release of these agents could help improve CL performance by improving comfort and reducing dryness associated with CL wear. The second factor is determining the optimal frequency of replacement for a patient, as it is entirely possible that optimal performance may decline well before the scheduled replacement.<sup>48</sup>

This article provides a review of current research exploring the enhancement of CL performance by focusing on the release of wetting agents and the influence of lens replacement frequency on comfortable CL wear, with a particular emphasis on how this may impact materials designed to release wetting agents.

## Methods

This review was conducted using information sourced from a wide variety of databases, including PubMed, Scopus, Web of Science, and ScienceDirect. Additional online resources, such as Contact Lens Spectrum, were referenced where necessary. The search strategy was designed to achieve the objective of the review: examining the impact of comfort-eluting agents and replacement frequency on enhancing CL performance.

## Release of Wetting Agents

The concept of using CLs for the sustained release of a wetting agent shares many similarities to that seen in the design of CL materials for topical ocular drug delivery.<sup>49</sup> The use of CLs to deliver topical drugs or comfort agents offers two key benefits. First, any agent released from the lens into the post-lens tear film experiences less influence from removal mechanisms such as blinking and tear drainage, resulting in an extended residence time and contact with the cornea. Second, soft CLs naturally absorb water and other compounds, including drugs. These absorbed agents can interact with the lens polymer, creating a drug reservoir that can be tuned to be released in a sustained manner.<sup>49–51</sup> Different strategies, such as modifying the polymer composition or incorporating nanoparticles, liposomes, and coatings, can be employed to control and prolong the release duration of the drug from the CL material.<sup>49–52</sup>

Similarly, wetting agents, such as surfactants, can be added to the lens during the manufacturing process, with the intention of releasing them during wear to enhance CL performance.<sup>52–63</sup> By increasing lens surface wettability with a wetting agent, the surface tension is lowered, facilitating the spreading of the tear fluid over the lens. Increased lens wettability is also associated

with reducing friction between the lid and the lens surface, which is believed to enhance CL comfort.<sup>39</sup> Additionally, wetting agents can also interact with the tear film, increasing tear film stability and preventing dewetting of the lens surface.<sup>64</sup>

Several methods have been explored to load wetting agents into lenses, including their incorporation into blister pack solutions,<sup>47,53–56,58,65–71</sup> incorporating them into the lens material,<sup>53–62</sup> adding wetting agents to MPS that soak reusable lenses overnight,<sup>72–81</sup> and applying rewetting drops over the lens surface.<sup>37,39,82–86</sup> In most cases, the wetting agents are rapidly released from the CL within a few hours,<sup>56,65,70</sup> thus the overall comfort boost may only be temporary. In an attempt to prolong comfort, manufacturers are investigating designing lens materials that can provide sustained release of agents for longer periods.<sup>58,87</sup>

Table 1 summarizes the various wetting agents that are released from CL materials to enhance their performance. Only studies that included measuring the release of a wetting agent or its effect over at least two time points have been included.

There are four broad ways by which wetting agents can be “added” to a CL material: Incorporating them into the blister packaging; incorporating them into the lens material; incorporation into the multipurpose solution or incorporating them into an ocular lubricant.

## Wetting Agents Incorporated into the Blister Packaging

Historically, blister pack solutions consisted of buffered saline.<sup>94</sup> These solutions have evolved over time to include various other components, including wetting agents. The specific wetting agents used in the blister pack are often not explicitly mentioned on the packaging or the package inserts, making it a challenge to determine their exact composition. Some identified components in commercial products include polyethylene glycol (PEG),<sup>66,70</sup> polyvinylpyrrolidone (PVP),<sup>66</sup> polyvinyl alcohol (PVA),<sup>53–57,65</sup> poloxamines (Tetronics®),<sup>66,69</sup> hydroxypropyl-methylcellulose (HPMC),<sup>54,70</sup> hyaluronic acid (HA),<sup>59</sup> and poly(oxyethylene)-co-poly(oxybutylene) (PEO-PBO).<sup>58</sup> A wide range of wetting agents have been used by different manufacturers, but a single “best” agent is yet to be identified. Unsurprisingly, due to variations in components, the surface tension of commercial blister pack solutions has been shown to vary greatly, between 22–70 dynes/cm.<sup>47,67</sup> The ideal range that is suggested to promote comfortable CL wear is between 42–46 dynes/cm,<sup>95</sup> and a large portion of blister pack solutions appear to fall in this range.

The release of wetting agents from CL that are merely soaked in a blister pack solution is typically temporary, providing only an initial comfort boost following initial CL insertion. Studies investigating the hydrogel material etafilcon A that was soaked in a solution of wetting agents including poloxamine, PEG, and PVP have shown increased subjective comfort within the first 30 minutes of wear, which also correlated with a reduced measured surface tension during this same time period.<sup>66</sup> Clinical studies with the PVA-based nelfilcon A hydrogel material that contains non-polymerized PVA that “leaks” into the blister pack have demonstrated improved non-invasive break-up time (NIBUT) and subjective comfort on lens insertion, although comfort ratings decreased over time.<sup>53</sup> In vitro studies with PVA, HPMC, and PEG and various CL materials have indicated that the majority of the release from the lenses occurs within the first few hours of wear.<sup>56,65,70</sup> These observations, which follow a burst release, are in line with those of therapeutics released from commercial CLs that have not been specifically designed for sustained delivery.<sup>49</sup> Notably, wetting agents incorporated into the blister pack solution are thought to be primarily surface-bound, as washing or rinsing the blister pack solution from lenses has been shown to reduce the lens wettability as compared to when lenses are removed directly from the packaging.<sup>71</sup> Interestingly, one study has shown sustained release of a high molecular weight, amphiphilic, non-ionic, wetting agent, PEO-PBO, from a blister pack for up to one week.<sup>58</sup> This innovative technique allows for up to 80% of the absorbed wetting agent to become irreversibly trapped within the lens material (serafilcon A) while the remaining portion is available for release over a period of up to one week,<sup>58</sup> although its impact on sustained comfort is unknown. In another in vitro study, Phan et al showed that serafilcon A released a fluorescently tagged version of PEO-PBO over 7 days in a simulated wear and cleaning regimen.<sup>87</sup>

Currently, there is limited research on leveraging the uptake and release of wetting agents from blister packs, with most studies suggesting that these agents are only used to provide improved comfort within a short period after CL insertion.

## Wetting Agents Incorporated into the Lens Material

Silicone hydrogel CLs, due to their siloxane components, can exhibit poor wetting properties compared with hydrogel materials. To address this issue, wetting agents can be incorporated into the lens material or added as a surface treatment during the lens manufacturing process to enhance the intrinsic wettability of the material.<sup>14,16,39</sup> Various compounds have

**Table 1** Summary of Wetting Agents Released From CLs to Improve Lens Performance

	Study Type	Ref	CL Material	Wetting Agents	Key Results
<b>Blister</b>	In vitro	Phan et al <sup>70</sup>	Nelfilcon A	HPMC, PEG	Burst release within the first 1.5 hours following lens insertion. Release performed in an eye model with low volume and flow rate
	Ex vivo	Tonge et al <sup>66</sup>	Etafilcon A	Poloxamine 1107	Lenses treated with surfactant had better wettability and rated more comfortable than control lenses. Surfactants retained on lens for at least 8 hours
<b>Blister and Incorporated</b>	Clinical	Peterson et al <sup>53</sup>	Nelfilcon A	PVA	Release of additional non-functionalized PVA from lenses seems to enhance comfort - NIBUT and subjective comfort improved, but subjective comfort decreased with time
	Clinical	Müller et al <sup>54</sup>	Nelfilcon A, etafilcon A, omafilcon A	HPMC, PVA	Nelfilcon had better NIBUT than other lens types, attributed to its wetting agents; etafilcon A had better wettability at 5 min compared to end-of-day wear
	In vitro	Winterton et al <sup>55</sup>	Nelfilcon A	PVA	Rapid release of PVA within first 8 hours but maintained up to 20 hours. Release performed in 50 mL of saline
	In vitro	Phan et al <sup>65</sup>	Etafilcon A, nelfilcon A, and omafilcon A	PVA	Burst release of PVA in the first few hours. Release performed in an eye model with low volume and flow rate
	In vitro	Phan et al <sup>56</sup>	Nelfilcon A	PVA	Burst release of PVA within the first few hours. Release performed in 2 mL of saline.
	In vitro	Zheng et al <sup>58</sup>	Serafilcon A	PEO-PBO	Sustained release for 7 days. Release performed in 20 mL of saline.
	In vitro	Maulvi et al <sup>59</sup>	Model PHEMA materials	HA	HA incorporated into CL showed sustained release up to 15 days compared to soaking method which released within 48 hours. Release performed in 2 mL of simulated tear fluid in vial
	In vitro	Phan et al <sup>87</sup>	Serafilcon A	PEO-PBO	Sustained release for 7 days. Release performed in 1 mL of saline, replaced daily
<b>Incorporated</b>	In vitro	Lieu et al <sup>60</sup>	Model nelfilcon A materials	PVP, HA, dextran	PVP showed a rapid release, whereas dextran and HA showed sustained release, improvement in wettability over 72 hours
	In vitro	Ali et al <sup>61</sup>	Model nelfilcon A materials	HA	HA can be delivered at therapeutic doses for 24 hrs, but can be extended for days to months by tuning the material. Release performed in 20 mL of artificial lacrimal solution
	In vitro	Weeks et al <sup>62</sup>	Model CH and SH materials	HA	HA released for 21 days from conventional hydrogels and up to 7 weeks for SiHy. Release performed in 1 mL of saline
	In vitro	Yañez et al <sup>88</sup>	Model PHEMA CL	PVP	Release of PVP sustained over 30 days with improvement in friction of the model lens materials. Release performed in 20 mL of water
	In vitro	White et al <sup>89</sup>	Model SH CL – molecular imprinting	HPMC	Release from 10–53 days depending on formulation. Release was performed on a microfluidic device with low volume and flow rate

<b>MPS</b>	Clinical and in vitro Clinical In vitro	Simmons et al <sup>81</sup>  Fagehi et al <sup>90</sup> Scheuer et al <sup>91</sup>	CH CLs  Senofilcon A Polymacon, alphafilcon A, etafilcon A, balaafilcon A, lotrafilcon B, lotrafilcon A, galyfilcon A, senofilcon A, comfilcon A	HPMC  Various MPS HA	MPS with HPMC improved wetting of lenses and comfort, HPMC releases gradually with detectable amounts beyond 12 hours in saline In vivo lens wettability higher at 15 minutes than 8 hours for most MPS Slow release over 20 h, release rate dependent on lens material. Release was performed in a modified lens case, infused with low flow rate
<b>Loading</b>	In vitro  In vitro	Pitt et al <sup>92</sup>  Pitt et al <sup>93</sup>	SH CL  SH CL	DMPC  DMPC	Burst release within 10 h but can be sustained up to 70 h. Release performed in 3 mL of artificial tear fluid or water; release was 5X faster in ATS than water  Release within 10 h into ATS was diffusion controlled and proportional to amount of DMPC loaded on lens. Release performed in 3 mL of artificial tear fluid or water

**Abbreviations:** ATS, artificial tear solution; CH, conventional hydrogel; CL, contact lenses; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; HA, hyaluronic acid; HPMC, hydroxypropylmethylcellulose; NIBUT, non-invasive break-up time; PEG, polyoxyethylene glycol; MPS, multipurpose cleaning and conditioning solutions; PEO-PBO, poly(ethylene oxide)-poly(butylene oxide); PHEMA, poly(hydroxy ethyl methacrylate); PPG, polypropylene glycol; PLTF, pre-lens tear film; PVA, polyvinyl alcohol; PVP, polyvinyl pyrrolidone; SH, silicone hydrogel.

been successfully employed for this purpose, including PVA, PEG, HPMC, HA, N-vinyl pyrrolidone (NVP), PVP, methacrylic acid (MA), poly-2-ethyl-2-oxazoline, glycidyl methacrylate, dextran, phosphorylcholine, phosphocholine, phosphatidylcholine, and poloxamers.<sup>16,39,60,92,93,96–98</sup> The majority of these agents become embedded within the lens material itself as internal wetting agents, whereas others modify the surface wettability.<sup>14,16,39,96,97</sup> Only a very small fraction of these wetting agents, in particular PVA,<sup>53–57,65</sup> HA,<sup>60</sup> PVP,<sup>60</sup> dextran,<sup>60</sup> and phosphocholine<sup>92,93</sup> have been shown to be released from the lens rather than remaining fixed within the lens.

PVA has garnered the most attention among these releasable wetting agents, particularly in relation to its release from the nelfilcon A material.<sup>53–57,65</sup> PVA has a wide range of biomedical applications due to its biocompatibility and lubrication properties.<sup>99</sup> Nelfilcon A is made from photo cross-linked PVA and non-polymerized PVA is released from the material into the blister pack and subsequently from the lens onto the ocular surface during wear.<sup>53,55,57,63</sup> Several clinical studies have demonstrated that nelfilcon A CLs do indeed provide enhanced comfort, which can be attributed to the release of PVA.<sup>53,54</sup> Initial in vitro studies with nelfilcon A suggested that PVA is released from the CL over 8 hours.<sup>55,63</sup> However, later studies showed that the majority of the PVA is released within a few hours,<sup>56,65</sup> limiting its impact over the course of the day. However, it may be possible that the released PVA becomes trapped beneath the post-lens tear film, resulting in longer than expected residence time on the eye. The nelfilcon A material also releases two other wetting agents, PEG and HPMC.<sup>70</sup> It is thought that the HPMC provides initial comfort immediately after lens application, PEG release provides an early-day comfort boost, and PVA release is sustained for a longer period.<sup>57</sup>

Aside from PVA, there have been limited attempts in the industry to develop CLs capable of releasing other wetting agents. Some studies have focused on incorporating HA<sup>59–61</sup> and phosphocholine<sup>92,93</sup> into model CL materials. HA is a hydrophilic polymer commonly used in ophthalmic applications for its wetting properties and ability to stabilize the tear film.<sup>100,101</sup> Studies have demonstrated sustained release of HA from model CL materials ranging from 24 hours to several weeks.<sup>59–62</sup> Molecularly imprinted CLs with HPMC showed that these lenses can provide release of the wetting agent for up to 53 days in vitro.<sup>89</sup> Model hydrogel CLs made from HEMA with PVP showed that this lens material could release PVP for up to 30 days, with measured improvements in the friction of the lens material surface.<sup>88</sup> These findings suggest that HA, 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and HPMC, may be potential wetting agent candidates for release from a CL, but studies thus far have only been performed on model CL materials in the laboratory. Moreover, the uptake and release of these agents from a simple soaking procedure already seem to be sufficient for a daily wear modality, so incorporating them into the lens material for a longer release duration may not be needed.<sup>59</sup>

## Wetting Agents Incorporated into Multipurpose Solutions

A multipurpose solution (MPS) plays a crucial role in restoring the performance of reusable CLs by effectively cleaning, disinfecting, and restoring the lens to a usable state following an overnight soak. Contemporary MPS formulations are complex, comprising a combination of buffers, biocides, surfactants, chelating agents, and hydrating agents for soft CL storage.<sup>39,43</sup> Similar to that seen with respect to the situation described previously relating to blister pack solutions, CLs can also uptake components from the MPS, including biocides, surfactants and wetting agents.<sup>36,39,43,102,103</sup> These sorbed components can be subsequently released onto the corneal surface during lens wear, potentially impacting the overall clinical performance, positively or negatively, of the CL on the eye.<sup>36,43,102,103</sup> While the majority of studies have focused on the negative effects of CL uptake and subsequent release of biocides or other components from the MPS,<sup>36,39,41,43,102–107</sup> it is equally important to recognize the potential opportunity for MPS to enhance CL performance with a fresh supply of wetting agents.<sup>34,43</sup>

Wetting agents commonly found in MPS vary among manufacturers and include poloxamers (Pluronic<sup>®</sup>),<sup>90,108</sup> poloxamines (Tetronics<sup>®</sup>),<sup>77,90,108</sup> PEO-PBO,<sup>78,80</sup> hyaluronic acid, aloe vera,<sup>73</sup> and PVP.<sup>73</sup> These wetting agents can be absorbed into the bulk of the lens material or adsorbed onto the lens surface, depending on the presence of a surface coating.<sup>109</sup> Numerous studies have demonstrated that the use of MPS generally enhances lens wettability and performance.<sup>37,39,72–81,90,91,110</sup> A study also showed that an MPS containing wetting agents demonstrated improved ocular comfort, reduced blink frequency, enhanced visual performance, and improved tear film quality compared to an MPS without wetting agents.<sup>79</sup> Some studies have also suggested that certain wetting agents, such as PEO-PBO, may offer slightly superior comfort compared to others,<sup>78,80</sup> while agents such as aloe vera or PVP may not have significant



effects on wettability.<sup>73</sup> While there is substantial evidence supporting the positive effect of wetting agents in MPS on lens wettability,<sup>37,72–81,90,91,110</sup> only a few have examined the release of these agents from the CL over time.<sup>81,90,91</sup>

Similar to blister pack solutions, it can be postulated that the release of wetting agents sorbed onto a lens from an MPS would likely occur rapidly,<sup>56,65,70</sup> resulting in only an initial impact on comfort, with little sustained benefit. Studies observing the uptake and release of biocides from MPS have shown that the release of biocides occurs rapidly, within the first few hours.<sup>102,111–113</sup> Although limited studies have investigated the release of wetting agents following an MPS soak, the available evidence indirectly suggests that the majority of the release is also within hours.<sup>39</sup> A clinical study using tear interferometry conducted with senofilcon A using various MPS solutions demonstrated that in vivo lens wettability was higher at 15 minutes compared to 8 hours.<sup>90</sup> The decline in wettability may have already occurred within the first few hours, but the study did not measure this time point.

Some studies, however, have suggested that the release of wetting agents can be sustained from a lens exposed to an MPS soak. A study investigating the uptake and release of a HPMC-containing MPS reported improved lens wettability and comfort, with detectable levels of HPMC released even beyond 12 hours.<sup>81</sup> An in vitro study looking at the retention of fluorescently tagged HA to commercial CLs also showed that while there is a burst release within 4 hours, almost all of the materials tested could release HA for up to 20 hours.<sup>91</sup> Studies with radiolabeled DMPC demonstrated that these phospholipids can be absorbed into a SiHy material and then subsequently released from the lens materials for up to 70 hours, although a burst release does occur within the first 10 hours, with more elution of the drug into an artificial tear solution than water.<sup>92,93</sup>

To date, there is clearly a lack of studies on the uptake and release of wetting agents from MPS to enhance CL performance, highlighting the need for further research in this area.

## Wetting Agents Incorporated into Ocular Lubricants

One strategy to improve CL performance is through the use of rewetting drops, which are commonly referred to as lubricating drops or comfort drops.<sup>39</sup> These drops are frequently recommended for CL wearers experiencing dryness and discomfort, and can be applied just before or during lens wear.<sup>83,114</sup> Rewetting drops contain a variety of wetting agents, such as HPMC, PVA, PVP, HA, poloxamines (Tetronics®), PEG, carboxymethylcellulose (CMC), dextran, and povidone, each with distinct molecular weights, shear strengths, viscosities, and mucoadhesive properties that impact their performance.<sup>39,82,115,116</sup>

It is worth noting that the efficacy of rewetting drops can differ between materials, with some studies suggesting greater improvements in wettability for hydrogel CLs compared to SiHy lenses, where wettability improvement may be inconsistent or even diminished.<sup>83,117</sup> A study investigating the impact of a rewetting drop containing two surface active agents (RLM-100 and Tetronic® 1304) on a SiHy material (lotrafilcon A) when used on a 30-day continuous wear basis found that the rewetting drop provided greater subjective satisfaction, reduced lysozyme and total protein deposition, and reduced denatured lysozyme than a rewetting drop containing saline alone, each applied four times daily.<sup>118</sup> Notably, one study found that HA, HPMC, and CMC had greater comfort properties than other agents tested.<sup>116</sup> Several strategies have been proposed to improve the performance of rewetting drops, such as increasing viscosity at low shear rates without exceeding the blur threshold, or using a high molecular weight wetting agent with low polydispersion index.<sup>83,119</sup> A study with HA showed that formulations with 0.1% HA improved the in vivo wettability of hydrogel CLs for 5 minutes, whereas a more viscous 0.3% HA solution improved the wettability for 30 minutes.<sup>83</sup>

Most rewetting drops typically have a very short residence time on the eye.<sup>84,115</sup> Improvements after instilling a rewetting drop during CL wear are typically transient, lasting less than 10 minutes.<sup>37,39,84,85</sup> Moreover, while subjects may experience improved subjective comfort after using the rewetting drop, there is currently no other evidence suggesting enhanced tear film stability or optical quality.<sup>120</sup> The benefits of using a rewetting drop are also not immediate and may take months to manifest for CL wearers.<sup>86</sup> A study also indicated uncertainty as to whether the improved comfort was due to the specific wetting agent used or if saline solution alone would suffice.<sup>121</sup> Nonetheless, most studies suggest that rewetting drops do improve comfort and reduce ocular symptoms associated with CL wear.<sup>82,118,121–124</sup>

To date, there have been no studies that have actively examined the release of wetting agents from rewetting drops when applied to CLs in-situ, and this may be an area of future exploration. Existing research has indicated that certain

components in ophthalmic formulations can be absorbed by soft lenses and gradually released onto the ocular surface over time. A noteworthy example is benzalkonium chloride (BAK), a commonly used preservative in glaucoma medications, which can unintentionally be absorbed by a soft CL material and subsequently released on the eye, potentially leading to adverse effects on the ocular surface.<sup>125</sup> In such scenarios, it is recommended to allow a minimum of 15 minutes between instilling medication and wearing lenses.<sup>125</sup> Rather than presenting a negative impact, these underlying mechanisms could also be leveraged to deliver wetting agents to improve CL performance.

A notable limitation in the current literature is the reliance on *in vitro* studies to measure the release of wetting agents from lenses, often using non-standardized, vial-based models. The release medium's environment has been shown to significantly impact release rates.<sup>92,126,127</sup> For instance, DMPC was released five times faster in an artificial tear solution compared to water.<sup>92</sup> Additionally, drug delivery studies with CL materials indicate much slower release in advanced *in vitro* models with low tear volume and flow than in vials.<sup>126,127</sup> The lack of standardization and use of different models complicate comparisons across studies and underscore the importance of also carefully considering system parameters before extrapolating results to predict the performance on the eye.

In reviewing the literature on wetting agents, it is clear that the incorporation of surface-active agents into the blister pack, into the lens material itself, in the MPS used to disinfect and clean reusable lenses overnight or by direct application over the CL can all bring potential benefits to lens wearers and enhance the wearing experience. However, these approaches can be impacted by the lens material used and the frequency with which the lens is replaced. What evidence exists that can assist the prescribing practitioner on the most appropriate lens replacement period, and how could that be linked to the potential incorporation of wetting agents? The literature on wetting agent release from soft lenses remains limited, highlighting the need for further studies to advance sustained-release technologies and assess their clinical impact on lens comfort. Research into using multipurpose solutions or ocular lubricants to enhance comfort with wetting agents would also be valuable.

## Replacement Frequency and Contact Lens Comfort

Increasing the frequency of replacement is widely recognized as advantageous for promoting ocular health and enhancing lens wearer comfort.<sup>34,41</sup> Indeed, there is a growing trend towards the prescribing of daily disposable CLs.<sup>31,128</sup> However, the daily disposable modality comes with significantly increased costs for full-time wearers<sup>129</sup> and growing concerns regarding their environmental impact.<sup>130</sup> Reusable modalities address these shortcomings but, in turn, have their own challenges. For this reason, the optimal replacement frequency varies between patients, as it depends on several factors, including CL performance, cost, and patient compliance.

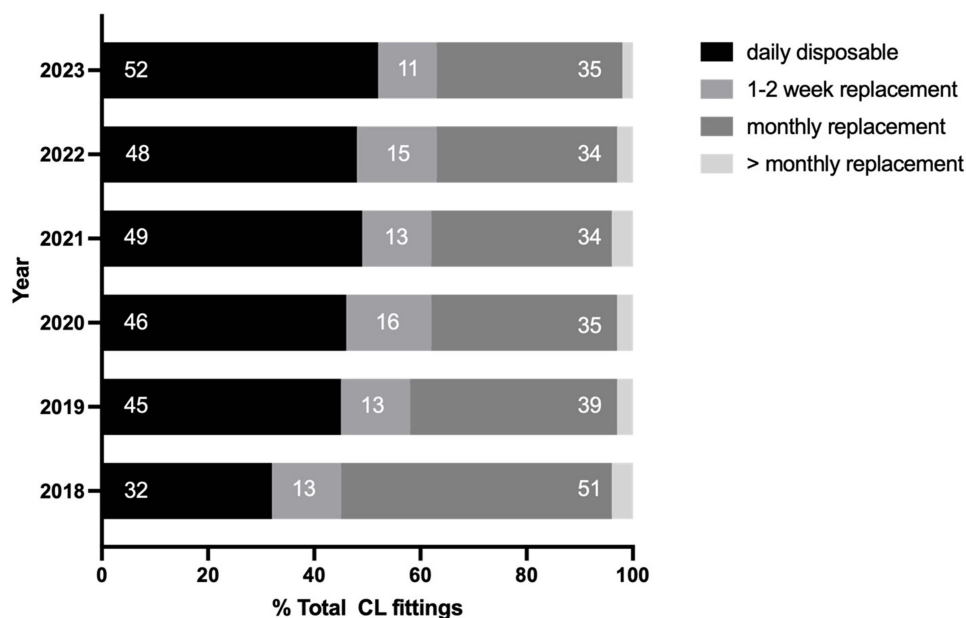
## Current Wear Modalities and Performance

There are two primary modalities for soft CL wear, namely daily disposable and reusable, with the latter requiring lenses to be removed, disinfected overnight and replaced after a certain period. Reusable lenses are typically replaced after 2 weeks or 1 month, with some lenses being replaced for durations exceeding 1 month.<sup>31,128</sup> The preference for each modality varies based on geographic location, with daily disposables being more popular in Australia, Canada, the UK, and Japan, while reusable lenses are more commonly fit in France and The Netherlands.<sup>31</sup> There has been a noticeable shift towards an increase in daily disposable lens wear such that there is now an almost 50:50 split of reusable to daily disposable fits (see Figure 1).<sup>31,128,131–134</sup> In 2018, daily disposable CLs accounted for approximately 32% of fittings, rising rapidly over the past 6 years. Among daily disposable lenses, SiHy options are increasingly becoming the preferred choice, now accounting for 73% of all daily disposable materials fit.<sup>31</sup>

The increasing preference for daily disposable CLs may be attributed to their advantages over reusable CLs. Daily disposables offer greater convenience, improved ocular health, fewer adverse events, and better compliance with replacement schedules compared to lenses that require regular cleaning and reconditioning.<sup>29,30,135</sup> Reusable lenses have an increased risk of corneal infiltrates compared with daily disposable lenses,<sup>136–138</sup> and silicone hydrogel reusables show an approximate 2x increased risk of infiltrates compared with hydrogel reusable materials.<sup>136,137,139,140</sup> Disinfection and overnight cleaning with MPS may also result in unwanted uptake of biocides and other agents, which can result in poor lens performance and corneal staining.<sup>30,36,39,41,43,102,103,107</sup>

One of the primary drawbacks of using daily disposable CL relates to the higher cost, but advancements in manufacturing methods may address this concern in the future. Another factor to consider is that manufacturers need





**Figure 1** Contact lens fitting modalities worldwide from 2018 to 2023.

to tackle the challenge of increased packaging waste, particularly for the daily disposable modality.<sup>130,141</sup> Full-time daily disposable wearers generate 27% more waste annually compared to their reusable counterparts.<sup>130</sup> Fortunately, most of the waste associated with CL, for both daily disposable and reusable modalities, can be recycled with the appropriate infrastructure for waste collection in place.<sup>130</sup> However, to date, there is no information on whether the majority of CL waste ends up in landfills or is actually recycled through programs.

The data in Figure 1 was collected from various countries, and the reported percentages are based on the global average. The fitting modality percentages for individual countries may vary from the average. There is a trend shift from monthly reusables to daily disposables.<sup>31,131–134,142</sup>

Based on economic factors alone, monthly replacement should be the most popular fitting option, since they are least expensive for full time wear, even when factoring in the cost of solutions.<sup>129</sup> However, in many countries daily disposables have the highest CL fitting rate,<sup>31</sup> suggesting that cost considerations may no longer be a significant barrier for the adoption of daily disposables CL for many wearers. In comparison, based on CL performance, it would be natural to assume that daily disposables would be the most widely fit modality, followed by 1–2 week lenses, and then monthly replacement. In a survey-based study, a daily disposable modality recorded higher end of day comfort than a 2-week or 1-month replacement frequency.<sup>143</sup> Daily disposables also offer convenience for patients, as they eliminate the need for cleaning solutions and storage cases.<sup>29,144</sup> Clinical trials with daily disposables show fewer ocular adverse events and better comfort compared to their reusable counterparts.<sup>29</sup> Review of the overall data from various studies suggests that there are relatively small differences in performance between 2-week and monthly modalities. However, monthly fittings are currently more than double that seen for 1–2 week lenses,<sup>31</sup> suggesting there are other key factors than performance that drive practitioners to fit monthly replacement lenses, including cost and availability of products.

## Patient Non-Compliance

Non-compliance with lens-wearing schedules, replacement schedules, and lens care regimens continues to pose a challenge, leading to reduced CL performance, complications and an increased chance of CL dropout.<sup>143,145</sup> Although manufacturers do provide specific instructions for optimal performance, these details can become unclear or lost as they are passed from practitioners to patients.<sup>146</sup> Not surprisingly, patients who are compliant, in particular replacing their lenses based on the recommended schedule, achieve improved CL subjective performance for both

comfort and vision.<sup>143</sup> However, effectively managing and ensuring patient compliance remains a complex endeavour that requires further attention and innovative approaches.<sup>143,145,146</sup>

Non-compliance with CL wear and care is extremely high, with reported rates ranging from 50% to 99%, and it exists even in situations where patients are aware of the risks associated with non-compliance.<sup>22,40,145,147–154</sup> However, despite these issues, there is a lack of comprehensive data on strategies to improve compliance. Studies have shown that compliance varies among different replacement modalities, with daily disposables demonstrating the highest compliance with replacement frequency, followed by monthly lenses, with 2-week lenses showing the poorest compliance for replacing lenses on time.<sup>148,152,155–157</sup> Reasons for noncompliance include “forgetting” to replace lenses and saving money.<sup>29,155–157</sup> These findings are not surprising, as replacing lenses daily or on the same date each month is inherently easier to remember than tracking a 2-week schedule.

## Determining Optimal Replacement Frequencies

Determining an optimal replacement frequency is challenging due to complex factors, including the material interactions with tear film components, MPS and wetting agents.<sup>39</sup> The lens material characteristics also play a crucial role in determining the optimal frequency of replacement.<sup>158</sup> Additionally, individual patient factors and compliance with cleaning and maintenance instructions further contribute to variability in lens performance.<sup>143,145</sup> Moreover, each patient physiology is also different, and so responses to CL wear may also vary greatly, and personal preferences may also play a role.

To maintain optimal lens performance, the recommended replacement frequency for most patients can range anywhere from 1 week to several months.<sup>48</sup> For symptomatic patients, a shorter replacement interval down to 1 week has been suggested.<sup>48</sup> In vitro studies with reusable CLs show increased deposition of proteins and lipids over time, with more deposits at 1 month than 2 weeks.<sup>10,159–164</sup> In vivo studies on protein and lipid deposition indicate that there may be an optimum point for hydrogel lens replacement between 1 and 7 days: protein deposition stabilizes within 7 days, while lipid deposition reaches a maximum within 1 day on group IV lenses but gradually increases on group II materials over 4 weeks.<sup>159</sup> However, the direct link between increased deposition and clinical discomfort remains unclear, and further investigation is required.<sup>41</sup> Nonetheless, for a reusable lens wearer, a replacement schedule of 1 week or less may be optimal in order to mitigate the potential issues associated with longer replacement intervals.

The 2-week replacement modality was initially chosen for the etafilcon A material when it was not prescribed on an extended wear, one-week replacement schedule.<sup>165</sup> There is no clinical data or publications to suggest why this particular replacement schedule was originally determined. Once daily disposable lenses became available, the 2-week modality continued to be widely used to strike a balance between the convenience of daily disposables and the lower cost of monthly lenses. However, as detailed above, in terms of compliance, the 2-week modality can create problems with remembering when to replace the lenses,<sup>29,155–157</sup> leading to potential impacts on lens performance. In addition, many practitioners opt to advise patients to replace their 2-week replacement materials every month.<sup>155,157</sup>

To-date, there is no widespread availability of a 1-week replacement frequency, daily wear material.<sup>87</sup> However, intuitively, the replacement frequency would be simple to remember (as is 1 day and 1 month) and the clinical performance should conceptually be closer to that seen with daily disposables, while still offering the cost advantages of reusable lenses. Ideally, practitioners would be able to “personalize” a replacement schedule for a specific material for each wearer, with the lens being replaced prior to a reduction in performance. Such an approach would hopefully improve the wearer’s experience, reduce the risk of complications and optimize the cost to the wearer. Indeed, previous work has shown that patient deposition is highly individual<sup>166–168</sup> and that adopting a blanket replacement schedule for a particular material is not an ideal approach. However, while indeed ideal, such an approach is fraught with difficulties relating to what key metrics would drive the decision and how such a system would be administered by the prescribing practitioner. Given this, then an option to replace a lens on a weekly basis may be a viable consideration.

## Summary

CL performance, particularly in terms of comfort, is influenced by a multitude of factors.<sup>34,35,44–46,169–171</sup> Existing research has primarily focused on investigating the physical properties of CLs, their interactions with the tear film and ocular surface, as well as the impact of MPS on CL performance over time.<sup>23,32,34,37–39,41,172,173</sup> This review has

investigated two specific aspects that also play a crucial role in enhancing CL performance: the interaction and release of wetting agents from CL materials and their replacement frequency.

The release of wetting agents from CL materials, particularly nelfilcon A that is based on PVA, has been associated with improved comfort.<sup>53–57,65</sup> However, a challenge in achieving sustained release is the tendency for these wetting agents to be released within a few hours.<sup>55,56,65</sup> While methods used for CL drug delivery could potentially enhance the duration of wetting agent release,<sup>52,59–61,88,89</sup> this approach would introduce additional complexity to the manufacturing process, resulting in increased costs for both manufacturers and wearers. Moreover, designing CLs specifically for delivering wetting agents may subject them to the same regulatory scrutiny as lenses intended for drug delivery.<sup>49</sup>

Several methods have been explored to incorporate wetting agents into CL materials, including their inclusion in blister pack solutions,<sup>47,53–56,58,65–71</sup> MPS,<sup>72–81</sup> and rewetting drops.<sup>37,39,82–86</sup> Overall, the longer the incubation period and the higher the concentration of the wetting agent, the longer its effect is felt. Hence, blister packs and MPS have demonstrated better outcomes compared to rewetting drops. However, the consensus is that these wetting agents only provide temporary relief, with effects lasting minutes to at most an hour.<sup>39</sup> Thus, end-of-day comfort for CLs continues to remain an issue that cannot be addressed with the current release technology approaches used to deliver wetting agents. Recent research has demonstrated that it is possible to release wetting agents such as PEO-BEO for up to one week,<sup>58,87</sup> but to-date there are no published clinical studies to validate whether this release is correlated to improved comfort. The investigation of wetting agent release from CLs remains a relatively unexplored area of research, presenting a valuable opportunity for further exploration around methods to enhance CL performance.

Despite the known importance of replacement frequency for ensuring optimal CL performance,<sup>41</sup> there is a lack of comprehensive research investigating its impact, in particular with contemporary materials. It is intuitive that simply replacing a CL frequently would address issues related to tear film deposition and interactions with tear film components over time. This is reflected in the increasing popularity of daily disposable CLs over the past decade,<sup>128,131–134,142</sup> which accounted for nearly 50% of all CL fittings in 2023.<sup>31</sup> Daily disposables offer numerous advantages, including convenience, improved ocular responses, fewer adverse events, and enhanced patient compliance.<sup>29,30</sup> However, it is worth considering the increased costs associated with daily disposables. Moreover, since these lenses are disposed of each day, there is less incentive and more cost constraints to designing more advanced CL materials. Advanced lens materials refer to those with more complex polymer chemistries, incorporating internal wetting agents and modified surfaces for improved wettability, interaction with the tear film, and compatibility with multipurpose solutions.

Among the reusable CL modality, the monthly replacement schedule has emerged as the dominant choice worldwide, significantly surpassing the popularity of the 2-week replacement schedule.<sup>31,128</sup> The preference for a monthly modality is likely driven by cost savings and factors related to non-compliance with replacement schedule, which is better for monthly replacement than 2-week replacement.<sup>148,152,155–157</sup> Studies have demonstrated that patients show higher levels of non-compliance with 2-week replacement lenses, often attributed to forgetfulness.<sup>29,155–157</sup> Indeed, the challenges associated with remembering to change lenses every 2 weeks can easily be understood, considering the irregular gaps within the replacement frequency. A 1-week replacement schedule balances the cost advantages of reusables and the benefits of frequent lens replacement. While it may improve patient compliance compared to a 2-week modality, it would likely not be as good as daily disposables. It also shares drawbacks with other reusables, such as the need for a cleaning regimen, lens case, and solution. With only one lens currently approved for weekly use,<sup>87</sup> more time is needed to assess its adoption by practitioners and its potential to compete with daily disposables and monthly replacement lenses.

A deeper understanding of the impact of replacement frequency on comfort, particularly through additional clinical studies, could help guide the field in determining the optimal frequency that balances lens performance with cost and environmental considerations. Much of the existing evidence relies on intuition and logic rather than scientific substantiation. While the ideal replacement frequency will inevitably vary between patients, a new modality between daily disposables and reusable lenses may offer the advantages of both. If the field can determine an optimal frequency for most of the population, then manufacturers and researchers can more effectively focus on developing technologies to sustain the release of wetting agents during that period. At present, it remains unclear whether to prioritize release technologies for daily disposables or reusables; a more targeted focus would ensure commercialization success. Overall, further research in these areas will help establish a stronger framework for manufacturers and practitioners to develop and prescribe CL with higher comfort.

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