The concept of using hydrogen peroxide to disinfect contact lenses was originally introduced in the early 1970s (Aquavella, 1971). Subsequently, a family of 3% hydrogen peroxide-based lens care solution products were developed and commercialized. Currently, peroxide solutions remain a significant part of the US soft contact lens care solutions market and are used by approximately 20% of contact lens wearers (Nichols, 2014).

Hydrogen peroxide-based lens cleaning and disinfecting systems need to achieve adequate disinfection and also reduce the 3% hydrogen peroxide to residual levels that are safe for the human corneal surface. For any 3% hydrogen peroxide system, the residual hydrogen peroxide concentration following neutralization must result in minimal to no change in the cellular structure or integrity of the corneal epithelium and also must not elicit a physiological response that may lead to patient discomfort. Although the safety threshold levels reported in the literature remain controversial, these values typically range from 100 – 250 ppm (Chalmers and McNally 1988, Paugh, Brennan et al. 1988, Konynenbelt, Mlnarik et al. 2011).

Two different types of peroxide lens care systems have been introduced to clean and disinfect soft contact lenses and reduce the 3% hydrogen peroxide to a safe residual level. They are classified as either one-step or two-step contact lens disinfecting systems based on the method used to neutralize the hydrogen peroxide.

Two-step systems require a separate neutralizing agent, typically a tablet, which is added during the disinfection step and releases an enzyme such as catalase. Hydrogen peroxide levels remain at 3% until the catalase is released from the coated tablet and then rapidly decrease to safe residual levels. Two-step hydrogen peroxide systems are generally considered very effective at disinfection based on the initial high peroxide concentration. However, it has been shown that the catalase tab-
Platinum Modulating Compounds
Platinum modulating compounds (PMCs) are organic molecules that typically consist of nitrogen, carbon, and oxygen. Two examples are carbamide and thiourea (Figure 1), which when added to a 3% hydrogen peroxide solution may effectively control the neutralization process (Millard et al, 2013). Depending on the compound properties, this interaction may be reversible or irreversible (Millard et al, 2013). PMCs have the ability to slow peroxide neutralization during the initial disinfection time (i.e., the first 30-60 minutes) leaving a solution virtually free of viable organisms while at the same time rendering residual peroxide concentration levels that are non-irritating to ocular tissues in only four hours (Millard et al, 2013).

Mechanism of Action
To further understand the mechanism of action of PMCs and how they could be applied to develop a next generation hydrogen-peroxide system, the interaction between peroxide neutralizing discs and PMCs has been evaluated (Millard et al, ARVO, 2014). Although many PMCs were screened (Millard et al, GSLS, 2014), carbamide and thiourea were selected for further study. These compounds are structural analogues that differ only by one atom and yet their neutralization profiles are distinctly different. Equimolar amounts of carbamide and thiourea were added to 3% hydrogen peroxide solution and the neutralization profiles were measured. In addition, a solution of 3% hydrogen peroxide without the addition of a PMC was used as a control. Figure 2 shows that the addition of the PMCs significantly changed the neutralization profile of the 3% peroxide solutions based on titration measurements of hydrogen peroxide concentration. Compared to the 3% peroxide control, carbamide delayed or initially slowed the neutralization while the addition of an equimolar amount of thiourea resulted in virtually no peroxide neutralization even after...
To better understand the mechanism of action, the interaction of carbamide and thiourea test solutions with platinum discs was studied using two complementary surface sensitive analytical techniques; time of flight secondary ion mass spectroscopy (ToF-SIMS) and X-ray photoelectron spectroscopy (XPS). While ToF-SIMS analysis provides qualitative information and determines the structural constituents of a molecule, XPS was used to identify the elements present on the surface and quantitate them.

Platinum discs were incubated overnight with 10 mL of 2% carbamide or thiourea in 20 mM phosphate buffer saline (PBS) solutions. The discs were rinsed with purified water then carefully cut and mounted for ToF-SIMS and XPS characterization.

The ToF-SIMS results definitively showed that both carbamide and thiourea were present on the platinum disc surface. The images in Figure 3 show the relatively uniform distributions of carbamide or thiourea observed on the platinum surface.

XPS analysis was used to quantitate the concentration of the detected elements distributed over the surface of the platinum discs. Concentration of nitrogen, the element common for both PMCs, was used to compare affinity of carbamide and thiourea to platinum substrates. The data is shown in Table 2. The calculated atomic concentration of nitrogen for the discs exposed to thiourea buffered solution (N1s = 11.6 ± 2.1) was two times higher than the value calculated for the discs soaked in carbamide buffered solution (N1s = 5.8 ± 1.8). These results indicated stronger attraction of thiourea to the platinum discs and correlated well with the differences in neutralization profiles displayed in Figure 2.

Additionally, the XPS results demonstrated a decrease in platinum concentration (Pt4f7) for the discs incubated in any PMC solution (Pt4f7 = 19.6 ± 4.7 (carbamide), Pt4f7 = 14.2 ± 1.8 (thiourea), respectively) compared to the fresh platinum substrates (Pt4f7 = 25.3 ± 8.0). This indicates that the discs soaked either with carbamide or thiourea were covered with PMC compounds and therefore lower platinum concentrations were detected by XPS.

Coverage of the platinum discs with PMC components was of interest in these studies. Spatial distribution of the elements such as nitrogen and sulfur over the platinum cut discs was examined by XPS mapping (Figure 4). Concentration of the element of interest was displayed using a color-coded intensity scale. While black indicated no particular element was detected, the areas of intensity that appeared yellow-to-white corresponded to its highest concentration.
PEROXIDE SOLUTIONS

on the surface. XPS mapping performed for the discs incubated in carbamide and thiourea showed uniform distribution of PMCs over the platinum disc surfaces and no evidence of PMC component aggregation was detected.

Leveraging PMCs in Novel Lens Care Solution Development

The PMC interaction with the platinum sites on the neutralizing disc is new technology that allows for the controlled neutralization of a 3% peroxide solution. PMCs help one-step peroxide systems mimic the slow initial neutralization of a two-step peroxide system without the inconvenience of a second step. This PMC technology was incorporated into the development of a one-step peroxide system — PeroxiClear cleaning and disinfection solution — which utilizes a combination of three different moisturizing agents to attract, spread and retain moisture on the surface of the lens. Carbamide, one of these three ingredients, serves a dual purpose as both a natural moisturizing factor to help prevent dehydration, and as a platinum modulating compound.

The addition of a PMC in PeroxiClear solution alters the typical peroxide neutralization profile compared to other peroxide contact lens cleaning and disinfecting solutions. For example, in a comparison of total peroxide exposure for PeroxiClear and Clear Care (Alcon), the mean total AUC measurements were calculated at 4 hours for PeroxiClear and 6 hours for Clear Care. Both product systems were tested four times and peroxide concentrations were plotted to generate neutralization curves. As a result of the slower initial neutralization produced by the PMC, PeroxiClear had a statistically significantly higher total peroxide exposure in 4 hours compared to Clear Care after 6 hours (based on manufacturer recommended disinfection times) (p<0.0001) (Figure 5).

In addition to total peroxide exposure, the mean residual hydrogen peroxide concentration for PeroxiClear 3% hydrogen peroxide system was also tested. Ten lens cases were cycled one time with 10 mL aliquots of the solution and soaked for the recommended regimen time of 4 hours. Residual peroxide...
Concentrations were measured using redox titration with a Mettler Toledo T50 Auto-Titrator. The mean residual peroxide level for PeroxiClear solution after 4 hours was 64.8 ± 12.3 ppm, well below thresholds for ocular detection or cellular changes (Chalmers et al, 1988; Paugh et al, 1988; Konynenbelt et al, 2011).

**Physico-Chemical Changes**

When XPS elemental composition data was used to quantitate the relative amounts of carbamide adsorbed to the platinum sites during the neutralization process for PeroxiClear at 0, 5, 15, 30 and 60 minutes, an increase in the carbamide detected on the platinum sites on the coated disc surface was evident from 0-30 minutes. At 60 minutes, the atomic coverage (%) decreased.

The loss in affinity of carbamide for the platinum surface after 60 minutes may be attributed to the simultaneous physico-chemical changes in temperature, pH and osmolality within the case during the first 60 minutes of neutralization. This is evidenced by the results of timed evaluations of temperature, pH and osmolality during the neutralization process. Within the first 0-60 minutes of neutralization, the temperature of the carbamide test solution increases, the pH increases and the osmolality decreases rapidly.

**Conclusion**

Combination of a suitable PMC such as carbamide with 3% hydrogen peroxide was shown to be a breakthrough approach that may improve the performance of peroxide-based lens care solutions. Application of this technology in PeroxiClear cleaning and disinfecting solution allowed for a higher total hydrogen peroxide exposure, in only 4 hours, and residual peroxide levels that are non-irritating to ocular tissues. **CLS**

**References**


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