A Systematic Review on Multiple Purpose Solution of Contact Lens Ingredients: Benefits and Risks

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ABSTRACT

Since the past decades, the prevalence of microbial keratitis (MK) has risen notably among contact lens (CL) wearers. The main contributor to this infection is the use of an inefficient CL disinfecting solution. This paper highlights a systematic review of articles from journals on the multipurpose solution (MPS) of CL ingredients available currently in the market. This review emphasizes the compositions of MPS to evaluate their effectiveness and risks to lens wearers. A search for original articles published was conducted through Scopus, PubMed, and Google Scholar databases, focusing on the keywords contact lens ingredients and preservatives, MPS, polyquaternium, biguanides, and MK. A thorough review was conducted to extract the data on the subjects from the generated searches. The review revealed that hydrogen peroxide (H2O2), polyhexamethylene biguanide (PHMB), povidone-iodine (P-I), and polyquaternium-1 (PQ-1) are the preferred MPS formulations in the current industry of CLs. These chemical ingredients are effective against causative agents of keratitis for faster disinfection and lower risks of microbial infections in CL users. Thus, proper hygienic practices must follow the guidance from the respective product manufacturers to prevent harmful risks of ocular diseases.

INTRODUCTION

Contact lenses (CLs) provide safe and effective vision correction, which is currently used by over 140 million wearers worldwide.1 CL care system involves the application of specific formulations such as multipurpose solution (MPS) to clean and disinfect the use of CLs to provide safe and clean lenses for the wearers. Microbial infections were reported in CL users, with more problematic cases involving amoebic infection of the cornea of infected individuals. The commonly reported cases of CL applications are microbial keratitis (MK) disease, distinguished by the onset of discomfort, conjunctival hyperemia, and corneal ulceration, besides a stromal inflammatory cell infiltrate.2 Pathogens that can cause MK include bacteria, viruses, protozoa, and fungi. MPS formulation from different manufacturers and amoebic keratitis infections in CL wearers is discussed. This review aims to evaluate the formulated use of MPS in the market currently, especially in reducing MK risks of infection.

MATERIALS AND METHODOLOGY

Search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis criteria (PRISMA) shown in Figure 1.3 Articles were obtained by searching in Scopus, PubMed, and Google Scholar databases, with the key terms “contact lenses,” “ingredients,” “preservative components,” “multipurpose solution,” “polyquaternium,” “biguanides,” and “microbial keratitis.” Recovered texts were searched to find additional references.
Figure 1 Flow diagram using the PRISMA for studies identification

Screening criteria and data extraction

The outputs of the search were reviewed twice. First, the title, keywords, and abstracts of each of the matched journal articles were studied and analyzed. The records of electronic search were transferred to an EndNote database. The full texts of relevant publications for the review were received to determine relevance based on the inclusion and exclusion criteria as follows:

1. Only scientific journal articles published in English were selected in the search.
2. No specific time frame was specified for this review.
3. All types of available literature, including review articles, original articles, and reports, were included.
4. Non-English articles, duplicated articles, and books were excluded.
5. The population included CL users and MPS manufacturers.
6. Intervention (location, type, and names of chemical ingredients in the MPS).
7. Outcomes (benefits and risks of chemical ingredients in the MPS).

RESULTS

A total of 5419 articles from Scopus, PubMed, and Google Scholar were retrieved using the search strategy. About 40 relevant articles were selected after further screening and selection processes. The review involved several known brands by manufacturers producing MPS for CL. Next, the search highlight of the review process was focused on the chemical ingredients used as disinfectants in the MPS formulation. The study localities were mainly from the United Kingdom (UK), the United States of America (USA), and Australia, while no similar study was recorded in Malaysia.

The findings found that the preservatives quaternary ammonium compound polyquaternium-1 (PQ-1) and polyhexamethylene biguanide (PHMB) are the most frequently used compositions in the MPS formulation worldwide. The benefits and risks of the current MPS products offered on pharmacy shelves are reported and discussed.

DISCUSSION

Disinfecting system of contact lens (CL)

CLs require proper cleaning and disinfection procedures after use according to the manufacturer’s recommendations. Cleansing, disinfection, and storage protection are among the crucial procedures in the CL care system to ensure the safety of the lenses before application to the eyes of the users. Therefore, the compositions of a CL care system often comprise several antimicrobial solutions, surfactants, buffering, chelating, and wetting agents. Wet storage application using a specific solution formulation is also essential to protect CL from damage and contamination. It is necessary to remove deposits, debris, and microbiological biofilms prior to disinfection.

MPS is a single-use solution for rinsing, disinfecting, and storing lenses, usually made of a preservative, buffer system, and other ingredients. These components act as antibacterial agents, essential for CL safety and more convenient for use. Manufacturers enhance their MPS solution formulations to improve disinfection efficacy and
reduce microbial contamination in CLs. Manufacturers of MPS often provide a disinfecting system that includes hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) combined with other ingredients such as PHMB and PQ-1 (polyquad)/myristamidopropyl dimethylethanolamine in their products.\textsuperscript{7,9}

**Risks of microbial keratitis (MK) in contact lens (CL) wearers**

CL wearers are commonly unaware of microbial contamination risks, including bacteria, fungi, and protozoa, such as amoeba, which increases the risk of corneal infections from the use of CL. MK is a corneal infection brought on by these microorganisms, which leads to corneal epithelial ulcers, stromal inflammation, corneal exposure, bullous keratopathy, corneal anesthesia, and dry eyes.\textsuperscript{10,11} The virulence factor and ability of these pathogens to survive on CL, in storage cases, and the ocular environment are the major contributors to its pathogenicity.\textsuperscript{12} The American Academy of Ophthalmology Cornea/External Disease Panel reported that the most common bacteria that cause CL-related MK are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.\textsuperscript{13} CLs were frequently contaminated with *P. aeruginosa*, *Citrobacter amalonaticus*, *S. aureus*, *Viridans streptococci*, *Klebsiella pneumoniae*, *Pseudomonas fluorescens*, *Staphylococcus epidermidis*, and *Stenotrophomonas*.\textsuperscript{14}

Reusing solutions and improperly closed lens storage case, which causes evaporation, are examples of non-compliance, a major contributing factor in CL-related MK. To mitigate this issue, the effect of partial evaporation on the antibacterial effectiveness of MPS was examined.\textsuperscript{15} Researchers discovered that partial evaporation could reduce the biocidal effectiveness of MPS and may have played a substantial role in an increase in *Fusarium keratitis* occurrences. This finding is confirmed by a risk factor analysis performed by a study, which found that lens hygiene and avoiding night-time lens use reduce the risk of infection by 60%–70%.\textsuperscript{16}

Selecting the right solution that can eliminate all microorganisms is crucial. Saline solution, cleaning chemicals, surfactants, digital rubbing, and washing are typically applied to remove the risks of microorganism contamination in the lens. Tap water should also be avoided for lens rinsing as it will increase the likelihood of Acanthamoeba contamination.\textsuperscript{17}

**Multipurpose solution (MPS) in the market**

MPS is an all-in-one care system comprising lens cleaning, rinsing, disinfecting, and storage. Disinfection refers to the elimination of microorganisms on the surface of CLs while cleaning refers to removing deposits and debris from the CL surface.\textsuperscript{18} Disinfectants, such as quaternary ammonium compounds, biguanides, H\textsubscript{2}O\textsubscript{2}, alcohol, sorbic acid, and thimerosal, are extensively used in CL care solutions worldwide.\textsuperscript{19} Preservatives in MPS can prevent CL-related MK, which is important to keep the storage case free from Acanthamoebae.\textsuperscript{20} These solutions must be proven effective in eliminating a wide range of microorganisms while still being gentle enough to be used around the eyes. According to Kilvington et al.,\textsuperscript{21} the use of MPS with effective disinfectant properties in conjunction with good lens care hygiene compliance will decrease the incidence of MK. This supports the findings by Lin et al.,\textsuperscript{22} who revealed that MPS containing a combination of chlorhexidine, polyaminopropylbiguanide (PAPB), and EDTA could help reduce the incidence of MK among CL users.

The preservatives PQ-1 and PHMB may be used singly or in combination, comprising high molecular weight molecules that act as antimicrobial agents.\textsuperscript{20} The small size of the preservatives renders their less chance of uptake and release from CLs, reducing the risk to the ocular surface. The biguanides, present in modern MPS of CLs and include PHMB, polyhexanide, polyaminopropyl biguanide, chlorhexidine, and alexidine, are among the most widely used high-molecular weight preservatives. According to Allen et al.,\textsuperscript{23} biguanide can enter microbial cells and interact with DNA by interfering with DNA function, leading to cell death.

The antibacterial efficacy of CL products is normally evaluated according to the ISO 14729 guidelines. The commercial treatments are effective against bacteria and fungi at six hours of contact time, according to the ISO 14729 Primary Stand Alone (biocidal) requirements.
Unfortunately, if an MPS meets the secondary regimen criterion but fails to meet the biocidal criteria, it can still be sold.\textsuperscript{21,24} According to Bradley et al.,\textsuperscript{20} the optimum preservative is safe and effective at high concentrations. A preservative has a large “margin of safety” if it satisfies these requirements. Table 1 lists the preservatives present in each commercially marketed MPS available on the market.\textsuperscript{8,20,21}

Table 1. Prominent MPS available in the global market from the 1980s to the present

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Solution name</th>
<th>Preservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcon</td>
<td>OptiFree PureMoist</td>
<td>Polyquad</td>
</tr>
<tr>
<td></td>
<td>OptiFree Replenish</td>
<td>(polyquaternium-1) 0.001% Aklox</td>
</tr>
<tr>
<td></td>
<td>OptiFree Express</td>
<td>Polyquaternium-1 0.005% Pylydimethylamine</td>
</tr>
<tr>
<td></td>
<td>Opti-Soft</td>
<td>Polyquad (polyquaternium-1 0.001% Thimerosal 0.004% Thimerosal 0.001% Chlorhexidine gluconate 0.005%</td>
</tr>
<tr>
<td>AMO (Johnson &amp; Johnson Vision)</td>
<td>Acuvue RevitaLens</td>
<td>Polyhexamethylene biguanide 0.001%</td>
</tr>
<tr>
<td></td>
<td>Complete Moisture (Comfort) Plus MPS</td>
<td>Polyhexamethylene biguanide 0.0001%</td>
</tr>
<tr>
<td>Bausch + Lomb</td>
<td>Renu Advanced Formula</td>
<td>Polyhexamethylene biguanide 0.0001% Polyquaternium-1 0.001% Alexidine (alexidine dihydrochloride 0.0006%)</td>
</tr>
</tbody>
</table>
|              | Renu Multiplus | DYMED® (polyaminopropyl biguanide 0.0001%)
|              | BioTrue | Polyaminopropyl biguanide 0.00013% Polyquaternium 0.00001%
|              | SoftLens | Thimerosal 0.001% Chlorhexidine 0.005%
| CIBA (Johnson & Johnson Vision) | Vision SOLOCare Plus | Polyhexamethylene biguanide 0.0001%
|              | AQuify | Polyhexamethylene biguanide 0.0001%
| Optics       | Cladew | Povidone-Iodine |
| Abbott Medical Optics | RevitaLens OcuTec | Alexidine dihydrochloride 0.00016% Polyquaternium-1 0.00003% |
| CooperVision® | Avaira Vitality™ | Polyhexamidine (0.0001%) |
| Soffcon      | Septicon* | Thimerosal 0.004% (second step with 3% hydrogen peroxide) |
| Menicon      | MeriCare Soft | Polyhexamethylene biguanide 0.0001%

Efficiency of the existing MPS products

MPS is made of an antimicrobial agent that also acts as a preservative and disinfectant, surfactant, antibiotic chelator, wetting agent, and buffering agent to maintain the pH of the solution.\textsuperscript{25} PHMB was discovered to have amoebic and cysticidal effects against several strains of Acanthamoeba.\textsuperscript{26} It is a complex of cationic polymeric biguanides, which can bind to bacterial cell membranes and cause damage by lysis. PHMB may also interact with nucleic acids, resulting in microbial alterations.\textsuperscript{27} According to Reindel et al.,\textsuperscript{28} the disinfection efficacy of MPS against Acanthamoeba polyphaga and Acanthamoeba castellanii cysts and trophozoites was determined in a previous study.\textsuperscript{29} They revealed that ReNu, with MoistureLoc, successfully killed trophozoites and cysts (>3 log) within the manufacturer-recommended soaking time through biocidal assay.

Biotrue MPS, comprising PHMB and PQ-1, helps CLs stay clean and moist while being used. Moreover, this MPS is pH buffered and isotonic to match the pH of tears, prevent pH shifts, and preserve homeostasis when the lenses are applied to the eyes. It also contains sodium hyaluronate, a type of hyaluronan, the natural lubricant found in the eyes.\textsuperscript{30} According to the US Food and Drug Administration (US FDA) and Centers for Disease Control and Prevention (CDC), PHMB-based treatments are efficient against bacteria in vitro, including P. aeruginosa and S. aureus.\textsuperscript{31} While PQ-1 is a quaternary ammonium compound that is more effective against bacteria than fungi by causing cytoplasmic leakage through cell membrane disruption.

A study by Dosler et al.\textsuperscript{32} on in vitro activities of multipurpose lens solutions showed that Opti-Free, BioTrue, and Renu were the most effective MPSs against P. aeruginosa and S. aureus biofilms in 24 hours, as assessed via TKC tests. Renu, Opti-Free, and Bio-True were the most effective MPSs against Candida albicans in 48 hours. They discovered that the chemical components and contact times of MPS, the type of infectious agent, and particularly the CL type and usage duration had an impact on the biofilm activities of MPSs. According to Eryilmaz et al.,\textsuperscript{33} myristamidopropyl dimethylamine (MAPD) and other chemicals were added into MPS, together with PQ-1, to boost its antifungal efficacy. Kilvington et al.\textsuperscript{21} claimed that COMPLETE® RevitaLens (NuMPS) dual disinfection combination of PQ-1 and bis-biguanide alexidine demonstrated a broad antibacterial activity, including Acanthamoeba with 3-4 log10 reduction in viability after 6 hours of contact time. NuMPS also passed...
the ISO 14729 9 assessment and, thus, is classified as an effective MPS in the global market. Narayana et al.\textsuperscript{34} also reported that Opti-Free® Express, which contained Polyquad (polyquaternium 0.001%) and Aldox (myristamidopropyltrimethylamine 0.0005%), was effective against \textit{P. aeruginosa} and \textit{S. aureus} for 72 hours. H$_2$O$_2$ is an effective microbicidal compound, and due to its potent oxidizing properties, it could quickly damage biological macromolecules, such as proteins, lipids, and nucleic acids, by producing oxygen radicals. It also encourages better compliance, effectiveness, comfort, and ocular surface results.\textsuperscript{35,36} Prior to re-insertion into the eye, lenses exposed to these compounds must be neutralized by an oxidizing agent. According to Bradley et al.,\textsuperscript{20} H$_2$O$_2$ cleaning systems are classified as safe and widely demonstrated to be effective against \textit{Staphylococcus spp., P. aeruginosa, Serratia marcescens, Candida spp., and Aspergillus spp.} Povidone-iodine (PI), another oxidative system-based disinfectant, has been used on the eye surface prior to intraocular surgery because of its broad-spectrum antibacterial properties and low cytotoxicity to human tissues.\textsuperscript{37} CL care products should be able to reduce the number of bacteria that cause these illnesses. The results of a stand-alone test (EN ISO 14729) on the microbicidal activity of six CL care solutions, Aosept Plus, which contains 3% H$_2$O$_2$, demonstrated a reduction factor of $>5$ log units for bacteria and $>4$ for fungi in all cases.\textsuperscript{38} The efficiency of commercial MPS solutions, Bio-True® and OptiFree® Puremoist, were compared with the experimental MPS formulation, ASP-57, which contains stabilized ClO$_2$ (as sodium chlorite), alkyl(ethylbenzyl) dimethylammonium chloride, and ammonium chloride. The viability analysis of \textit{A. castellanii} trophozoite demonstrated a statistically significant difference in the performance of ASP-57 when compared to the commercial comparator care solutions.\textsuperscript{39} Therefore, novel compounds should be included in future MPS development to improve disinfection and further lower the exposure of CL cleaning systems.

Since MPS is used daily, it can bring harmful effects to the ocular cell system, such as eye surface irritation. It was reported that MPS might impair corneal epithelial function, resulting in clinically significant discomfort among CL users. Bradley et al.\textsuperscript{16} added that the preservative and disinfectant agents in MPS that come into contact with the eyes are exposed to toxicity on the cornea-conjunctival surface, affecting the ocular surface cells. Delayed hypersensitivity reactions were more prevalent with solutions that contained mercury-based preservative thimerosal, chlorhexidine, and benzalkonium chloride. Another concern is the complexity of the solution, which may cause adverse reactions due to the variety of ingredients added to it. The incompatibility of the lens material was also highlighted as a factor in the irritation and discomfort of the eyes. The solution and new silicone hydrogel materials were not the best combinations, although this material offers high oxygen permeability to the CL.\textsuperscript{40} CONCLUSION Contact lens (CL) solution is critical in the CL care system since a highly effective product could reduce microbial contamination in the CLs, thus, reducing the risks of microbial keratitis (MK). Multipurpose solution (MPS) for CL contains more than one preservative and is the most popular product to cleanse and disinfect lenses. The findings from this review study noted that the MPS marketed currently contains a disinfecting system that includes H$_2$O$_2$ combined with other ingredients, such as polyhexamethylene biguanide (PHMB) and polyquaternium-1 (PQ-1, polyquadi)/myristamidopropyl dimethylamine. The development or refinement of new MPS products should consider modifying the formulation or introducing novel chemical elements that are effective against pathogens causing the risk to MK in CL wearers. ACKNOWLEDGMENT This work is fully funded Prototype Research Grant Scheme (PRGS/1/2020/UKM/02/1) of Ministry of Higher Education Malaysia. The authors would like to thank the Research Management Centre of International Islamic University Malaysia, Universiti Malaysia Terengganu and Universiti Sultan Zainal Abidin
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