Antimicrobial study and in vitro evaluation of coated contact lenses with polyelectrolyte complex based on Chitosan and Sodium Alginate

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Summary

Ametropia correction by contact lenses can improve visual quality. However, their use may be burdensome and uncomfortable, particularly when poor wearer care increases the possibility of microbial contamination. The aim of this work is to coat silicone hydrogel contact lenses with a polyelectrolyte complex based on sodium alginate and chitosan, to study their antimicrobial power and their physicochemical characteristics. A preliminary study on the antimicrobial activity of the electrolyte complex was carried out. The latter exhibited antimicrobial activity on all strains studied (i.e.: *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis* and the fungus *Candida albicans*) with inhibition zone diameters ranging from 11 to 15 mm. The antimicrobial study of coated contact lenses was performed on the same strains and showed a more bacteriostatic than bactericidal effect. To estimate the water

retention capacity of these lenses, swelling and erosion tests were performed. Contact lenses coated with the ALG/CTS polyelectrolyte complex showed a maximum swelling rate of 343% after 360 minutes of contact with artificial tears and an erosion rate of 37% after 48 hours. This study will be followed by an *in vivo* study to comfort level evaluation of the coated lenses.

Key words
Contact lens, Sodium Alginate, Chitosan, Polyelectrolyte complex, Antibacterial activity

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Introduction

Over the past few decades, contact lenses have become increasingly popular, especially during the COVID-19 period.[1] According to LENTECHS President and CEO "Robin Sears", the contact lens market rebounded quickly and positively during the pandemic.[1] In fact, contact lenses can provide multiple benefits, such as mechanical protection of the cornea against the eyelids' abrasive action during blinking,[2] hydration and protection against tears' evaporation.[3]

Nevertheless, contact lens use demands an equilibrium between the correctional and protective results on ametropias and keratoconus on one hand, and tolerance levels for the cornea, local comfort and ease of daily wear, on the other hand. However, this is not without consequences on the eye, which may undergo physiological changes that may be acceptable, but sometimes pathological and cause potential undesirable effects or possible complications.[4-8] At the same time, the lenses are in permanent contact with the ocular surface and the external environment (pollution, dust, cosmetics...), when they are worn, handled or stored, which means that microbiological contamination potentially pathogenic to the eye is possible. It can originate from the hands when handling lenses, improperly maintained lens cases, or the local environment of contact lens wearers (eyelids, airborne germs etc.).[9-12] Contact lens wear is the most common cause of infectious keratitis. The latter can be caused by bacteria,[13-18] fungi,[19-22] parasites or viruses.[23-25] Another problem encountered when wearing contact lenses is dry eyes.[26-28] Such symptoms are very common in contact lens wearers.[29-31] Indeed, wearing contact lenses will increase the tears' rate evaporation. The lipidic layer stagnation of the pre-lens tear film modifies the dynamics of the latter. The tear film evaporation and the aqueous secretion deficit cause an ionic concentration increase which leads to hyperosmolarity.[32,33] Epithelial and conjunctival cells dehydration causes damage to cell metabolism and can lead to apoptosis.[34]

The aim of this work is therefore to coat the surface of contact lenses, by the dip-coating method, with a polymeric film based on a polyelectrolyte complex, obtained by the electro-association of two biodegradable polysaccharides of opposite charges. It consists of investigating their antibacterial effect to prevent the germs proliferation on the contact lenses surface or between the lens and the ocular surface. The chosen pair for this study is sodium alginate as much as a polyanionic polysaccharide and chitosan as much as a polycationic one.

The antimicrobial activity of chitosan (considering its characteristics such as degree of polymerization, degree of acetylation and average molecular weight)

has been extensively described and published. It has a broad antimicrobial spectrum to which gram-negative and gram-positive bacteria and fungi are very sensitive.[35-37] The two biopolymers studied are hydrophilic polymers capable of storing large quantities of water between their macromolecular chains.[38-40] The goal is to enhance humidity of the contact lenses surface to prevent the adhesion of micro-organisms on it[12 41] and increase water retention, thus maintaining a constant tear film in contact with the cornea while limiting its evaporation. This study begins with a preliminary antimicrobial study of polymer solutions alone. It consists on studying the antimicrobial effect of different concentrations of the two polymers alone and combined against various bacterial strains, such as *Pseudomonas aeruginosa* (gram negative) and *Staphylococcus aureus* (gram positive), which represent the strains most frequently isolated during bacterial keratitis from contact lens wearers.[15 42] The antifungal study was carried out on the yeast strain *Candida albicans*, which is at the origin of several cases of keratomycosis.[19,20] The antibacterial and antifungal study on coated contact lenses was performed on the same previous strains. This was followed by a swelling and erosion study to determine the water retention capacity of the polymeric coats studied.

Material and methods

Material

N,N-dimethylacrylamide (DMA), tris(3-[tris(trimethylsiloxy)silyl]propyl methacrylate), HEMA, and HPMA were purchased from Sigma Aldrich (France). Alginate de sodium (ALG) with an average molecular mass (Mw) of 380 000 g mol^{-1} was obtained graciously from Cargill (Baupte, France), It is a linear copolymer with homopolymeric blocks of (1–4)-linked β-d-mannuronate (M) and its C-5 epimer α-l-guluronate (G) residues.[43,44] Chitosan (CTS) with Mw of 210 000 g mol^{-1} and 81.4% deacetylated was purchased from Sigma Aldrich (France). Artificial tears ARTELAC® were purchased from Chauvin (Montpellier, France). *Staphylococcus aureus (S.aureus) ATCC 6538/P, Escherichia coli (E.Coli) ATCC 8739, Pseudomonas aeruginosa (P.aeruginosa) ATCC 9027, Bacillus subtilis (B.subtilis) ATCC 6633* and *yeast (Candida albicans (C.Albicans) ATCC 10521)* was supplied by Antibiotical-Saidal (Medea, Algeria), Trypticase soy agar, Sabouraud's agar and acetic acid were purchased from Sigma Aldrich (France) and Riedel-de Haën™ Honeywell (Germany), respectively. All chemicals are of analytical or pharmaceutical grade and, are used without further purification.

Methods

Preparation of polymer solutions

A range of CTS solutions were prepared at different concentrations (i.e. 0.1%, 0.2% and 0.5% (w/w)) (Table 1). Another range of ALG solutions was also prepared with the same previous range of concentrations (Table 1). CTS-based solutions are prepared in a 1% acetic acid solution.[45] ALG-based solutions are prepared in distilled water. The different solutions were agitated overnight at 250 rpm under a laminar flow hood to prevent microbial contamination.

The alginate and chitosan solutions, prepared previously, were mixed with a ratio of (ALG / CTS) (1:1) (Table 1) and stirred at 500 rpm in a laminar flow hood for one hour to allow the electro-association between the alginate negative charges and the chitosan positive charges.

Table 1 Range of polymer concentrations and coated contact lenses (CL) studied

ALG (%) (w/w)	F1	F2	F3
	0.1	0.2	0.5
CTS (%) (w/w)	F4	F5	F6
	0.1	0.2	0.5
ALG/CTS (%) (1:1) (v/v)	F7	F8	F9
	0.1	0.2	0.5
CL_{ALG}	CL1	CL2	CL3
	0.1	0.2	0.5
CL_{CTS}	CL4	CL5	CL6
	0.1	0.2	0.5
$CL_{ALG/CTS}$	CL7	CL8	CL9
	0.1	0.2	0.5

Antimicrobial study of polymers solutions

The method used to study the antimicrobial activity of the polymer solutions studied is the agar diffusion method with antibiotic discs.[46] The bacterial strains selected for this study are: *S.aureus, E.Coli, P.aeruginosa, B.subtilis* and yeast *C.albicans*.

The bacterial suspension of the germ being tested is inoculated using a sterile swab in Petri dishes containing Trypticase soy agar for bacteria or Sabouraud's agar for yeast.

All of the utensils and the growth medias were sterilized at 120°C by an autoclave for 4 hours while all the polymer solutions were sterilized within luminaire flow hood.

Sterile 9 mm discs pre-soaked in the polymer's solutions are then placed on the agar; then the Petri dishes are incubated at 37°C in the incubator for 24 hours in the case of bacteria and 48 hours in the case of yeast. After incubation, each inhibition zone diameter was measured using a caliper on the plate lower surface, without opening the lid. The tests were performed in triplicate on the same Petri dish.

Preparation of coated contact lenses

The contact lens synthesis was performed according to the Lee and Sung protocol.[47] The resulting contact lenses were washed 3 times with absolute ethanol to sterilize the surface. They were coated with the various solutions prepared previously by the dip-coating method (table 1). The coated lenses (CL) were subsequently dried in the open air under a laminar flow hood. They were washed three times in distilled water for three minutes and put back in the laminar flow hood for a second drying.

Bacterial growth study in the presence of coated contact lenses

The method used to study the antimicrobial activity of coated contact lenses is the dilution method.[48] To carry out the antimicrobial test on the coated contact lenses, they were first cut into small pieces and placed in a test tube containing 5mL of sterile distilled water.

Subsequently, 0.1mL of several microbial suspensions of the different strains tested (i.e.: *S.aureus, E.Coli, P.aeruginosa, B.subtilis* and *C.albicans*). The tubes are left for a contact time incubation of 18 hours. The same steps were applied to three control tubes, with Ampicillin standard solution, uncoated contact lenses and without contact lenses.

Finally, two drops were taken from different solutions and spread on a petri dish containing the appropriate culture medium (i.e. Trypticase soy agar or Sabouraud's agar) using a Pasteur pipette. The plates were then incubated for 24 hours at 37°C. The dishes were then incubated for 24 hours at 37°C. The tests were performed in triplicate.

In vitro pH determination

The pH measurements were carried out according to the Jingsong protocol.[49] Previously prepared coated contact lenses were incorporated into 9 mL of artificial tear solutions and wired at 4°C. After 30 minutes, the pH of the solutions was measured using a SELECTR® pH meter.

Swelling Study

The technique of swelling kinetics analysis is based on a gravimetric method. This method consists in measuring the quantity of liquid absorbed by the polymeric films as a function of time until equilibrium.

The lenses were put in a microwave for 3 minutes at 180 watts to remove all traces of water. The dry samples were then weighed using a KERN ALS 220-4N balance. The dry coated contact lenses were each incorporated into a 5 mL volume of artificial tear solution. At regular intervals, they were removed, weighed and reincorporated into the same solution. The test was performed in triplicate.

The swelling rates are determined by the following formula:

$$Swellingrate\ (\%) = \frac{(w_s - w_i)}{w_i} \times 100 \quad \textbf{(1)}$$

Where w_i is the mass of the coated lenses in the initial state (at time t_0) and, w_s is the mass of the same lenses in the inflated state (at time t).

Erosion study

After swelling studies, the coated contact lenses were kept in the same artificial tear solution for 48 hours. Then they were dried and weighed (w_E). The tests were performed in triplicate.

The gel erosion kinetic was estimated from the following equation:

$$Erotionrate\ (\%) = \frac{(w_i - w_E)}{w_i} \times 100 \quad \textbf{(2)}$$

Results and discussions

Antimicrobial study of polymers solutions

The antibacterial and antifungal activity of the solution of the polyelectrolyte complex (i.e. ALG/CTS) was evaluated based on the comparison of their inhibition zones against *S.aureus, E.Coli, P.aeruginosa, B.subtilis* and yeast *C.albicans*. Solutions of the two polymers alone (i.e. ALG and CTS) were used as controls.

The results obtained are presented in the table (Table 2) and compared with those of the antibiotics generally used in anti-infectious ophthalmic treatments, namely; ampicillin, vancomycin and gentamicin.[50] The two polymers studied, as well as their combination, showed an antibacterial effect on almost all reference strains studied as well as the fungus *C.albicans*.

Indeed, the two separate polymers as well as their association, have a significant inhibition effect on the bacteria *S.aureus* (gram positive) and *E.Coli* (gram negative), whose inhibition diameters vary between 11 and 14 mm. This is close to the inhibition effect of ampicillin on *E.coli* [46 51 52] and vancomycin on *S.aureus*.[46 52]

As for the *P.aeruginosa* bacteria, ALG alone and the ALG/CTS polyelectrolyte complex had a significant

and increasing inhibition effect by increasing the dose (an inhibition zone that reached 14 and 13 mm, respectively). In contrast, CTS alone had no inhibitory effect on this bacterium. The inhibition zones of gentamicin on *P.aeruginosa* vary between 16 and 21 mm.[46 51 52]

ALG alone has an antibacterial effect, regardless of its concentration, on biofilm bacterial strains (*S.aureus, E.Coli* and *P. aeruginosa*.[53]) In fact, biofilm bacteria can be 10 to 1000 times more resistant to antimicrobial agents.[54 55] Biofilm protects the bacteria and allows them to survive in hostile environmental conditions.[53]

The growth of the *B.subtilis* bacterium was affected by the two separate polymers ALG and CTS, as well as their combination using the solution at 0.5%. ALG at a concentration of 0.5%, CTS at 0.2 and 0.5%, and the combination of ALG/CTS at 0.1, 0.2 and 0.5% had an inhibitory effect on the *C.albicans* fungus. These results are in line with the results of ongoing scientific research on this topic.[51]

Acetic acid had a weak inhibition effect on *S.aureus* and *P. aeruginosa* with an inhibition diameter of 7.5 and 8 respectively. On the other hand, it had no effect on the other strains (*E.Coli, B.subtilis* and *C.albicans*)

Antimicrobial study of coated contact lenses

Bacteria are responsible for more than 90-95% of non-viral infectious ulcers and keratitis in industrialized countries.[56] However, infection can be associated with other pathogens, such as amoebae or fungi, particularly in patients who wear contact lenses.[56 57] The study of the bacteriostatic and bactericidal activity of coated contact lenses with the different biopolymer films studied revealed promising and very important results.

When comparing the results obtained with coated contact lenses (table 3) and those obtained with polymer solutions alone, the results clearly show that coated contact lenses with ALG alone lead to growth inhibition on the surface of the contact lenses. ALG therefore has a bacteriostatic effect on all the bacterial strains used as well as the fungus *C.albicans*. As for the CTS polymer, it had a bacteriostatic effect on *E.Coli* and *P.aeruginosa* (Gram negative); on the other hand bactericidal effect is clearly observed in the case of the two bacteria *S.aureus* and *B.subtilis* (Gram positive), as well as the fungus *C.albicans*. When the two polymers are combined, the antibacterial effect of the polyelectrolyte complex (ALG/CTS) is similar to that of CTS alone. Indeed, it showed a bacteriostatic effect in the case of the *E.coli* and *P.aeruginosa* (Gram negative) as well as the *C.albicans* fungus, but a bactericidal effect in the case of the two bacteria *S.aureus* and *B.subtilis* (Gram positive). This may be due to the presence of CTS.

Table 2 Antibacterial activity of polymers solutions studied against S.*aureus, E.coli, P.aeruginosa, B.subtilis*, and *C.albicans* expressed in terms of diameter of inhibition zone.

		Inhibition zone results (mm)				
		C.albicans	*S.aureus*	*E.coli*	*P. aeruginosa*	*B.subtilis*
ALG%	F1	–	11	11	11	–
	F2	–	11	12	13	–
	F3	11	13	13	14	12
CTS%	F4	–	12	–	–	–
	F5	12	13	11	–	12
	F6	13	14	13	–	13
ALG/CTS%	F7	14	15	12	–	13
	F8	14	14	11	13	15
	F9	13	14	12	13	15
Acetic acid 1%	–	7.5	–	8	–	

(–): absence of inhibition

Table 3 Antimicrobial test results of coated contact lenses against *S.aureus, E.coli, P.aeruginosa, B.subtilis*, and *C.albicans* expressed in terms of diameter of inhibition zone.

		Inhibition zone results (mm)				
		C.albicans	*S.aureus*	*E.coli*	*P. aeruginosa*	*B.subtilis*
CL_{ALG}	CL1	–	–	–	–	–
	CL2	–	–	–	–	–
	CL3	–	–	–	–	–
CL_{CTS}	CL4	–	+	–	–	–
	CL5	+	+	–	–	+
	CL6	+	+	–	–	+
$CL_{ALG/CTS}$	CL7	–	–	–	–	+
	CL8	–	–	–	–	+
	CL9	–	+	–	–	+
Uncoated contact lens		–	–	–	–	–
Blank		–	–	–	–	–
Ampicillin solution		+	+	+	+	+

a) (+): Inhibition; b) (–): absence of inhibition

The results thus show that the different formulas have a more bacteriostatic than bactericidal effect. This has an advantage over the saprophytic conjunctival flora, which opposes the proliferation of germs that are more aggressive to eye structures.[58] Therefore, the bacteriostatic effect of coated contact lenses will inhibit their growth but will not entirely eliminate them.

In vitro pH determination

The physiological pH of tears is estimated to be 7.5±0.23 in human precorneal tear fluid.[59] The latter is a very important parameter in eye comfort and tolerance to contact lens wear.[60] For this reason, we performed a study of the pH of contact lenses in artificial tear solution.

The pH obtained varies between 6.8 and 6.98. This shows that the medium is slightly acidic after deposition of the coated contact lenses. Indeed, the lacrimal pH is strongly influenced by various factors such as lacrimal secretion, mucus cell secretions, conjunctival metabolism and variations in CO_2 concentration due to exchanges with the ambient air.[61] This pH lowering can be increased and normalized by the tears buffering power. In the case of an acidic medium, the tearing reflex induces a concentration decrease of excess H^+ ions in the medium and will lead to a rapid normalization of the lacrimal pH.[62]

Swelling study

One of the problems encountered when wearing contact lenses is dry eyes.[29 30 31] According to Nichols et al.,[27] the thinning times of the tear film could be explained by fluid wetting due to surface tension gradients of the tear film or hydrophobic regions on the lens surface. It is therefore important that the contact lens remains "wet" with a coherent tear film on its surface.[27] This requires studying the swelling of these polymers over time. The results of the swelling kinetics of coated contact lenses are presented in (Figure 1).

The graphs indicate that the swelling of the different polymers is rapid during the first 30 minutes. Indeed, the swelling rate reaches 114, 121 and 174% for ALG, CTS and ALG/CTS respectively. It reaches a maximum of 177, 343 and 267% for ALG, CTS and ALG/CTS respectively after 360 minutes of contact with the solution of the artificial tears, marking stability over time beyond 360 minutes.

These results also show that chitosan exhibits a higher swelling rate than ALG alone and the ALG/CTS complex. This result is supported by results from Gupta[38] and Baysal.[39] This may be due to the difference in average molecular weight between the two polymers. Indeed, the swelling of the polymers is based on the dispersion of the chains as long as possible in the solvent in order to reduce its free energy.

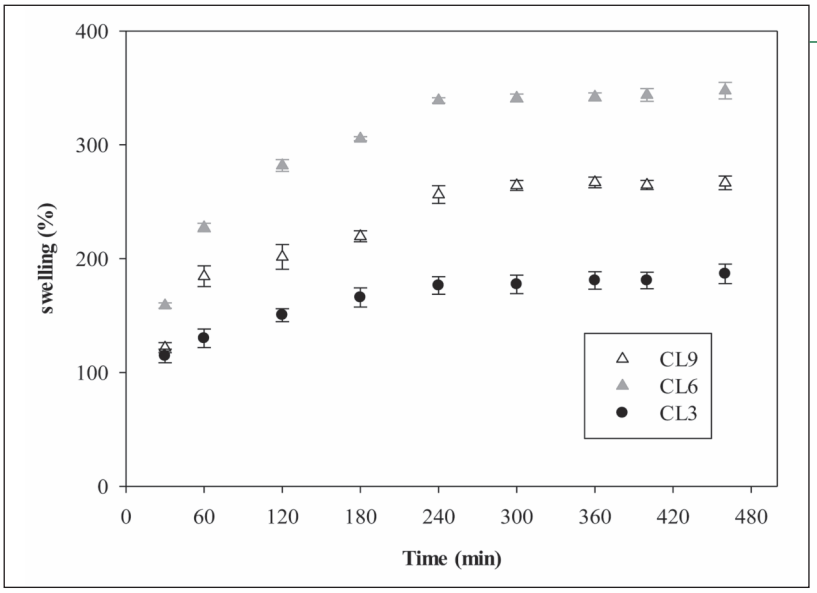
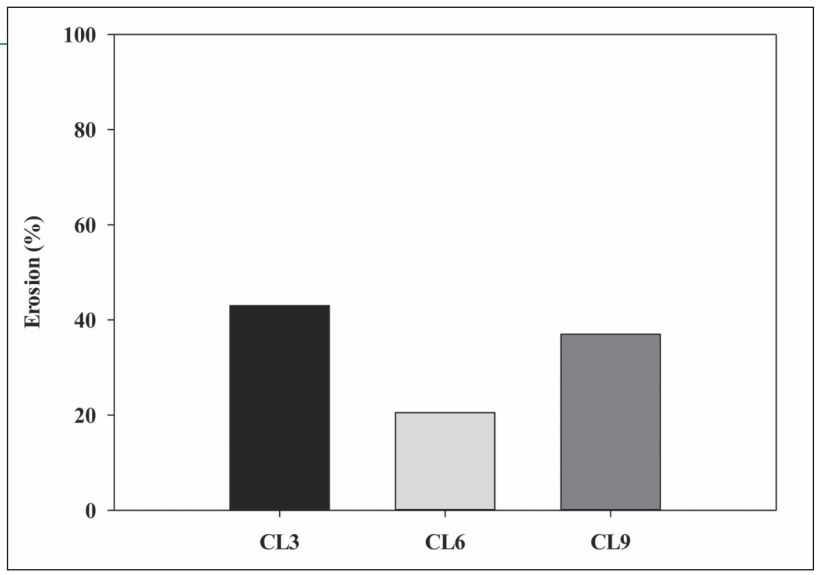


Figure 1

Swelling evolution as a function of time of coated contact lenses with ALG "CL3" (●); CTS "CL6" (▲) and ALG/CTS "CL9" (△).

Figure 2

Film erosion of coated contact lenses in artificial tears solution: CL3 (Black), CL6 (Gray), CL9 (Dark gray).



The low average molecular weight of chitosan helps it disperse easily when compared to ALG alone. This result can be supported by the results obtained by Gupta et al.,[38] which clearly show the effect of the average molecular weight on the degree of swelling of a polymer. But also, of the presence of the electrostatic bonds that exist between the two polymers in the case of the ALG/CTS polyelectrolyte complex, which will prevent the polymer chains from dispersing freely.

The swelling stability, subsequently marked as a function of time, is due to the competition between the forces that tend to disperse the chains and the forces that tend to bring the average conformation of the chains back to their state of equilibrium, i.e. without stretching.

Erosion study

The permanent contact of the coated contact lenses with the tear film causes the constant diffusion of water inside the polymeric film. For this reason, the degree of erosion of the polymeric film has been studied and the results obtained are shown in Figure 2.

The results obtained show a significant decrease in the mass of the polymers for the three formulas. The degree of erosion reaches a value of 20, 37 and 43%

for contact lenses CL9, CL6 and CL3 respectively. The results show that formulas containing alginate are more resistant to erosion, which corresponds to the results obtained by Miyazaki et al.[63] Indeed, alginate is at the leading edge of polymers that represent a high bioadhesivity and are used for drug delivery systems.[60] These results can also be explained by the difference in average molecular weight between the two polymers, the more the average molecular weight increases the less the surface erosion.

Conclusion

In summary, Silicone hydrogel contact lenses were coated with dip-coating method using a polyelectrolyte complex based on sodium alginate and chitosan. Different concentrations of this polyelectrolyte complex were studied and showed a significant antimicrobial effect especially against *S.aureus, P.aeruginosa*, and the fungus *C.albicans* which are the most isolated strains of infectious keratitis. Moreover, alginate alone has shown an antibacterial effect, regardless of its concentration. With the appropriate ALG/CTS concentration (0.5%), the pH, the swelling rate and erosion were studied. The results showed that the films surrounding the lenses have a high hydride power that allows them to maintain a significant amount of water that will be in contact with the cornea. This can ensure permanent hydration of the eye surface and prevent dry eyes, which is the cause of many eye problems. This work can be followed by an in vivo study that will evaluate the inflammatory effect of these films on the cornea and eyelids. The immunological reaction of the eye to these coated lenses is also of primary importance.

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Conflict of interest

The authors have declared no conflict of interest.

Περίληψη

Αντιμικροβιακή δράση και in vitro αξιολόγηση επίστρωσης φακών επαφής υδρογέλης σιλικόνης με σύμπλεγμα πολύ-ηλεκτρολυτών με βάση τη χιτοζάνη και το αλγινικό νάτριο

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Η διόρθωση της αμετρωπίας που επιτυγχάνεται με τους φακούς επαφής βοηθά στη βελτίωση της όρασης. Ωστόσο, μερικές φορές η χρήση τους οδηγεί σε προβλήματα, λόγω της κακής φροντίδας τους από το χρήστη, γεγονός που αυξάνει την πιθανότητα μικροβιακής μόλυνσής

τους. Σκοπός αυτής της μελέτης ήταν η επίστρωση φακών επαφής υδρογέλης σιλικόνης με σύμπλεγμα πολύ-ηλεκτρολυτών με βάση το αλγινικό νάτριο και τη χιτοζάνη, για τη μελέτη της αντιμικροβιακής τους δράσης και των φυσικοχημικών χαρακτηριστικών τους. Πραγματοποιήθηκε μια προκαταρκτική μελέτη για την αντιμικροβιακή δράση του συμπλόκου του ηλεκτρολύτη. Αυτό παρουσίασε αντιμικροβιακή δράση σε όλα τα στελέχη που μελετήθηκαν (δηλαδή: *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis* και τον μύκητα *Candida albicans*) με διαμέτρους ζώνης αναστολής που κυμαίνονται από 11 έως 15 mm. Η αντιμικροβιακή μελέτη των επικαλυμμένων φακών επαφής πραγματοποιήθηκε στα ίδια στελέχη και έδειξε μεγαλύτερη βακτηριοστατική από βακτηριοκτόνο δράση. Για να εκτιμηθεί η ικανότητα συγκράτησης νερού αυτών των φακών, πραγματοποιήθηκαν δοκιμές διόγκωσης και διάβρωσης. Οι φακοί επαφής επικαλυμμένοι με το σύμπλεγμα πολυηλεκτρολυτών ALG / CTS έδειξαν μέγιστο ρυθμό διόγκωσης 343% μετά από επαφή 360 λεπτών με τεχνητά δάκρυα και ρυθμό διάβρωσης 37% μετά από 48 ώρες. Αυτή η μελέτη θα συνεχιστεί με *in vivo* μελέτη αξιολόγησης των επικαλυμμένων φακών.

Λέξεις κλειδιά
Φακοί επαφής, αλγινικό νάτριο, χιτοζάνη, σύμπλοκο πολυηλεκτρολύτη, αντιβακτηριακή δράση

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