Novel silver-cerium EDTA complexes with high antimicrobial and antibiofilm efficacy

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BACKGROUND

Biofilms are complex communities of microorganisms that adhere to surfaces and are encased in a protective matrix. These structures are notoriously difficult to eradicate and are a significant contributor to antimicrobial resistance (AMR). This growing threat underscores the urgent need for new antimicrobial technologies. Innovative approaches, such as bacteriophage therapy, antimicrobial peptides, and nanotechnology-based solutions, are being explored to combat biofilms and overcome AMR, aiming to ensure effective treatments for bacterial infections in the future.

5D's solution: a globally patent MMC technology specialised for biofilm management. MMC is based on the combination of EDTA/DTPA with two or more specific metal ions attached, which offers the employment of an almost limitless combination of metal ions. We demonstrate here the MMC's key factors based upon Ag-Zn and Ag-Cu MMC.

Key Features	*5D Technology*
• ***Globally granted patent for use on any wound dressing and anything touching the skin***	✓
• ***Kills microorganisms in the planktonic state***	✓
• ***Disrupts biofilms***	✓
• ***Kills micro-organisms within a biofilm***	✓
• ***Downregulates MMPs***	✓
• ***Prevents attachment and formation of a biofilm***	✓
• ***Provides rapid and sustained antimicrobial activity over 1-7 days***	✓
• ***Works synergistically with other antimicrobials***	✓
• ***Broad Spectrum of activity (Gram positive, negative, yeast, fungi, parasites)***	✓
• ***Biocompatible (Cytotoxicity, Sensitisation, Irritation)***	✓
• ***Effective over a range of pHs***	✓
• ***Can be Sterilised – Gamma, Ethylene Oxide, Steam***	✓

Cerium and its derivatives have been used as remedies for wounds, especially in the treatment of deep burns since the early 20th century. Its ability to mimic and replace calcium is presumed to be a major mechanism of its antimicrobial efficacy. The ***aim*** of this study is to investigate the antibacterial and antibiofilm efficacy of silver-cerium EDTA complex based materials.

Methods

Microorganisms: *Pseudomonas aeruginosa* ATCC 15442, *Staphylococcus aureus* ATCC 6538, *Candida albicans* ATCC 10231, and *P. acnes* ATCC 6919, *S. epidermidis* ATCC 35984

Test samples: Ag-Ce MMC was prepared by mixing $AgNO_3$, $Ce(NO_3)_3$ and EDTA solution at the molar ration of 2:2:1, and then diluted in pure water or in a synergistic combination with poloxamer at 2% P188 and P407.

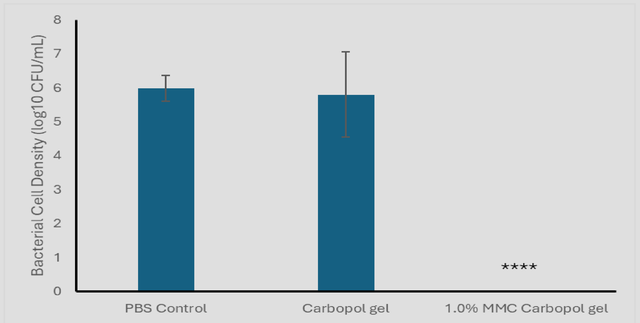
Method: A variety of *in vitro* antimicrobial and biofilm models were utilised to evaluate the ability of Ag-Ce MMC in different platforms (liquid/gel) to sequester microbes, prevent dissemination, and manage bioburden.

RESULTS

- ***Ag-Ce MMC demonstrates a broad-spectrum antimicrobial activity with a lower Minimum Inhibitory Concentration (MIC) when used in conjunction with a surfactant (Poloxamer)***

Ag-Ce MMC	*P. aeruginosa*	*S. aureus*	*C. albicans*
water	0.050000%	0.008333%	0.008333%
2% P188	0.003229%	0.001563%	0.001563%
2% P407	0.002604%	0.005000%	0.003125%

- ***Ag-Ce MMC Carbopol hydrogel shows strong antibiofilm/antibacterial efficacy in CDC biofilm bioreactor***

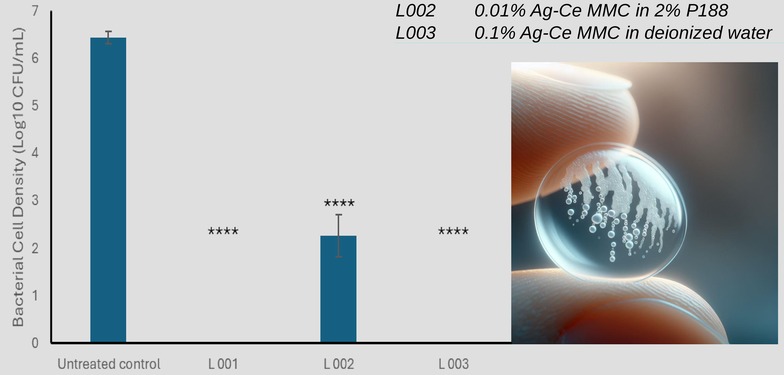


*Bacterial cell density of P. acnes, S. epidermidis following 24 hours treatment with PBS, Carbopol gel, and 1.0% MMC (ETDA-Silver-Cerium) Carbopol gel on 48 hour biofilm formed in a CDC biofilm bioreactor. The results showed completely killed by the MMC loaded Carbopol gel. ****: p<0.0001 compared to PBS control. The differences were tested for statistical significance using a one-way ANOVA.*

RESULTS

- ***Ag-Ce MMC lavages demonstrates antibacterial / antibiofilm activities in contact lenses model***

Lavage	*Samples description:*
L001	*0.1% Ag-Ce MMC in 2% P188*
L002	*0.01% Ag-Ce MMC in 2% P188*
L003	*0.1% Ag-Ce MMC in deionized water*



*Bacterial cell density of P. aeruginosa following 6 hours treatment on 24 hour biofilm growth on contact lenses. The results showed completely killed by L001 and L003. L002 achieved >4 log reduction. ****: p<0.0001 compared to the PBS control. The differences were tested for statistical significance using a one-way ANOVA.*

CONCLUSIONS

5D's globally patented MMC technology and its antibiofilm effect is based on the EDTA moiety that carries two or more metal ions into a biofilm, where they can be released *in vivo* and kill both planktonic and sessile microbes. Once the active metal ions are released, the carrier (EDTA) then starts to sequester vital metal ions such as Ca^{2+}, Mg^{2+} and Fe^{3+} from the biofilm, effectively causing its destruction as well as 'starving' the microbes of vital metal ions and thereby causing cell death. At same time, the active metal ions, such as Ag+, Cu^{2+}, and Ce^{3+} can penetrate into microbes and bind to proteins and DNA to proliferation.

The data generated within the *in vitro* biofilm model demonstrates that the Ag-Ce MMC complexes are exceptional next generation antibiofilm agents for effective biofilm management and control in wound care.

REFERENCES

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