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## Controlled and Localized Nitric Oxide Precursor Delivery from Chitosan Gels to *Staphylococcus aureus* Biofilms

Sayed Hasan<sup>1</sup>, Nicky Thomas<sup>1,2</sup>, Benjamin Thierry<sup>3,4</sup>, and Clive A. Prestidge<sup>1,4\*</sup>

<sup>1</sup>School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, South Australia, Australia

<sup>2</sup>Biofilm Test Facility, Sansom Institute for Health Research, University of South Australia, Adelaide, South Australia, Australia

<sup>3</sup>Future Industries Institute, University of South Australia, Mawson Lakes, South Australia, Australia

<sup>4</sup>ARC Centre of Excellence in Convergent Bio and Nano Science and Technology, University of South Australia, Adelaide, South Australia, Australia

### ABSTRACT

Extracellular polymeric substances in bacterial biofilms reduce the penetration of antimicrobials and give rise to extreme recalcitrance and treatment challenges for many persistent biofilms and associated infections. Nitric oxide (NO) is a promising alternative to conventional antimicrobials, but is challenging to deliver at precise concentrations for significant periods in a convenient and non-toxic manner. Here we report a unique NO delivery platform by incorporating the NO precursor isosorbide mononitrate (ISMN) into chitosan gels to facilitate sustained ISMN release and effective delivery. The chitosan gels were characterised with respect to the drug release kinetics, rheological properties, as well as antimicrobial efficacy against biofilms of *Staphylococcus aureus* (*S. aureus*) in the absence and presence of the antibiotic ciprofloxacin. Chitosan gels loaded with ISMN alone (CS-ISMN) showed comparable antimicrobial effects compared to blank chitosan gel (approximately 2log<sub>10</sub> reduction). However, there was strong synergy of CS-ISMN when combined with ciprofloxacin, i.e. ~4 log<sub>10</sub> reduction of bacterial colonies of CS-ISMN-CIP compared to the single treatments. These findings were confirmed by confocal imaging and highlight a potentially effective new way to overcome recalcitrant *S. aureus* biofilms using NO precursors.

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\* Corresponding Author

Clive Prestidge; Professor: School of Pharmacy and Medical Sciences; Division of Health Sciences  
University of South Australia, Adelaide, South Australia 5001; t: +61 8 83023569; f: +61 8 83023683  
E-mail: clive.prestidge@unisa.edu.au

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