Entrapment of Precursors with Biodegradable Polymer Microparticles for Targeted Treatment of Infection without Antibiotics

Introduction

The problem of increasing antibiotic resistance is well understood (draft political declaration of the high level meeting of the UN general assembly on antimicrobial resistance). WHO Global Action Plan for Antimicrobial Resistance.

Alternative approaches to antibiotic treatment must be explored. To date 19 alternative therapies have been proposed (Czaplewski et al). We propose a 20th. Resistance is the problem. Find a way of delivering a therapy that won't give rise to resistance.

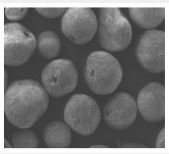
Mechanism of action

Utilize precursors for high energy oxidative molecules, protected in TIPS PLGA particles, capable of delivering controlled dosing, with design flexibility to potentially reach most clinical sites to eliminate infection with minimal side effects.

Biodegradable regulatory approved PLGA

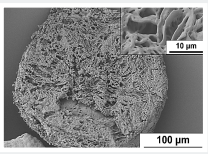
TIPS (Thermally induced phase separation) produced particles allow adequate quantified loading of reactive small molecule precursors

Example

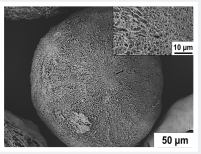


TIPS particles loaded with peroxygen and acetyl donor molecules

Reaction with water in vivo



Initial burst release to deliver impact dose of PAA/H_2O_2



Particles hydrolyse leading to continuous release of antimicrobial treatment over several days. Possible scaffold formation.

Wide spectrum of activity, MRSA, CRE, VRE, *C. diff.*

Wide scope for design makes for capability against a wide range of infections in many clinical sites.

Low cytotoxicity, subcutaneous toxicity and low predicted systemic toxicity indicating therapeutic promise.

Future tests

- Engineered particle size <50nm to micro size scaffold.
- Wide range of acetyl donors to investigate.
- Further animal model testing for different clinical conditions.
- Coat, pegylate and add biosensors and targeting ligands to particles.

Results

Efficacy against MDRO clinical isolates was demonstrated with excellent cytotoxicity and histology of subcutaneous implant site for experimental combined precursor loaded TIPS particles.

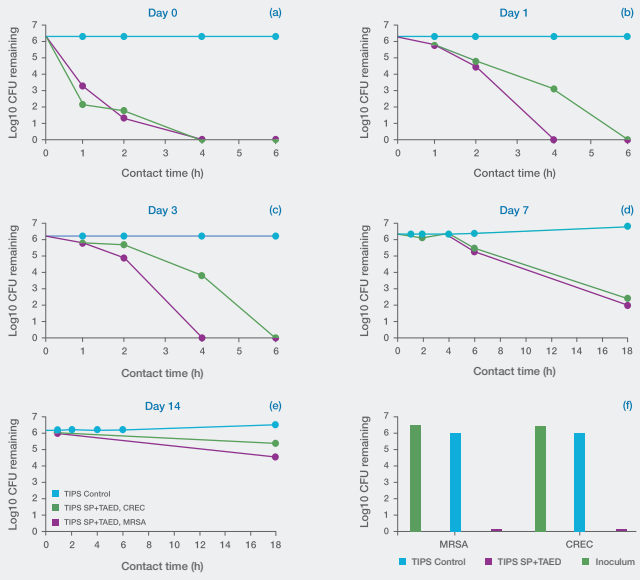


Figure 1 Antimicrobial activity of the microparticles loaded with TAED + SP against CREC and MRSA for 14 days. The antimicrobial activity for the hydration times (a) 1.5 hours, (b) 1 day, (c) 3 days, (d) 7 days & (e) 14 days and different contact times. Hydration time is the amount of time the samples are incubated in complete MEM medium before supernatant samples are collected. Contact time is the amount of time the supernatant is incubated with bacteria. The TAED+SP TIPS microparticles have antimicrobial activity that lasts for up to 14 days. (f) The loaded microparticles are bactericidal and not bacteriostatic. A bacterial inoculum challenge that had been exposed for 6 hours to the active supernatant, collected from the loaded microparticles and incubated for 48 hours, did not show any sign of growth. A Two-Way ANOVA with Dunnett's test for multiple comparisons was used to examine if there is a significance difference between the groups ($p<0.001$).

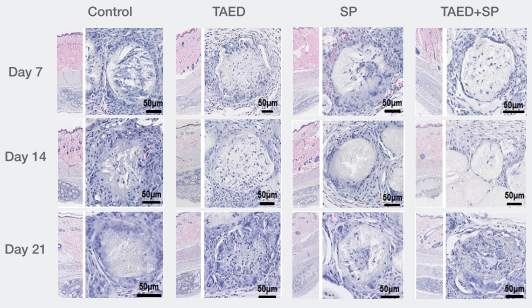
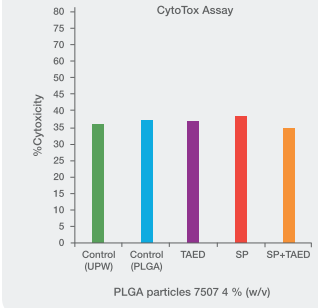


Figure 2 Histology of the implant site after 7, 14 and 21 days. No discernible difference in the tissue response was observed between the unloaded microparticles and those loaded with TAED and SP. The microparticles lose their structure over time and become infiltrated by inflammatory cells and fibrovascular tissue that forms part of the expected tissue response continuum as the microparticles degrade.



References

Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA, Foster S, Gilmore BF, Hancock RE, Harper D, Henderson IR. Alternatives to antibiotics—a pipeline portfolio review. The Lancet Infectious Diseases. 2016 Feb 29;16(2):239-51.

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