Doxycycline loaded thiol-ene microparticles made via suspension polymerization

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Statement of Purpose: Periodontal disease, a bacterial infection that harms the gum and jawbone, can be treated using oral or topical delivery of antibiotics. Thiol-ene based microparticles, made from alkene and thiol monomers, are showing potential for use in targeted drug delivery applications. Previous research has shown that they can carry a lipophilic drug, Thymol.[1] In this study, we aim to determine whether the microparticles can carry and release doxycycline, a hydrophilic antibiotic, for the treatment of periodontal disease. To achieve complete and sustained eradication of bacteria, we aim to achieve an initial burst release of the doxycycline followed by a gradual release. We prepared four microparticle formulations that had shown such drug release profiles in our previous research.[1] We hypothesized that changing the pH of the doxycycline solution from acidic to neutral will encourage drug encapsulation because the microparticles are anionic, and doxycycline is cationic.

Methods: *Particle formulation*. Microparticles were made using suspension polymerization as described earlier.[1] While stirring the aqueous phase (water and Hitenol) at 500 rpm, we added the organic phase (2-ene, 2-thiol, 4-thiol, and photo initiator) and cured using UV light for 10 min. The liquid was then decanted.

Table 1. Selected particle formulations

Formulation	Composition				
	2-Ene (µL)	2-Thiol (µL)	4-Thiol (µL)	Hitenol (mL)	Water (mL)
F1	78.5	6.4	272.5	0.4	9.6
F2	68.1	6.4	272.5	0.8	9.2
F3	78.5	12.8	242.3	0.4	9.6
F4	68.1	12.8	242.3	0.8	9.2

Particle sizes. Pictures of the particles were taken using a Keyence optical microscope and sizes of 50 particles were determined using Image J software.

Drug loading. 1 M NaOH was added to 1 mL doxycycline solution (20 mg/mL) in a dropwise manner until the pH changed to neutral. The particles were soaked in the doxycycline solution for 24 h. After the solution was decanted, PBS solution was added to the particles.

Drug release. A Nanodrop UV-Vis spectrometer was used to quantify the doxycycline released from the particles over a 7-day period by measuring the absorbance at 352 nm.

Statistical Analysis. Data are reported as mean ± 95% confidence intervals.

Results: *Particle sizes.* The microparticles were of uniform sizes with similar sizes (Fig. 1), with F2 and F4 showing the slightly larger diameters of 343 ± 17 µm than F1 and F3 showing diameters of 313 ± 16 µm and 330 ± 17 µm (Fig. 2).

Drug loading. Doxycycline solution was first changed from acidic to neutral pH because the acidic pH caused coagulation of the particles (Fig. 3).

Drug release. All formulations first show a burst release in the first 10 h. Thereafter, F1 and F2 show a gradual release of doxycycline. This is likely because they have a higher content of 4-thiol which promotes crosslinking and thus promoting gradual drug release. F3 and F4 show no further release of doxycycline after the initial burst release.

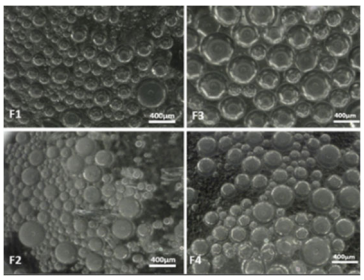

Fig 1. Optical microscopy images of microparticles. Scale bars = 400 µm.

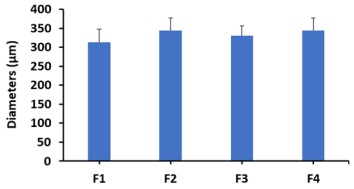

Fig 2. Average diameters of microparticles with four different formulations. n = 50 particles per formulation. Error bars = 95% confidence intervals.

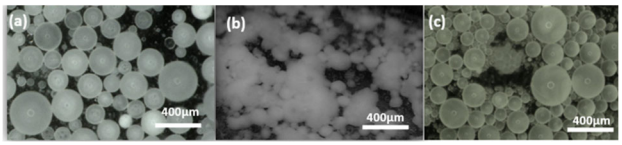

Fig 3. (a) Thiol-ene microparticles before the addition of doxycycline. (b) Coagulation of microparticles after doxycycline with acidic pH is added. (c) Microparticles after adding neutral pH doxycycline. Scale bars = 400 µm.

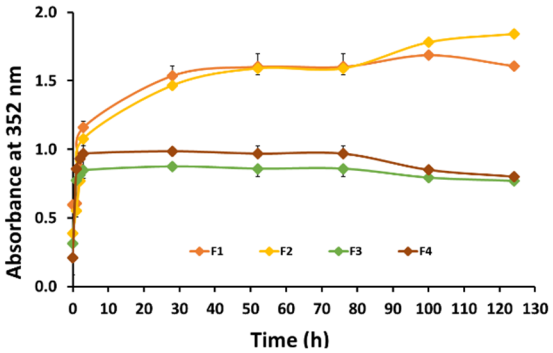

Fig 4. Drug release profiles of microparticles with four different formulations. n = 3 per formulation. Error bars = 95% confidence intervals.

Conclusion: Our results show that thiol-ene microparticles can be loaded with doxycycline and certain formulations release the doxycycline gradually over a one-week period. This shows their potential to provide a gradual delivery of drugs at the infection sites and eliminate unwanted side effects from systemic delivery of high antibiotics dosages.

Reference: [1] Cobb JS, *et al. Material Adv.*, 2021, 2:3378.