Embedding ultrasound responsive multi-cavity microparticles into arterial tissue with HIFU

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Background, Motivation and Objective

Atherosclerosis is an inflammatory disease of arteries, and results in stroke or heart attacks-the leading causes of death and disabilities in the developed world. Yet drug treatments for this chronic inflammatory disease remains to be addressed. Here, we developed a multi-cavity PLGA microparticles (mcPLGA MPs) capable of being remotely implanted at the site of arterial injury with focused ultrasound. The obtained mcPLGA MPs present with two to five submicron cavities with rough inner surfaces, allowing bubbles to be trapped. After exposure to ultrasound in an agarose tissue phantom, mcPLGA MPs extravasated beyond the lumen of the channel at an average distance of 4.29 ± 1.19 mm, and sustained release of rhodamine-B across 15 days. Similarly, mcPLGA MPs were able to be implanted into the sub-endothelial space of an ex-vivo porcine artery model without observable damage to the artery. The results here highlight the potential for ultrasound-guided implantation of mcPLGA MPs to improve local and sustained treatment of inflamed arterial tissue.

Statement of Contribution/Methods

mcPLGA MPs were manufactured using a modified water/organic/water double emulsion solvent evaporation process[1]. Analysis of the cavitation response of mcPLGA MPs was accomplished similarly to Kwan et al.[2]. Penetration depth from ultrasound-guided implantation of mcPLGA MPs in an agarose tissue phantom were measured at 1.1 MHz center frequency, 4 MPa peak negative pressure, and 10% duty cycle. Implantation of mcPLGA MPs in an ex vivo porcine artery model were evaluated at the same ultrasound conditions.

Results/Discussion

Figure 1 shows representative SEM image of a mcPLGA MP, emphasizing the polyhedral structure. The inertial cavitation event of mcPLGA MPs were measured at each pressure amplitude, and cavitation threshold was determined to be 1.1 MPa peak negative pressure. In contrast, hollow spherical PLGA MPs required 5.5 MPa to reliably nucleate cavitation.

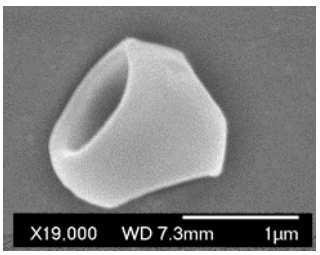

Figure 1. Representative SEM image of a mcPLGA MP

We measured the penetration of mcPLGA MPs into tissue mimicking agarose phantom. Fluorescence images of agarose flow phantoms indicated that mcPLGA MPs penetrated beyond the lumen of the channel up to 4.3 mm in depth, slowly decreasing in in fluorescence intensity across 15 days. Fluorescent images of porcine arteries (Figure 2) post treatment indicated that mcPLGA MPs were embedded into the artery only after ultrasound exposure. This result clearly indicated that mcPLGA MPs were implanted into primarily the sub-endothelial space of ex vivo porcine arteries, avoiding possible damage of the underlying smooth muscle cells during exposure to ultrasound. We acknowledge that this work was made possible through the support of the Singapore Ministry of Health's National Medical Research Council under its NMRC/OFYIRG/NOV006/2016.

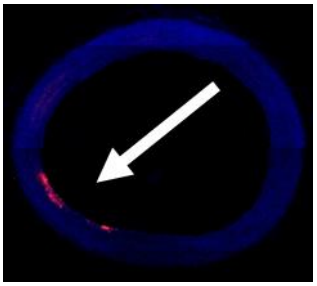
Figure 2. Fluorescent image of an ex vivo porcine artery with mcPLGA MPs implanted into the tissue after ultrasound exposure (arrow).

References

1. Ankrum et al., Nat. Protoc. 2014, 9, 233.
2. Kwan et al., *Small* 2015,11(39):5305-5314.