Noninvasive Characterization of Polymer Degradation and Erosion using Ultrasound Elastography (UE)

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Statement of Purpose: *In situ* forming implants (ISFI) consist of a biodegradable polymer (typically poly(lactic-co-glycolic acid), PLGA) dissolved in a biocompatible organic solvent (such as 1-methyl-2-pyrrilidinone, NMP), which precipitates into a solid depot upon injection into the body. When mixed with an active agent, ISFI become an attractive drug delivery platform. The rational design of this platform would greatly benefit from the ability to noninvasively monitor polymer degradation and erosion at the implantation site, since these processes are directly related to the rate of drug release and overall implant performance. Ultrasound elastography (UE) is a dynamic technique that uses ultrasound to assess the mechanical stiffness of materials by measuring material distortion or strain in response to external compression. In the current study, we aimed to characterize ISF implant degradation and erosion behavior noninvasively in a novel polyacrylamide based tissue-mimicking phantom through the use of UE.

Methods: Implants were prepared by dissolving PLGA and fluorescein in NMP in a 37°C incubator shaker overnight. A tissue mimicking phantom with scattering agent (titanium dioxide) was fabricated by crosslinking acrylamide: bis-acrylamide 37.5:1, 40% solution. Ammonium persulfate and TEMED were used as initiators in this process. Cubes of sucrose cut into small rectangles (5x5x2.5 mm) were embedded into the cross-linked polyacrylamide and were allowed to dissolve leaving empty voids for implant injection. Phantoms were swelled in PBS for 6 days. The created voids were flushed 3 times using PBS before injection. Then the polymer solution was injected into the empty voids to form solid implants. PLGA implants embedded in tissue-mimicking phantoms were kept in PBS at 37˚C for 25 days. PBS was replaced daily. Implants were scanned using a clinical ultrasound system (Toshiba Aplio500) with a linear array transducer (PLT-1204AX, centered at 12MHz) daily to evaluate their mechanical stiffness change overtime. A laboratory-designed stage and a linear actuator were used to induce uniform compression. (Fig 1) The erosion study was performed by gravimetrical analysis of freeze dried polymer excisions at 1, 3, 6, 9, 12, and 16 days.

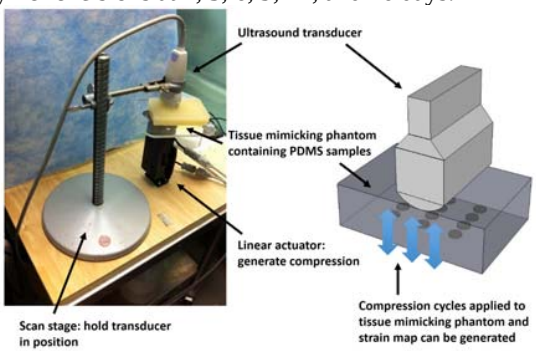
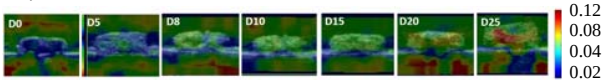


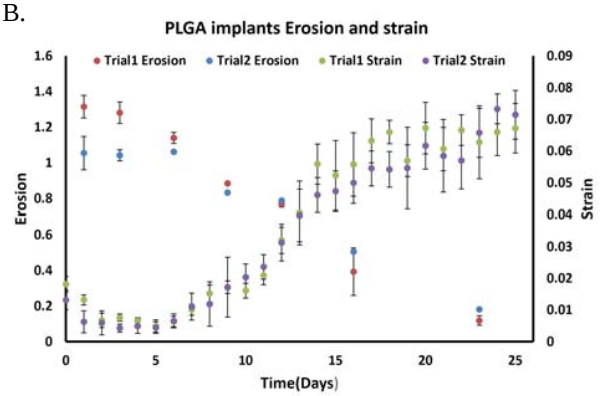
Fig1. Ultrasound elastography (UE) experiment setup

Results: An increase in strain due to implants becoming more pliable during the degradation and erosion period was noted in both of our trials (Fig 2A and B). Interestingly, a stiffening (reduced strain) period was seen within first five days. We attribute this stiffening period to be a result of polymer precipitation and phase inversion. This hypothesis was corroborated by another observation in the erosion profile in which erosion was above 1 due to the residual NMP. (Fig 2B) A linear inverse relationship (R^2=0.96) between strain and polymer erosion was observed after the stiffening process. (Fig2 C.).

A.



B.



C.

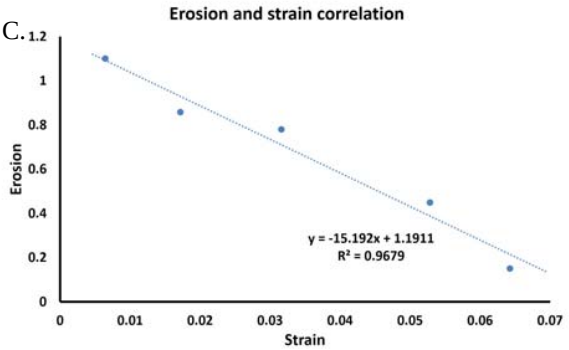


Fig 2. A) Color coded strain map superimposed on B-mode image; B) Absolute strain change and erosion of polymer implants overtime; C) Polymer erosion and strain correlation

Conclusions: Our experiments demonstrate that ultrasound elastography can be used as a noninvasive technique to quantitatively characterize changes in polymer mechanical properties which result from polymer degradation and subsequent erosion. Experiments measuring implant degradation via GPC are currently ongoing. Future studies will evaluate this technique *in vivo* in an animal model.

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