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Assessing Long-Acting Injectable Formulations Using In Vivo Imaging

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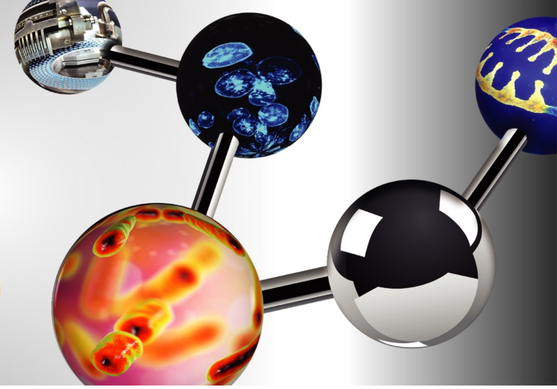

PURPOSE

Long-acting injectables such as *in situ* forming implants have attracted increasing attention especially for delivering proteins, peptides and new therapeutic modalities. The implant formation process can significantly affect the shape, surface area and drug distribution of the implant. However, there are limited approaches to investigate the phase inversion process in real time. We developed a non-invasive *in vivo* imaging approach to obtain improved understanding of implant formation *in vivo* and evaluate the impact of the implant formation on drug release.

OBJECTIVES

- To observe the formation of *in situ* forming implants in real time and understand the payload distribution within the implants.
- To understand the impact of injection angle, and location on the implant size and shape.

METHODS

- X-ray computed tomography (CT) was used for *in vivo* imaging and the CT contrast agent iohexol was used for observing implant formation. To prepare the injectable formulation, poly(lactic-co-glycolic acid) (PLGA) copolymer (50:50, acid endcap) was dissolved in N-methyl-2-pyrrolidone (NMP) and iohexol was added to the PLGA solution. The formulation was administered subcutaneously to each rat, with a horizontal or vertical needle orientation and different injection positions. The *in vivo* CT images were acquired using IVIS Spectrum CT system. After the rats were euthanized, the implants were excised for *ex vivo* CT imaging. ROI (region of interest) quantification was conducted based on *ex vivo* images.
- *In vitro* implants were prepared by directly injecting the formulation into 100 mL PBS (pH 7.4) at 37°C and the subsequent *in vitro* release of iohexol and NMP was determined by sampling at various time points up to 1 month, and different injection volumes were compared.

RESULT(S)

- Upon subcutaneous injection, the implant was clearly observed through CT as a round structure due to the CT contrast agent dispersed in the implant. The polymer matrix solidified as the solvent diffused out of the implant, but some CT contrast agent also diffused out together with the solvent, which yielded a shell layer with lower CT signal starting 30 min post administration as shown in Figure 1. Noticeably, the formation of cavities in the shell of the implants was observed *in vivo.* This observation was also demonstrated by *ex vivo* CT images in *Figure 2*.
- Core-shell signal differences were quantified through the *ex vivo CT image* ROI analysis, as shown in *Figure 3.* The outer layer depletion of iohexol correlated with the burst release, followed by a biphasic release of iohexol from the core layer after significant matrix degradation.

- There were no observable differences between injection angles with respect to implant shape and implant formation process.
- Different injection volumes did not significantly affect the initial release rate of both NMP and Iohexol, as shown in *Figure 4*, but lower volumes appears to have faster solvent release and slower second phase release rate for iohexol.

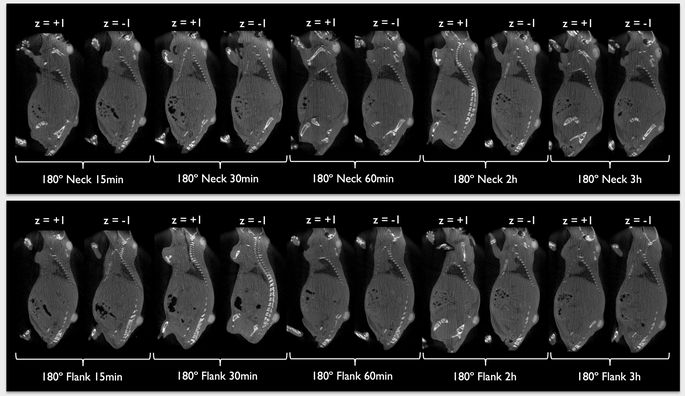

Figure 1. IVIS spectrum CT images showing the formation of *in situ* forming implants injected horizontally in different positions

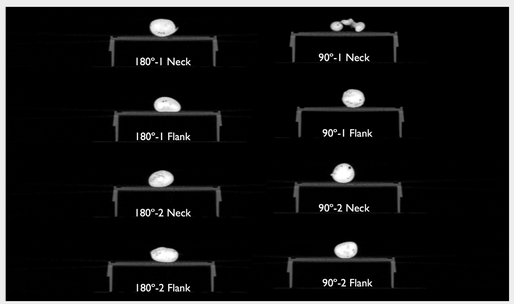

Figure 2. Ex vivo CT images of *in situ* forming implants formed *in vivo* for 3 hours

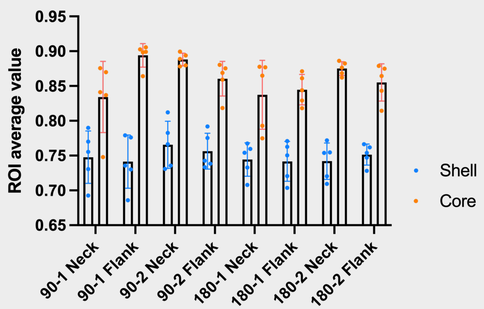

Figure 3. ROI values of the shells and cores in the implants 3 h post subcutaneous injection (mean ± SD, n=5)

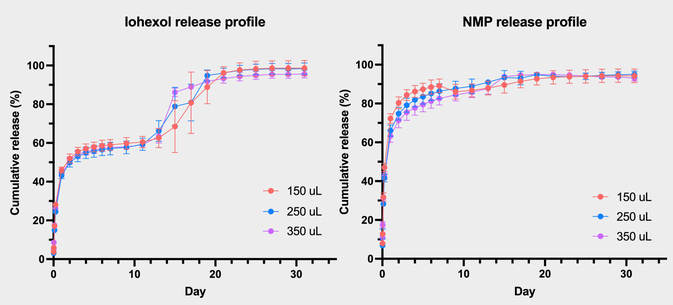

Figure 4. In vitro release profile of iohexol and NMP from the implants with different injection volumes (mean ± SD, n = 3)

CONCLUSIONS

From the *in vivo* and *ex vivo* images:

- Iohexol can enable the observation of *in situ* forming implants using CT imaging, assisting with the determination of morphological characteristics and release kinetics in real time during the implant formation process.
- The injection angle and position appear to have minimal influence on the implant's size and shape.
- Core shell structure of the implant is formed 3 hours post administration due to the fast diffusion of iohexol at the surface layer of the implants.

From the *in vitro* release study:

- The *in vitro* release correlates well with the observed core-shell structure of iohexol distribution within the implants formed *in vivo*.
- The comparison between the release kinetics of NMP and iohexol provided further understanding on the impact of solvent diffusion on the drug release.

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