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Assessing *In Situ* Forming Implants Using Real-Time Imaging

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PURPOSE

Long-acting injectables, especially *in situ* forming implants, have attracted increasing attention for delivering proteins, peptides and new therapeutic modalities. The implant formation process *in situ* can significantly affect the microstructure of the implant and subsequent drug release. However, it is challenging to directly characterize the process. We developed a non-invasive *in vivo* imaging approach to obtain improved understanding of implant formation under *in vitro* and *in vivo* conditions and the impact of drugs on implant formation and drug release.

OBJECTIVES

- To observe the morphology and inner structure of *in vitro* and *in vivo* formed implants in real time
- To understand how addition of drugs impacts implant formation and drug release profile

METHODS

An X-ray computed tomography (CT) contrast agent, iohexol, was used for imaging to observe implant formation. To prepare the injectable formulations, poly(lactic-co-glycolic acid) (PLGA) copolymer (50:50, acid endcap, 25 kDa) was dissolved in N-methyl-2-pyrrolidone (NMP) and then iohexol and leuprolide acetate (LA) were added to the PLGA gel.

- For *in vitro* formed implants, 250 µL of the PLGA formulation was injected into sample vials with 10 mL PBS (pH 7.4) and maintained in bath shaker at 37°C. Medium was replenished at each time point. The size of the implants was measured at each time point. *In vitro* release studies were also conducted under the same conditions to obtain drug and solvent release profiles.
- For *in vivo* formed implants, the same volume of the formulation was administered subcutaneously to rats (n=3). CT images were obtained using the IVIS Spectrum CT system (PerkinElmer, USA).

RESULTS

From the CT images of *in vitro* formed implants:

Formulation with only iohexol:

- Formulation with only iohexol shows a core-shell structure. Small black cavities exist in the shell starting at 8 hours after administration and form big black cavities around 11 days.
- Signals from the cores decrease with the time goes and the core-shell structure disappears at 13 days.
- Iohexol is observed to scatter out from the core at 3 hours after administration.

Formulation with iohexol and leuprolide acetate:

- There is no clear core-shell structure and black cavity inside the implants.

From the CT images of *in vivo* formed implants:

Formulation with only iohexol:

- Small black cavities are observed in the shell of the implants after administration.
- After 4 days, small cavities start to merge into larger cavities.

Formulation with iohexol and leuprolide acetate:

- There is no black cavity inside the implants and signal lost in 6 days.

From *in vitro* release profiles:

- Iohexol shows a multi-phasic release profile, the addition of leuprolide acetate inhibits the burst release of iohexol.
- Formulation with only leuprolide acetate and formulation with both iohexol and leuprolide acetate show similar LA release profiles.
- Addition of leuprolide acetate inhibits the burst release of NMP and shows a sustained release profile until reaching a plateau.

From the size change of *in vitro* formed implants:

- Addition of leuprolide acetate promotes the size increase of the *in vitro* formed implants.
- The peak size is observed on Day 13.

Figure 1. IVIS spectrum CT images showing the formation of *in vitro* formed implants with different drug compositions (LA: Leuprolide acetate)

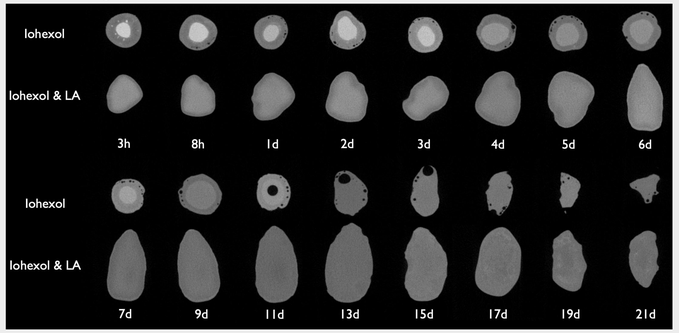


Figure 2. IVIS spectrum CT images showing the formation of *in vivo* formed implants with different drug compositions

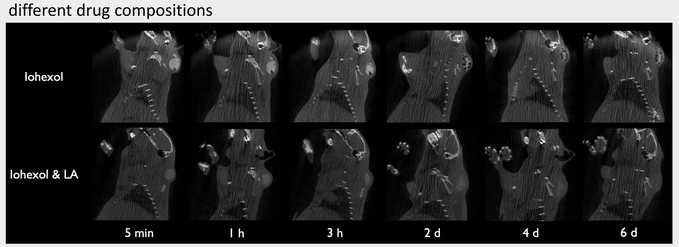
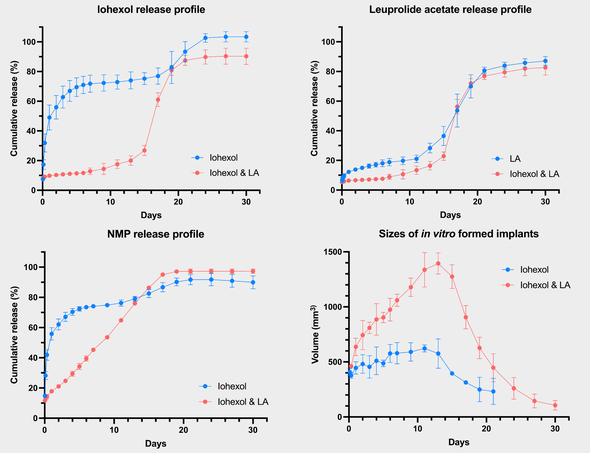


Figure 3. In vitro release profiles and size change of the implants (n=4, mean±S.D.)



CONCLUSIONS

From CT images:

- Addition of leuprolide acetate changes the inner structure of both *in vitro* and *in vivo* formed implants, where no core-shell structure and black cavity are observed.
- The size of *in vitro* formed implants containing leuprolide acetate showed more significant increase compared to leuprolide free implants.
- Scattering of iohexol from the core and formation of small black cavities in the shell may be caused by the fast solvent exchange, which is supported by the *in vitro* release profile of NMP.

From the *in vitro* release studies:

- Both iohexol and leuprolide acetate show multi-phasic release profiles.
- Addition of leuprolide acetate inhibits the burst release of both iohexol and NMP at early time points, whereas addition of iohexol does not change the release behavior of leuprolide acetate.

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