Effect of Polymer Characteristics on Formation of In Situ Forming Implants in Subcutaneous Tissue

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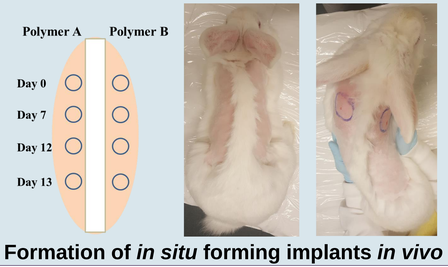
PURPOSE

In situ forming implants have been successfully used for the controlled release of therapeutic agents. These implants form solid polymer matrices in the subcutaneous environment through phase transition of poly(lactic-co-glycolic acid) (PLGA). However, the mechanisms of implant formation and changes in their microstructure that determine drug release behavior have not been well studied. The objectives of this study were to understand the effect of polymer characteristics on the formation of *in situ* forming implants and to investigate microstructural changes using a rabbit model.

METHODS

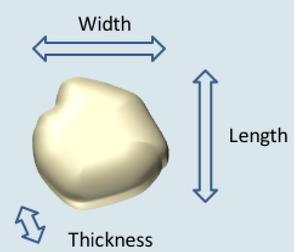
In situ forming implant formulations were prepared by a syringe-to-syringe mixing procedure. Briefly, 52% *w/w* of two equivalent PLGA polymers (lactide/glycolide ratio of 50:50, Mw 15,000-25,000, acid end) sourced from different US vendors were dissolved in an aprotic solvent (N-methyl-pyrrolidone, NMP), and each polymer solution was filled into a syringe (Syringe 1). Syringe 1 was connected and injected into Syringe 2 pre-filled with lyophilized leuprolide acetate (drug substance), and the contents were thoroughly mixed by pushing the syringes back and forth for 1 minute to obtain a uniform solution. The prepared implant formulations were injected under the back dorsal skin of three rabbits (n=3) and each rabbit was injected at different locations at four time-points (days 0, 7, 12, and 13). The rabbits were euthanized on day 14, and the injected implants were excised along with the surrounding tissue. Implant dimensions were measured, and cryosectioned to investigate their microstructure.



Formation of *in situ* forming implants *in vivo*

RESULTS

Figure 1 and 2 show roughly circular shaped implants formed in the subcutaneous tissue. The exterior features and dimensions of the implants were similar for implants prepared using both polymers in all test rabbits. However, significant changes in the interior of the implants were observed in the cross-sectional images. As shown in Figure 3, porous solid structures only appeared in implants prepared using polymer B, and a two-phase structure was observed in implants prepared using polymer B up to 48 hours after injection. The microstructural changes indicate that implant formation was completely different for implants prepared using polymer A compared to those prepared using polymer B.



	Polymer A	Polymer B
Width (cm)	1.69 ± 0.14	1.52 ± 0.3
Length (cm)	2.22 ± 0.12	2.23 ± 0.22
Thickness (cm)	0.21 ± 0.02	0.23 ± 0.02

Figure 1. Dimensions of implants (prepared using Polymer A and Polymer B) in rabbit subcutaneous tissues (n=3)

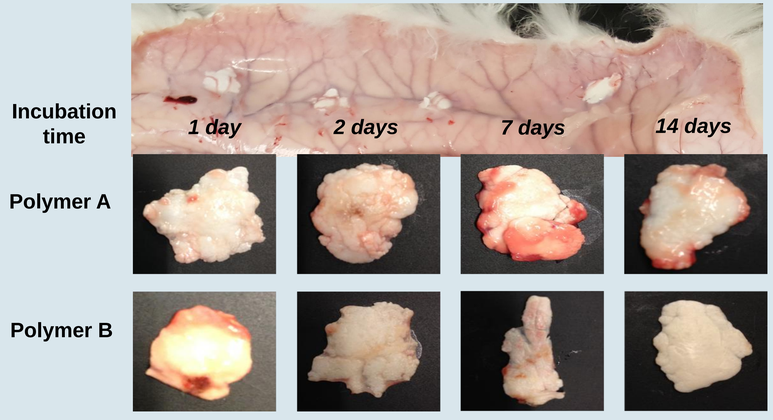


Figure 2. Formation and exterior features of implants in rabbit subcutaneous tissues at different time points (n=3)

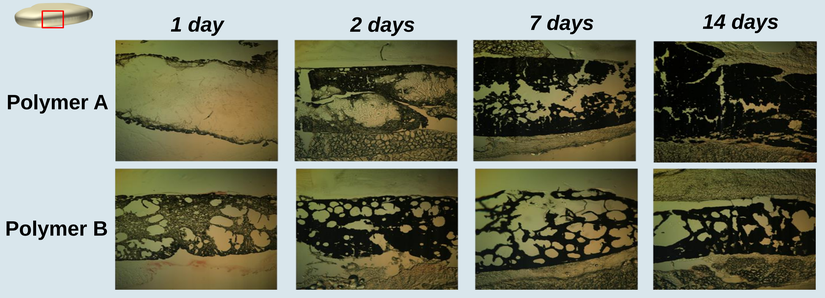


Figure 3. Microstructure of implants in rabbit subcutaneous tissues at different time points (n=3)

CONCLUSIONS

This work is the first morphological demonstration of in situ forming PLGA implants in rabbit models. The discriminatory interior features indicate that the polymer characteristics play a significant role in implant formation. Accordingly, our findings suggest that additional polymer characterization (beyond typical polymer specifications reported by the manufacturers such as molecular weight, monomer ratio, and endcap) are necessary to understand the complex behavior of *in situ* forming PLGA based implants.

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