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Formation and Microstructural Changes in *In Situ* Forming Implants: *In Vitro* and *In Vivo*

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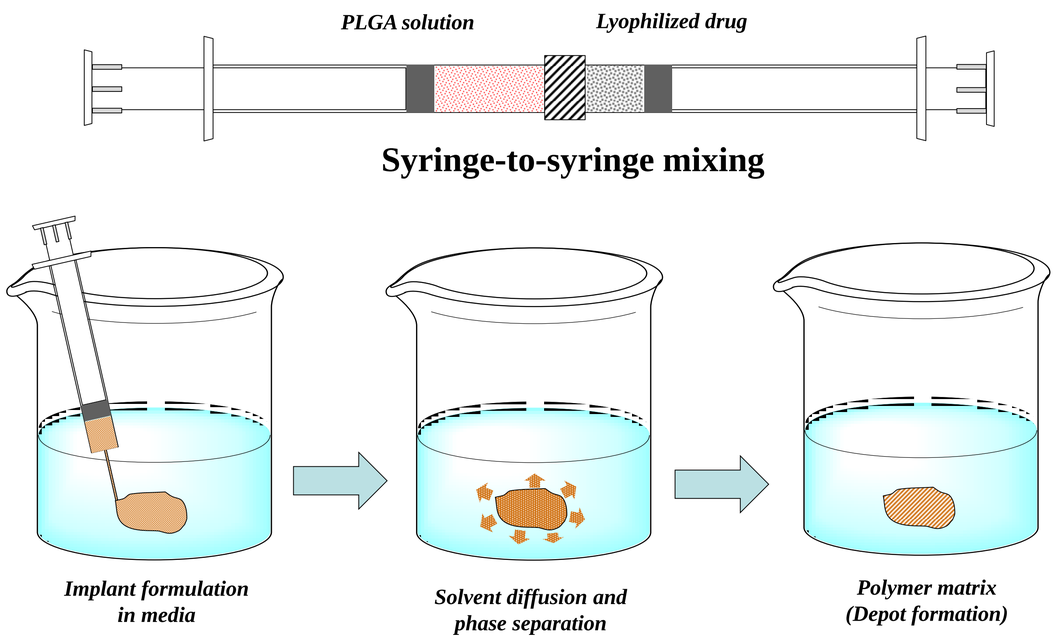
INTRODUCTION

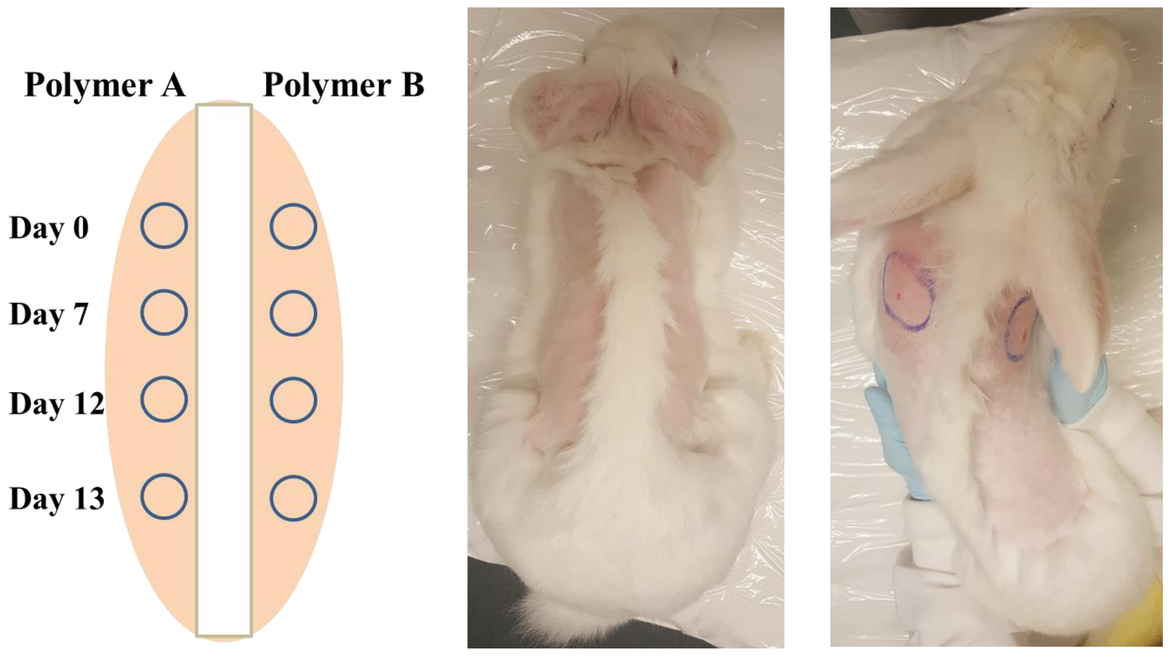
In situ forming implants are promising formulations for controlled release of drugs and as alternatives to preformed implants and microsphere formulations due to their simplicity of both manufacture and preparation for injection. The implant formulations form solid polymer matrices in subcutaneous tissues through phase separation of biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA) and poly(lactic acid) (PLA). However, the mechanisms of implant formation and changes in their microstructure that determine drug release behavior have not been well studies. The objectives of this study were to understand the formation of *in situ* forming implants and to investigate their microstructural changes *in vitro* and *in vivo*.

METHODS

Two groups of *in situ* forming implants were prepared by dissolving PLGA polymers (polymer A or polymer B, with the same certificate of analysis but sourced from different US vendors) and lyophilized leuprolide acetate in an aprotic solvent (N-methyl-pyrrolidone, NMP). For the *in vivo* studies, the same volume of the prepared implant formulations were injected under the back dorsal skin of three rabbits (n=3) at different 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. To prepare *in vitro* samples, *in situ* forming implant formulations were placed in aqueous media (PBS, pH 7.4) and incubated at 37°C for 24 hours. Implant dimensions were measured, and cryosectioned to investigate their microstructure.



Formation of *in situ* forming implants *in vitro*



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

RESULTS

As shown in **Figure 1 and 2**, roughly circular shaped implants formed in the subcutaneous tissues (*in vivo*), whereas more smooth shaped implants formed in aqueous media (*in vitro*). The overall dimensions were similar in all test animals (**Figure 3**). However, distinguishable interior features appeared in the cross-sectional images. Porous interior features were only detected in implants prepared using polymer B. A two-phase structure was observed in both types of implants after a one day study period *in vitro* and *in vivo* (**Figure 4**), but the patterns of implant formation were different for implants prepared using polymer A compared to those prepared using polymer B (**Figure 5**).

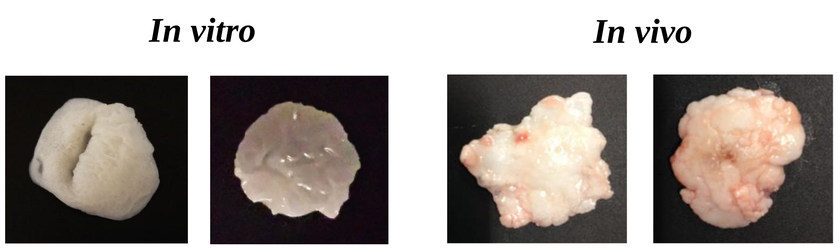
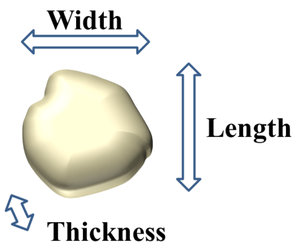


Figure 1. Implant formation *in vitro* and *in vivo* (Polymer A)



	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 3. Dimensions of *in situ* forming implants (*in vivo*)

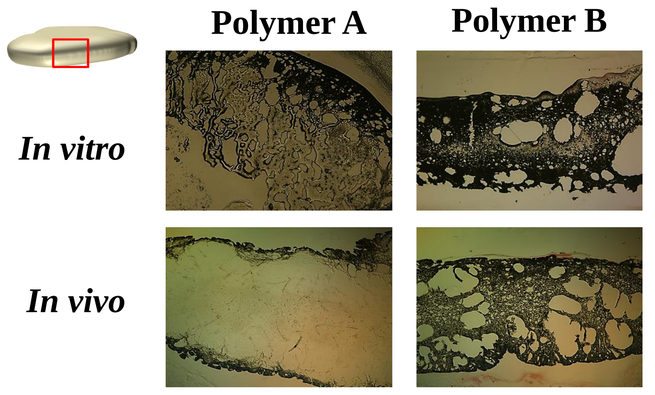


Figure 4. Comparison of cross sectional images of *in situ* forming implants *in vitro* and *in vivo*

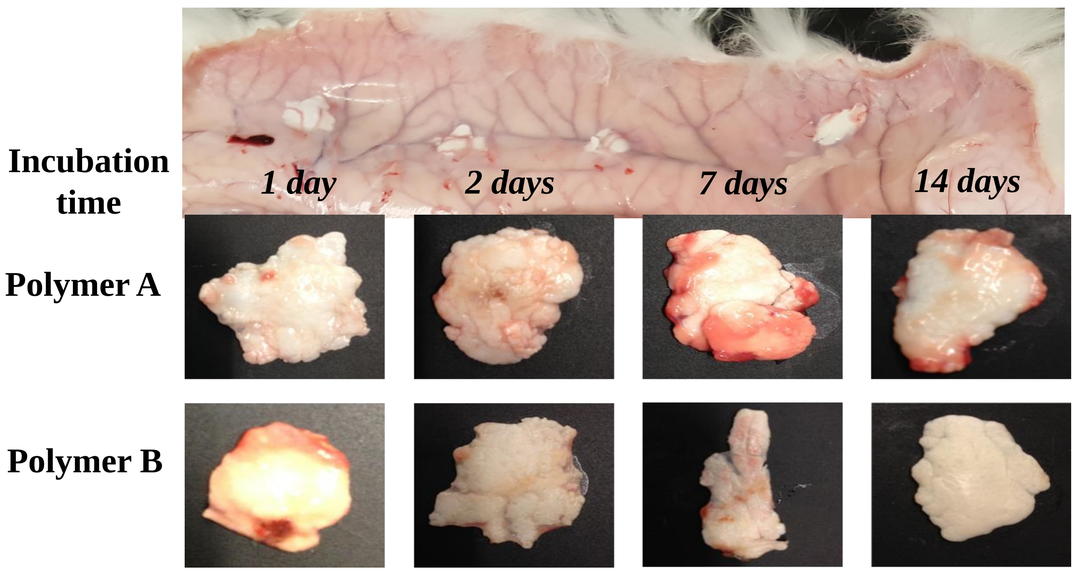


Figure 2. Implant formation *in vivo* at different time points

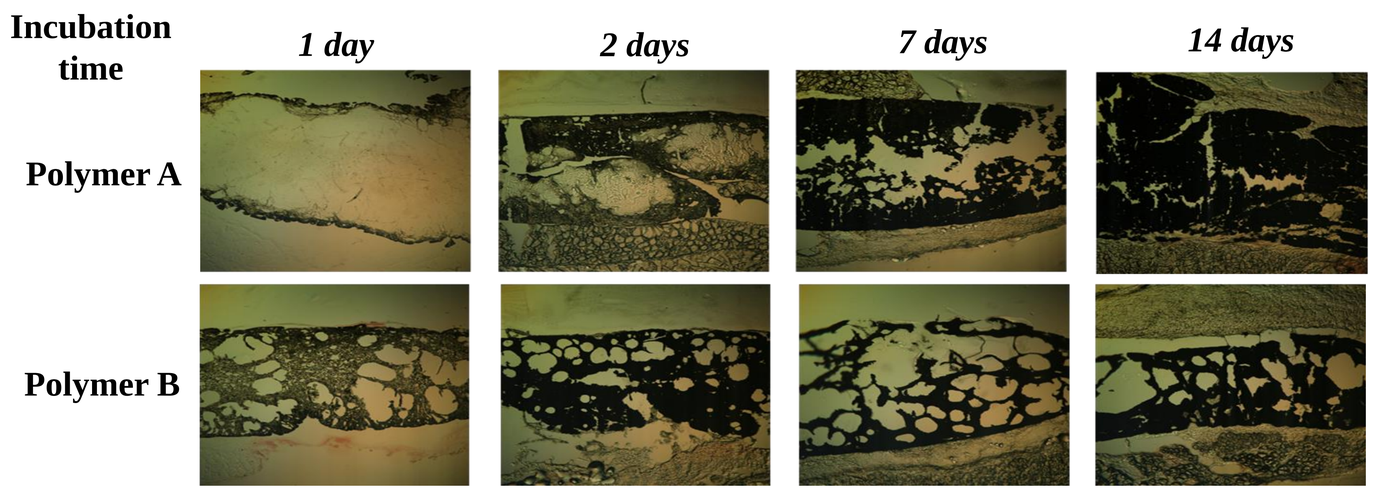


Figure 5. Cross sectional images of *in situ* forming implants formed at different time points

CONCLUSION

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

ACKNOWLEDGMENT

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