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Effect of Solvent Diffusion from *In Situ*-forming Implants on Drug Release

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PURPOSE

Polymer-based injectable drug products have been developed for the delivery of small molecules as well as proteins. These products can maintain effective drug concentrations over periods of months and minimize undesirable fluctuations in systemic drug concentrations, resulting in enhanced therapeutic effects and patient compliance. Currently, several products based on this concept have been approved by FDA. Most of these are composed of the biodegradable polymers poly(lactic-co-glycolic acid) PLGA and poly(lactic acid) (PLA). Polymer matrix-based gelling depot formulations (*e.g. in situ* forming implants) contain a polar aprotic solvent as an excipient. In such formulations, drug release kinetics depends on typical factors such as type of polymer/solvent or polymer-drug interaction. The present study discusses the role of solvent diffusion (Figure 1) as a potential factor affecting the *in vitro* release of leuprolide acetate from qualitatively and quantitatively (Q1/Q2) equivalent *in situ* forming implants prepared with minor manufacturing differences.

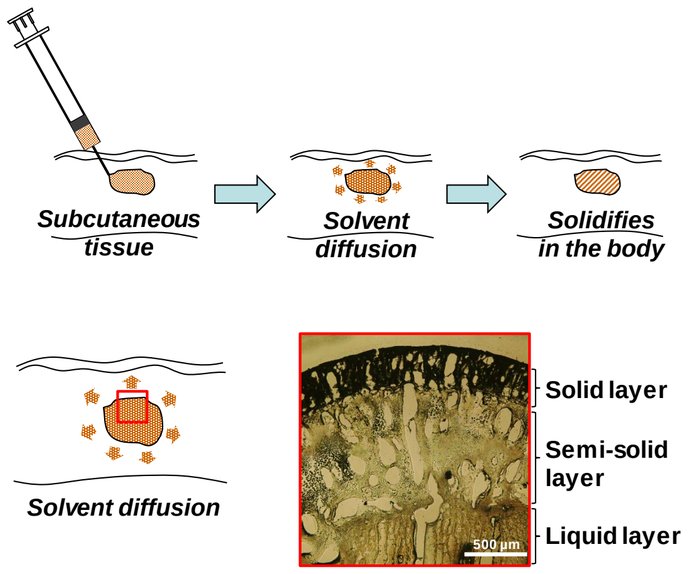

Figure 1. Depot formation and solvent diffusion of *in situ* forming implants

METHOD

Four *in situ* forming implant formulations were prepared *via* syringe-to-syringe mixing of poly (lactic-co-glycolic acid) (PLGA) in an aprotic solvent (N-methyl-2-pyrrolidone, NMP) with lyophilized leuprolide acetate (Figure 2). Three different manufacturing parameters were investigated: *1)* Polymer vendor (vendors A and B); *2)* water content in NMP; and *3)* freeze dried volume of leuprolide acetate. NMP with different water content was prepared immediately prior to *in vitro* release testing. The same amount of leuprolide acetate was dissolved in different volumes of distilled water to generate freeze dried cakes of varying volumes. *In vitro* dissolution testing of the drug and the solvent was performed in a shaker bath. Three replicates of the *in vitro* dissolution testing were investigated to understand experimental variability and precision. Implant formulations were placed in 100 ml dissolution media (PBS, pH 7.4 with 0.01% sodium azide and 0.01% Tween 80), and incubated at 37°C with 100 rpm shaking. One ml samples were withdrawn periodically and replenished with fresh media. Due to the drug stability, the dissolution media was replaced every two weeks. The drug and solvent content were determined using HPLC (C_{18} column, 1.0 ml/min, 220 and 202 nm, respectively).

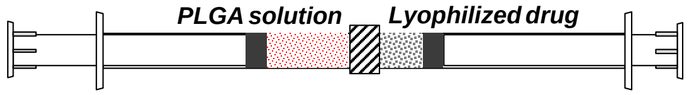

Figure 2. Preparation of *in situ* forming implant

Formulation	Polymer vendor	Water content in NMP (%)	Freeze-dried volume (ml)
1	A	0.05	0.5
2	B	0.05	0.25
3	A	0.5	0.25
4	B	0.5	0.5

Table 1. Q1/Q2 formulations with manufacturing differences

RESULTS

Q1/Q2 formulations with manufacturing differences are described in Table 1. *In vitro* release profiles of leuprolide acetate and NMP are shown in Figure 3. Formulations 1 and 3 (prepared using PLGA from vendor A with different manufacturing conditions) had similar release profiles. On the other hand, Formulations 2 and 4 (prepared using PLGA from vendor B under different manufacturing conditions) showed different burst release compared to each other and to Formulations 1 and 3. In addition, post burst release profiles of Formulations 2 and 4 were similar, but different from those of Formulations 1 and 3. NMP diffused rapidly from all four implant formulations within 24 hours. Only Formulation 4 exhibited slightly faster initial NMP diffusion and faster initial leuprolide acetate release.

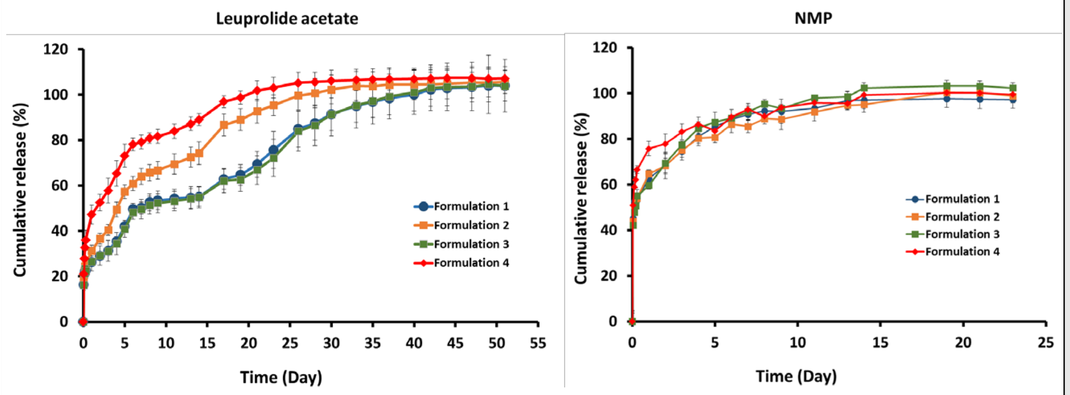

Figure 3. *In vitro* release profiles of leuprolide acetate and NMP diffusion

CONCLUSION

Polymer vendor was shown to be a significant manufacturing factor as it greatly affected drug burst release. The differences in drug release and NMP diffusion may be a consequence of slight variations in molecular weight, molecular weight range, and lactic acid to glycolic acid ratio between the polymers from different vendors.

FUNDING / GRANTS

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