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Effect of Polymer Source on the *In Vitro* Release Characteristics of *In Situ*-forming Implants

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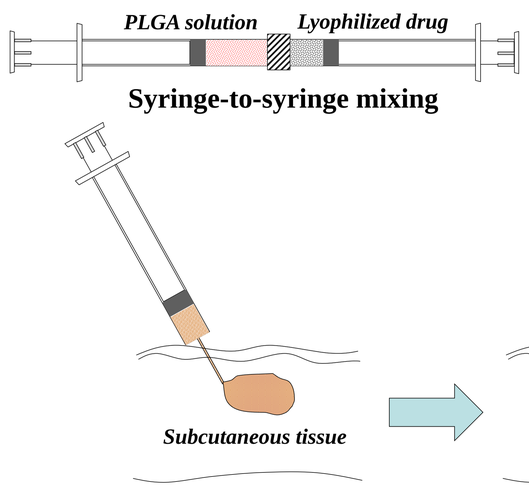
INTRODUCTION

Parenteral sustained release drug products have brought huge benefits to human health over the past few decades. These products can maintain effective drug concentrations over periods of months to years and minimize undesirable fluctuations in systemic drug concentrations, resulting in enhanced therapeutic effects and patient compliance. Currently, there are several FDA-approved parenteral sustained release implant products on the market. Most of these are composed of the biodegradable polymers poly(lactic-co-glycolic acid) PLGA and poly(lactic acid) (PLA). The objectives of the current study were to investigate the physicochemical characterization of polymers of the same grade but from different polymer vendors as a controlled release component of *in situ* forming implants, and to evaluate *in vitro* leuprolide acetate release of *in situ* forming implants with manufacturing differences.

METHODS

In situ forming implants were prepared by dissolving PLGA (either polymer A or polymer B, sourced from different US vendors) and lyophilized leuprolide acetate in an aprotic solvent (N-methyl-2-pyrrolidone, NMP) (syringe-to-syringe mixing, see detailed illustration). Manufacturing conditions were varied by changing the water content of NMP (0.05% and 0.5%) and freeze-dried volume of leuprolide acetate (0.25 mL and 0.5 mL). Gel permeation chromatography (GPC) analysis was conducted to compare the molecular weight distributions between two PLGA polymers. The glass transition temperature (Tg) of the implant formulations (F1, F2, F3, and F4, see detailed information in Table 1) was analyzed using modulated temperature differential scanning calorimetry (MTDSC, TA instrument Q2000). The content of NMP released from the formulations (NMP retention) was determined using a HPLC method. Furthermore, *in vitro* dissolution testing of the implant formulations in a shaker bath and USP apparatus 2 was performed to assess the effect of the polymer source and different manufacturing conditions on leuprolide acetate release.



Formulation	Polymer vendor	Water content in NMP (%)	Freeze-dried volume (ml)
F1	A	0.05	0.5
F2	B	0.05	0.25
F3	A	0.5	0.25
F4	B	0.5	0.5

Table 1. Composition of the *In situ* forming implant formulations.

RESULTS

As shown in **Figure 1**, there was no significant difference in the physicochemical properties (*e.g.* molecular weight distribution, Tg, and NMP retention). GPC data showed high similarity of the molecular distribution of two polymers. The Tg and NMP content of the implant formulations were similar (**Figures 1b** and **1c)**. *In vitro* release profiles of the prepared implant formulations obtained using a shaker bath method indicated that formulations 1 (F1) and 3 (F3) made of PLGA from vendor A had similar release profiles even though they were prepared under different manufacturing conditions (**Figure 2**). On the other hand, Formulations 2 (F2) and 4 (F4) made using polymer from vendor B showed different release profiles and burst release percentages. Moreover, the release rates from F2 and F4 were significantly faster than those from F1 and F3. **Figure 3** shows *in vitro* release profiles of the prepared implants tested in USP apparatus 2. Overall, similar trends were observed in both **Figures 2** and **3**.

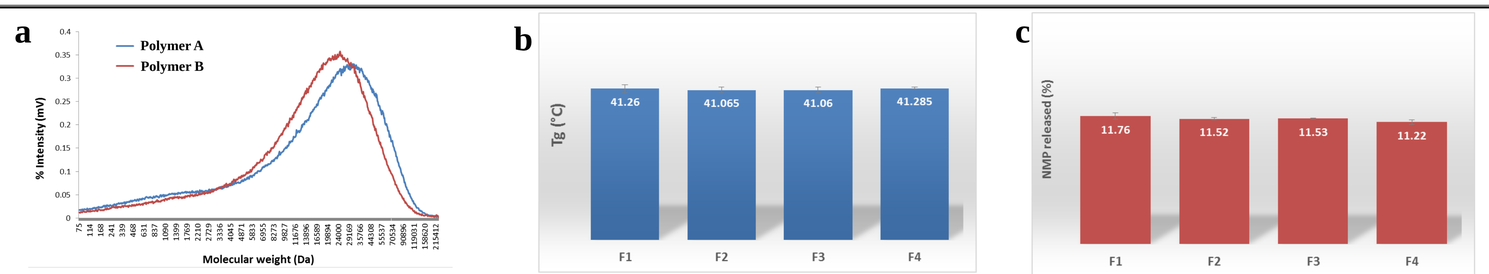


Figure 1. Physicochemical properties. (a) molecular weight distribution of two PLGA polymers from different vendors, (b) glass transition temperatures (Tg) of implant formulations, and (c) NMP released from implant formulations within 24 h in release media at 37°C and 100 rpm (in a shaker bath).

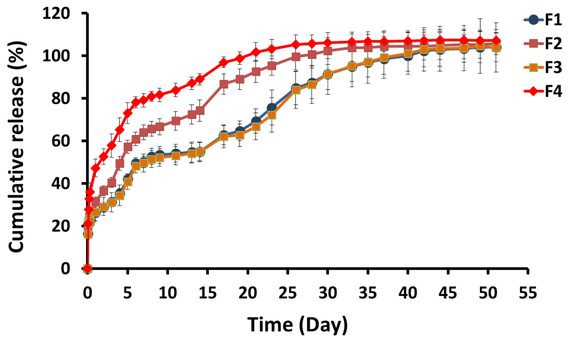


Figure 2. *In vitro* release profiles of leuprolide acetate *in situ* forming implants obtained in a shaker bath at 37°C and 100 rpm.

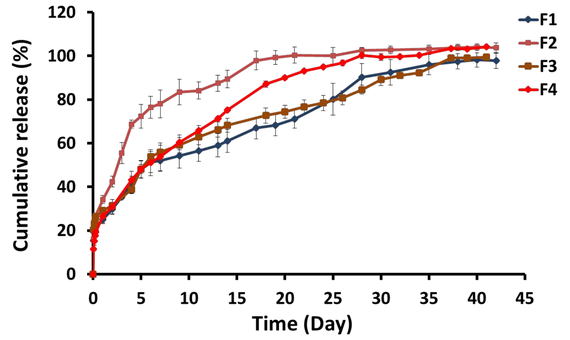


Figure 3. *In vitro* release profiles of leuprolide acetate *in situ* forming implants obtained in USP apparatus 2 at 37°C and 100 rpm paddle speed.

CONCLUSION

This work demonstrated that polymer characteristics (other than acid end group, monomer ratio, and average molecular weight), which are not usually taken into consideration, can significantly affect the performance of *in situ* forming implants, and a detailed comprehensive polymer characterization is necessary to ensure equivalency among formulations.

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