W4200

Effect of Polymer Source and Manufacturing Differences on *In Vitro* Release 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) and can be either pre-formed or *in situ* forming. The aim of the present study was to investigate the effect of polymer source and manufacturing differences on the physicochemical properties of leuprolide acetate-loaded *in situ* forming implants that are equivalent in formulation composition and components, and develop discriminatory *in vitro* dissolution testing methods for these implants.

MATERIALS & METHODS

One approved and commercially available drug product (Figure 1) containing leuprolide acetate was used as a reference to develop formulations that are equivalent in composition and components using a Design of Experiments (DOE) approach. PLGAs from Evonik or Polyscitech were used to prepare implants. The manufacturing differences investigated were polymer dissolution temperature, water content in N-methyl-pyrrolidone (NMP), leuprolide acetate freeze dry volume, and polymer vendor. The physicochemical characterization of the prepared formulations included morphology (scanning electron microscopy, SEM), thermal analysis (DSC), and solvent retention after implant formation. Two *in vitro* dissolution methods (using a shaker bath and USP apparatus 2) were developed. Syringe-to-syringe mixing was used to dissolve the lyophilized leuprolide acetate in the polymer solution. Following drug/polymer mixing, dialysis membranes were used to form implants for *in vitro* dissolution testing.

RESULTS

No significant differences were observed in the physicochemical properties (Tg) and NMP release within 24 hr of formulations (Figure 3) with the same composition prepared using the DOE approach (Figure 2). Morphological evaluation revealed a three-layer structure 2 days after implant formation. As shown in Figure 4, the three layers consist of a solid outer layer followed by a semi-solid and liquid layer.

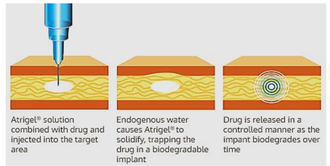

Figure 1: Commercial product and mechanism of in situ forming implant (images obtained from the manufacturer's website)

Formulation	Temperature (°C)	Water Content in NMP (%)	Freeze Dry Volume (ml)	PLGA Vendor
1	37	0.05	0.25	Evonik
2	60	0.05	0.25	Polyscitech
3	37	0.5	0.25	Polyscitech
4	60	0.5	0.25	Evonik
5	37	0.05	0.5	Polyscitech
6	60	0.05	0.5	Evonik
7	37	0.5	0.5	Evonik
8	60	0.5	0.5	Polyscitech

Figure 2: Design of Experiments (DOE) approach for in situ forming implant formulation

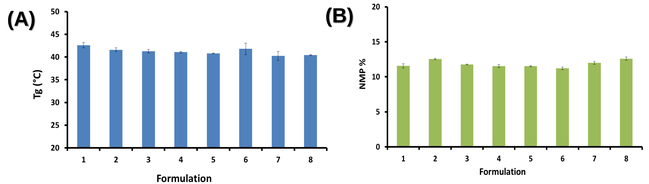

Figure 3: Thermal analysis and solvent retention of formulations, (A) Glass transition temperature (Tg) and (B) NMP release within 24 hr from formulations

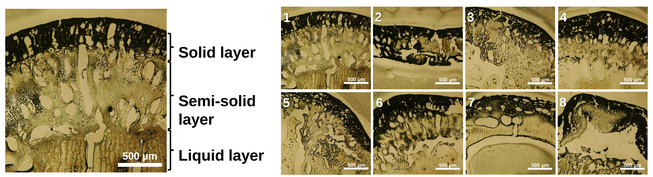

Figure 4: Morphological study of formulations: implant formation (20 ml PBS at 37 °C for 2 days in shaker bath). Image number denotes formulation (Figure 2)

RESULTS (cont.)

A new DOE study was conducted to obtain four formulations for *in vitro* dissolution testing since polymer dissolution temperature as a manufacturing parameter was excluded. The release profiles of the formulations were multi-phasic starting with an initial burst release phase followed by a prolonged lag phase. Major differences in the burst release of drug were observed. It is evident that the polymers obtained from different vendors had very different burst release profiles, with the Polyscitech polymer showing more than double the burst release compared to the Evonik polymer. The *in vitro* release profiles obtained using the USP apparatus 2 showed faster release rates compared to those obtained using the shaker bath method. Following the burst release phase, all formulations showed a slow release rate for approximately 8 days followed by a 10-day lag phase. At day 20, drug started releasing from all formulations until approximately day 40, after which the release profiles plateaued. Incomplete drug release was observed for all formulations (65-74% total release). This may be due to drug accumulation in the dialysis membrane and consequent degradation and/or breach of sink conditions.

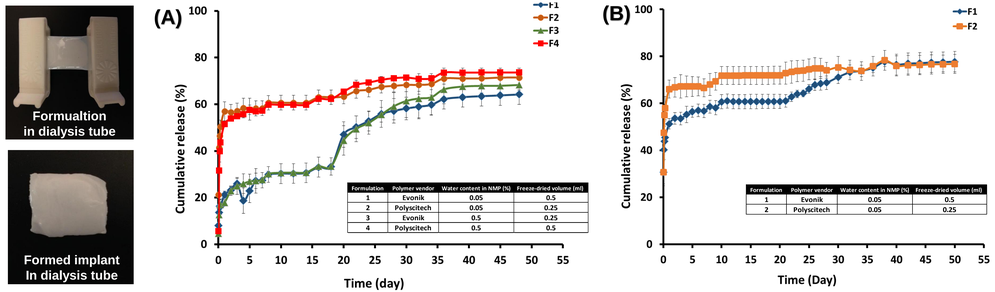

Figure 5: In vitro release profile of leuprolide acetate: (A) in shaker bath (n=3) and (B) USP apparatus 2. Formulations (in dialysis membrane) in 200 ml PBS (pH 7.4, 0.01% sodium azide) at 100 rpm at 37° C (n=3)

CONCLUSION

This work demonstrated that *in situ* forming implant formulations of similar compositions but with differences in the manufacturing process may have distinctly different *in vitro* release profiles. Moreover, the source of the polymer (vendor) was determined to be a significant factor in the release characteristics of *in situ* forming implants. Disclaimer: This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

ACKNOWLEDGMENT

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