Effect of Polymer Source Variation on *In Vitro* Drug Release and Degradation of Peptide Loaded Microspheres

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Introduction:

Poly(lactic-co-glycolic acid) (PLGA) polymers are inherently heterogeneous, different sources of PLGA may have the potential to alter the physicochemical properties and drug release characteristics of long-acting complex drug products such as PLGA microspheres. These alterations may affect the safety and efficacy of microspheres and limit the development of generic products. Thus, it is important to understand the impact of PLGA source variations on PLGA microsphere quality, drug release performance as well as microsphere degradation mechanisms.

Materials and Methods:

- Leuprolide acetate (LA) was purchased from Bachem Americas, Inc. Three PLGA polymers with similar molecular weight (Mw) (13-16 KD), lactic acid to glycolic acid (L/G) ratio and end groups as that used in the commercial product Lupron Depot®, were purchased from three different vendors.
- Physicochemical properties (*e.g.*, Mw, L/G ratio, blockiness (Rc), and glass transition temperature (Tg)) of the three different polymers were characterized.
- Three microsphere formulations were prepared *via* the single emulsion solvent evaporation method using these PLGA polymers (for example, Formulation 1 was prepared using Polymer 1).
- Various critical physicochemical properties (*e.g.*, drug loading, particle size and porosity) of the prepared microspheres were characterized.
- Real time *in vitro* release testing and an *in vitro* hydrolytic degradation study were conducted using a sample and separate method at 37° C.

Results:

- **Physicochemical properties of the PLGAs and prepared microsphere formulations**

Table 1. Physicochemical properties of PLGAs from different sources. * The experiments were performed triplicate. All values are expressed as mean ± SD (n=3).

	Reported Mw (kD) *	Observed Mw (kD) *	Reported glycolic unit (%)	Observed glycolic unit (%)	Rc	Tg (°C) *
Polymer 1	13.00	9.67±0.21	26	25.62	0.40	40.49±0.23
Polymer 2	16.40	15.02±0.11	26	24.66	0.37	44.34±0.03
Polymer 3	15.50	13.86±0.20	26	26.03	0.42	44.27±0.39

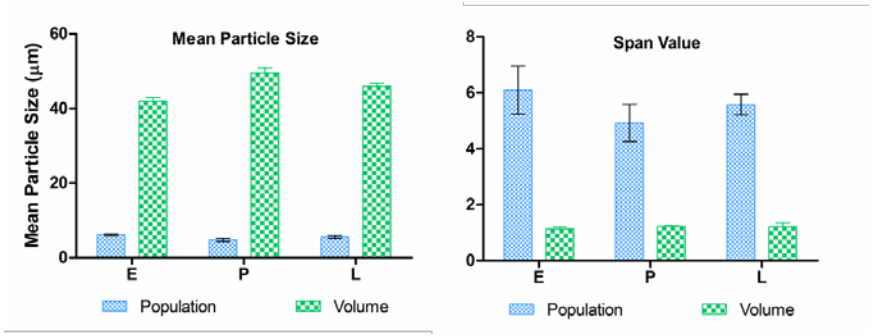

Figure 1. Particle size and particle size distribution (span) of the prepared LA microsphere formulations. All values are expressed as mean ± SD (n=3)

Table 2. Drug loading, Tg and porosity of the prepared LA microsphere formulations. * The experiments were performed triplicate. All values are expressed as mean ± SD (n=3).

	Drug Loading (w/w, %) *	Tg (°C) *	Porosity (%)	Avg. pore diameter (nm)
Formulation 1	10.41±0.85	48.04±0.28	53.41	87.60
Formulation 2	11.28±0.59	49.58±0.14	50.64	61.01
Formulation 3	11.12±0.67	49.05±0.19	44.96	55.86

- ***In vitro* release testing of the prepared microsphere formulations**

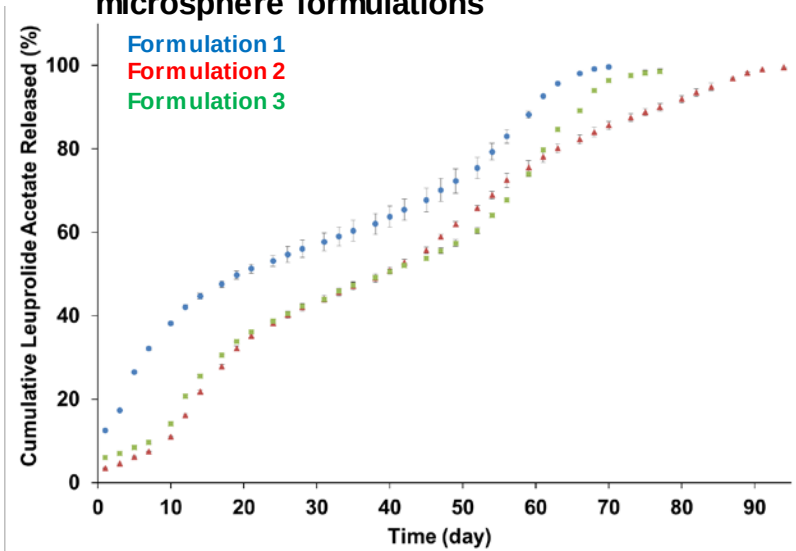

Figure 2. *In vitro* release profiles (33 mM PBS, pH 7.4) of the prepared LA microsphere formulations. All values are expressed as mean ± SD (n=3).

Results:

➢ ***In vitro* degradation studies of the prepared microsphere formulations**

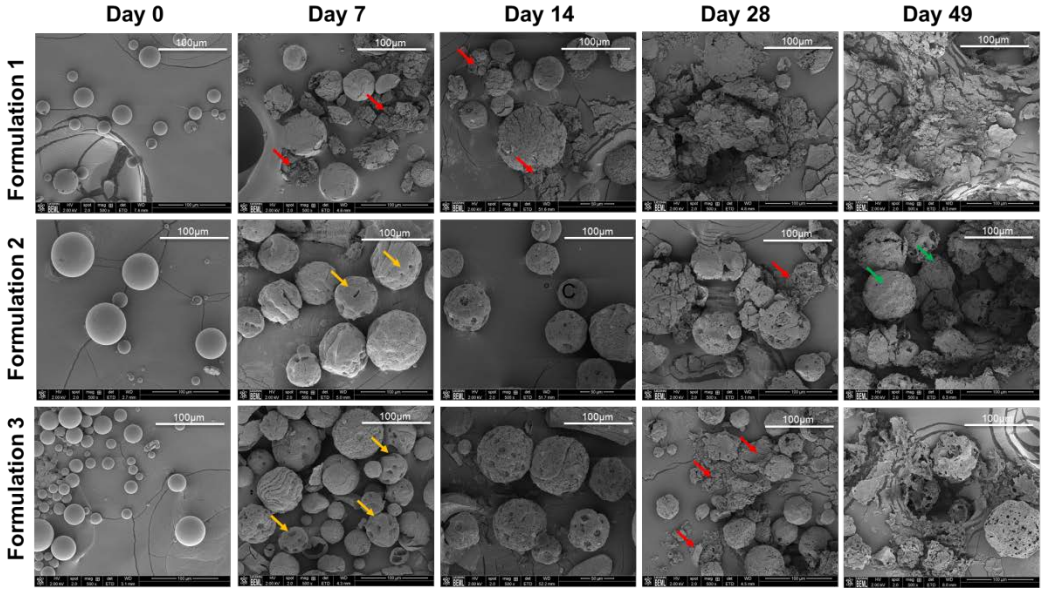

Figure 3. Morphological changes of the prepared LA microspheres under *in vitro* release testing conditions. (The yellow arrows point to surface pitting; green arrows point to microspheres; and the red arrows point to eroded particles.)

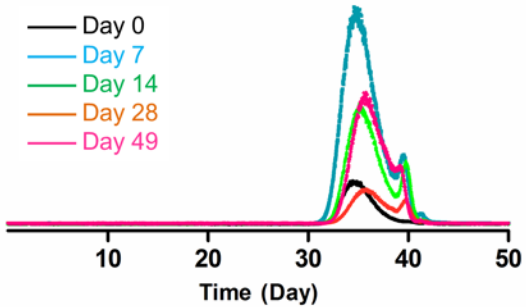

Figure 4. Representative gel permeation chromatography elution profiles of the prepared LA microspheres (Formulation 3) under *in vitro* release test conditions.

Conclusions:

- Variations of polymer sources can potentially alter the physicochemical properties (Mw and Rc) of PLGAs and in turn, the formulations (particle size, porosity);
- Prepared multi-phasic microsphere formulations were sensitive to minor differences in PLGAs.

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