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Effect of Polymer Source Variation on *In Vitro* Drug Release of Leuprolide Acetate Microspheres

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PURPOSE

- The purpose of the present work was to investigate the impact of poly(lactic-co-glycolic acid) (PLGA) source variations on PLGA microspheres quality and drug release performance.
- Differences in the manufacturing processes of the polymer as a result of different sourcing, as well as batch-to-batch variation may have the potential to alter the physicochemical properties and drug release characteristics of microspheres.
- Therefore, it is essential to understand the effect of polymer source variation on PLGA microspheres quality and drug release performance.

MATERIALS AND METHODS

- Leuprolide acetate (LA) (model drug) 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.
- Various physicochemical properties (*e.g.*, viscosity, Mw, Polydispersity (PDI), L/G ratio, Tg, *etc.)* of the three different polymers were characterized.
- Three microsphere formulations were prepared via the single emulsion solvent evaporation method using these PLGA polymers.
- Various critical physicochemical properties (*e.g.*, drug loading, particle size, morphology and porosity*)* of the prepared microspheres were characterized.
- Real time *in vitro* release testing and *in vitro* hydrolytic degradation study were conducted using a sample and separation method at 37℃.

RESULTS

1. Physicochemical properties of polymers from different sources

Table 1: Physicochemical properties of the PLGA polymers purchased from different vendors.

	Reported MW (kDa)	Observed* MW (kDa)	Reported PDI	Observed* PDI	Reported Glycolic unit (%)	Observed Glycolic unit (%)	Reported Monomer residue (%)	Observed Monomer residue (%)	Observed Tg (℃)
Polymer 1	13	9.67 ± 0.21	1.9	1.74 ± 0.04	26	25.62	1.6	1.94	40.33
Polymer 2	16.4	15.02 ± 0.11	1.76	1.54 ± 0.01	26	24.64	Not reported	1.26	44.99
Polymer 3	15.5	13.86 ± 0.20	2.1	1.56 ± 0.06	26	26.27	1.95	1.52	43.16

* The experiments were performed triplicate. All values are expressed as mean ± SD (n=3).

2. Physicochemical properties of the prepared PLGA microsphere formulations

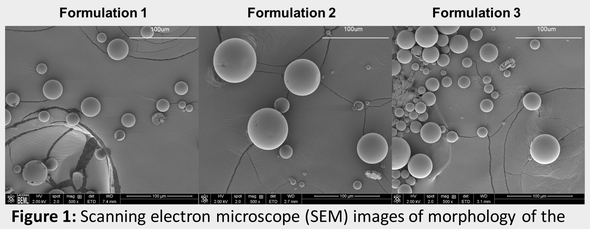

Figure 1: Scanning electron microscope (SEM) images of morphology of the prepared PLGA microspheres. (The scale bar is 100 µm)

Table 2: Physicochemical properties of the prepared microsphere formulations.

	Drug Loading (w/w) *	Particle Size (Population, µm) *	Particle Size (Volume, µm) *	Porosity (%)	Tg (℃)
Formulation 1	8.60±0.59	4.29±0.30	40.95±1.77	57.90	44.37
Formulation 2	10.11±0.96	4.64±0.27	51.02±4.74	52.11	43.33
Formulation 3	10.25±0.33	4.84±0.56	48.65±2.98	55.19	44.53

* The experiments were performed triplicate. All values are expressed as mean ± SD (n=3).

3. *In vitro* release test and degradation study

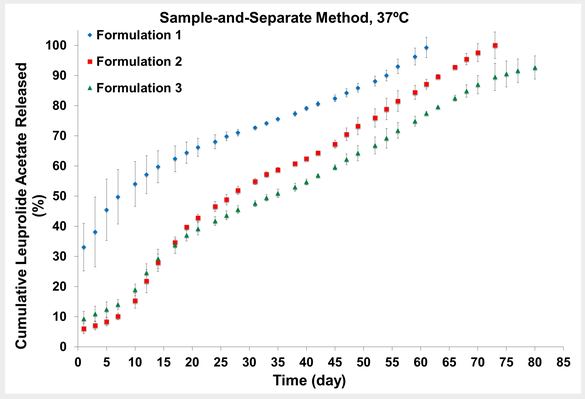

Figure 2: *In vitro* release profiles (33 mM PBS, pH7.4) of the prepared microsphere formulations. All values are expressed as mean ± SD (n=3).

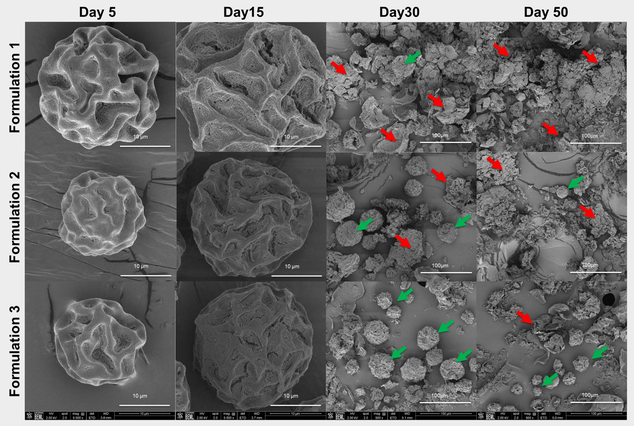

Figure 3: SEM images of microsphere formulations under *in vitro* release testing condition (33 mM PBS, pH7.4). (The green arrows point to microspheres and the red arrows point to eroded particles.)

- The polymers from different vendors showed differences in physicochemical properties (*e.g.*, Mw, PDI, and Tg).
- Formulations prepared using polymers from different sources showed differences in drug loading, particle size and porosity.
- The *in vitro* drug release characteristics of the prepared formulations were different. Formulation 1 showed the highest burst release and the fastest release rate compared to that of Formulations 2 and 3. This may be due to its smaller particle size, higher porosity and the lower molecular weight of its polymer.
- The larger particle size and lower porosity of Formulation 2 may enhance the autocatalysis effect, which results in more erosion of microspheres as shown in the SEM images as well as in the crossover in the *in vitro* release profiles.

CONCLUSIONS

- Physicochemical properties as well as the *in vitro* release characteristics of microspheres were determined to be sensitive to differences in polymers from different sources.
- Understanding the impact of polymer source variation on microsphere critical quality attributes is of great value in microsphere product quality control as well as in the development of regulatory standards.

ACKNOWLEDGEMENTS

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