M3151

Effect of Manufacturing Process Parameters on Physicochemical Properties of Peptide Microspheres

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PURPOSE

The objective of the present study was to understand the effect of manufacturing process parameters on the critical physicochemical properties as well as the burst release percentage of peptide microspheres.

METHODS

Preparation and Characterization of Peptide Microspheres: Leuprolide acetate was chosen as a model peptide and PLGA with similar molecular weight to that of the approved and commercially available leuprolide acetate microsphere product (one month) was used to prepare leuprolide acetate microspheres. Different preparation processes (*e.g.* emulsification, and solvent systems) were investigated in order to obtain leuprolide acetate microspheres that are equivalent in formulation composition and components but with manufacturing differences (Figure 1). Physicochemical properties (*e.g.* drug loading, particle size, size distribution, and morphology) of the prepared microspheres were determined. The physicochemical properties of the commercial microsphere product (RLD) were also determined.

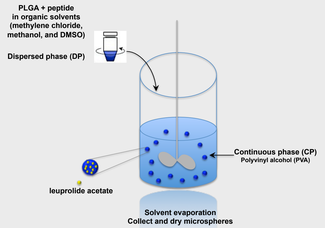

Figure 1. Schematic illustration of microsphere preparation procedures.

***In Vitro* Release Testing:** *In vitro* release testing of the prepared leuprolide acetate microspheres was conducted. Different release testing conditions (*e.g.* release media) were investigated.

RESULTS

Table 1. Physicochemical properties of leuprolide acetate microspheres.

Sample	PLGA	Preparation Procedure	Solvent	Drug Loading (%, w/w)
RLD	-	-	-	6.88±0.77
Formulation 1	DLG 2CA	Homogenization	DCM/methanol	8.36±0.3
Formulation 2	DLG 2CA	Homogenization	DCM/methanol	8.55±0.08
Formulation 3	DLG 2CA	Homogenization	DCM/DMSO	8.16±0.39

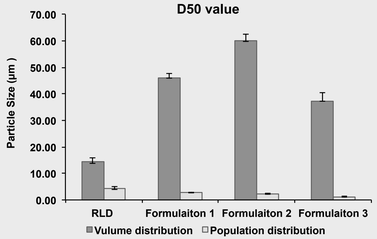

Figure 2. Particle size of leuprolide acetate microspheres.

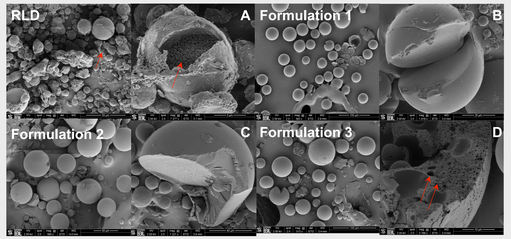

Figure 3. SEM micrographs of RLD (A) and leuprolide acetate microsphere Formulations 1-3 (B-D).

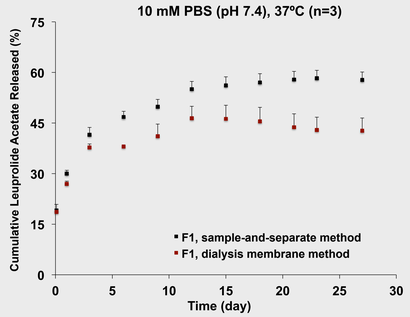

Figure 4. *In vitro* release testing of Formulation 1 (F1) using different release testing methods.

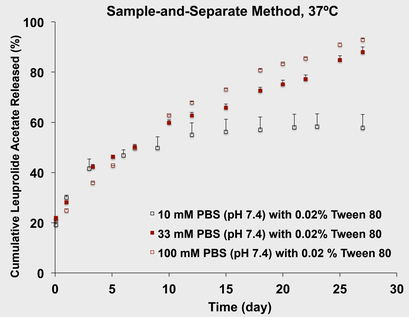

Figure 5. Effect of buffer salt concentration on *in vitro* release profiles of Formulation 1.

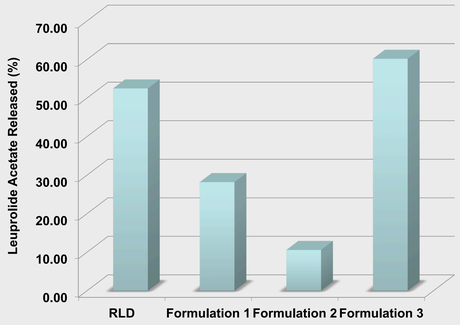

Figure 6. Burst release percentages (within 24 h) of leuprolide acetate microspheres in 33 mM PBS (pH 7.4) containing 0.02% (w/w) Tween 80.

CONCLUSIONS

The key physicochemical attributes (*e.g.* particle size, and inner structure) that affect peptide release from compositionally equivalent PLGA microspheres were shown to be sensitive to minor manufacturing changes (*e.g.* homogenization speed, and solvent systems). This in turn resulted in distinctly different burst release percentages of the leuprolide acetate microspheres. In addition, due to peptide instability issues, the sample-and-separate method appeared to be a better method compared to the membrane dialysis method. With increase in buffer capacity (buffer salt concentration), “complete” peptide release (>85%) was achieved using the sample-and separate method.

FUNDING/GRANTS

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