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

Leuprolide acetate was chosen as a model peptide and PLGA with similar molecular weight to that of the commercial product Lupron Depot® (one month) was used to prepare leuprolide acetate microspheres. Different preparation processes (e.g. emulsification, and solvent extraction) were investigated in order to obtain leuprolide acetate microspheres that are equivalent in formulation composition and components but with manufacturing differences. Physicochemical properties (e.g. drug loading, particle size and size distribution, porosity, and morphology) of the prepared microspheres were determined. Lastly burst release percentages of these leuprolide acetate microspheres were investigated using a sample-and-separate method. Different release testing conditions (e.g. release media) were investigated.

Results

Despite that different manufacturing processes were utilized, the prepared leuprolide acetate microsphere formulations had similar peptide loading (ca. 9%, w/w). The peptide microsphere formulation prepared using the one-step solvent extraction process (Formulation 1) had spherical and non-porous structure (D50: ~50 μm) (Figure 1A). The addition of salts (e.g. sodium chloride) in the aqueous phase during the microsphere preparation process created an osmotic pressure difference between the dispersion phase and continuous phase, which resulted in the formation of small pores in the PLGA microsphere matrix (Formulation 2) (Figure 1B). The addition of salts also affected the solubility of methylene chloride in the aqueous phase and hence delayed polymer precipitation and led to the formation of dense PLGA microspheres with smaller particle size (D50: ~31 μm). As a result of its porous structure and small particle size, Formulation 2 showed a slightly higher burst release percentage compared to that of Formulation 1. When the peptide microspheres were prepared using the two-step solvent extraction process (Formulation 3), solvent extraction occurred rapidly forming loosely packed microspheres with a highly porous structure (D50: ~50 μm) (Figure 1C). Formulation 3 had the highest burst release percentage among all the peptide microsphere formulations investigated due to its highly porous structure.

Conclusion

The key physicochemical attributes (e.g. particle size, and porosity) that affect peptide release from PLGA microspheres were shown to be sensitive to minor manufacturing changes. Minor changes in the solvent extraction process resulted in distinctly different physicochemical properties and burst release percentages of leuprolide acetate microspheres.

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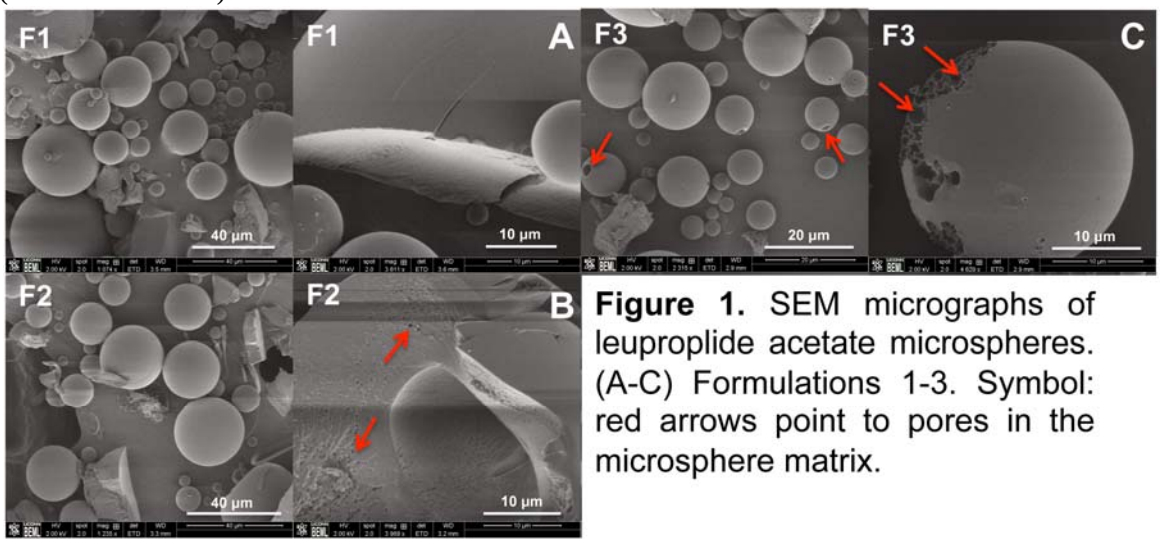

Figure 1. SEM micrographs of leuproplide acetate microspheres. (A-C) Formulations 1-3. Symbol: red arrows point to pores in the microsphere matrix.