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Single processing step toward injectable sustained-release formulations of Triptorelin based on a novel degradable semi-solid polymer.

Asmus LR[1], Kaufmann B, Melander L, Weiss T, Schwach G, Gurny R, Möller M.

Abstract

Poly(lactic acid) is a widely used polymer for parenteral sustained-release formulations. But its solid state at room-temperature complicates the formulation process, and elaborate formulation systems like microparticles and self-precipitating implants are required for administration. In contrast, hexylsubstituted poly(lactic acid) (hexPLA) is a viscous, biodegradable liquid, which can simply be mixed with the active compound. In this study, the feasibility to prepare injectable suspension formulations with peptides was addressed on the example of the GnRH-agonist Triptorelin. Two formulation procedures, of which one was a straight forward one-step cryo-milling-mixing process, were compared regarding the particle size of the peptide in the polymer matrix, distribution, and drug release. This beneficial method resulted in a homogeneous formulation with an average particle diameter of the incorporated Triptorelin of only 4.1 μm. The rheological behavior of the Triptorelin-hexPLA formulations was assessed and showed thixotropic and shear-thinning behavior. Viscosity and injectability were highly dependent on the drug loading, polymer molecular weight, and temperature. Nine formulations with drug loadings from 2.5% to 10% and hexPLA molecular weights between 1500 and 5000 g/mol were investigated in release experiments, and all displayed a long-term release for over 3 months. Formulations with hexPLA of 1500 g/mol showed a viscosity-dependent release and hexPLA-Triptorelin formulations of over 2500 g/mol a molecular weight-dependent release profile. In consequence, the burst release and rate of release were controllable by adapting the drug loading and the molecular weight of the hexPLA. The degradation characteristics of the hexPLA polymer during the in vitro release experiment were studied by following the molecular weight decrease and weight loss. Triptorelin-hexPLA formulations had interesting sustained-release characteristics justifying further investigations in the drug-polymer interactions and the in vivo behavior.