

In vivo biocompatibility, sustained-release and stability of triptorelin formulations based on a liquid, degradable polymer.

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Abstract

Hexylsubstituted poly(lactic acid) (hexPLA) is a viscous polymer, which degrades in the presence of water similar to the structure related poly(lactic acid). With hydrophilic active compounds, like Triptorelin acetate, the lipophilic polymer was formulated in form of parenterally injectable suspensions. This first in vivo study toward the biocompatibility of hexPLA implants in rats over 3 months in comparison to in situ forming poly(lactic-co-glycolic acid) (PLGA) formulations is presented here. The hexPLA implants showed only a mild acute inflammation at the injection site after application, which continuously regressed. In contrast to the PLGA formulations, hexPLA did not provoke an encapsulation of the implant with extracellular matrix. Prior to the formulation application, the stability of Triptorelin inside the hexPLA matrix was assessed under different storage conditions and in the presence of buffer to simulate a peptide degrading environment. At 5°C Triptorelin showed a stability of 98% inside the polymer for at least 6 months. The stability was still 78% at an elevated temperature of 40°C. HexPLA protected the incorporated peptide from the surrounding aqueous environment, which resulted in 20% less degradation inside the polymer compared to the solution. This protection effect supports the use of Triptorelin-hexPLA formulations for parenteral sustained-release formulations. In a second in vivo evaluation in Wistar Hannover rats, formulations containing 5% and 10% Triptorelin in the polymeric matrix released the active compound continuously for 6 months. The formulations showed a higher release during the initial 7 days, which is necessary for the clinical use to down-regulate all GnRH-receptors. Afterwards, a zero order drug release was observed over the first 3 months. After 3 months, the plasma levels decreased slowly but remained at effective concentrations for the total of 6 months. Furthermore, a qualitative in vitro-in vivo correlation was observed, possibly facilitating future optimization of the Triptorelin-hexPLA sustained-release formulations.