

Injectable formulations for an intravitreal sustained-release application of a novel single-chain VEGF antibody fragment.

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Abstract

Sustained-release formulations of a single-chain anti-VEGF-A antibody fragment were investigated in vitro toward their potential use for intravitreal applications. The hydrophobic polyester hexylsubstituted poly(lactic acid) (hexPLA) was selected as the sustained-release excipient for its biodegradability and semi-solid aggregate state, allowing an easy and mild formulation procedure. The lyophilized antibody fragment ESBA903 was micronized and incorporated into the liquid polymer matrix by cryo-milling, forming homogeneous and injectable suspensions. The protein showed excellent compatibility with the hexPLA polymer and storage stability at 4°C for 10 weeks. Additionally, hexPLA shielded the incorporated active substance from the surrounding medium, resulting in a better stability of ESBA903 inside the polymer than after its release in the buffer solution. Formulations of ESBA903 with hexPLA having drug loadings between 1.25% and 5.0% and polymer molecular weights of 1500 g/mol, 2500 g/mol, 3500 g/mol and 5000 g/mol were investigated regarding their in vitro release. All formulations except with the highest molecular weight formed spherical depots in aqueous buffer solutions and released the antibody fragment for at least 6-14 weeks. The polymer viscosity derived from the molecular weight strongly influenced the release rate, while the drug loading had minor influence, allowing customization of the release profile and the daily drug release. Size exclusion chromatography and SDS-PAGE revealed that the antibody fragment structure was kept intact during incorporation and release from the liquid matrix. Furthermore, the released protein monomer maintained its high affinity to human VEGF-A, as measured by surface plasmon resonance analysis. Formulations of ESBA903 in hexPLA meet the basic needs to be used for intravitreal sustained-release applications in age-related macular degeneration treatment.

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