Title	PLGA implants for long-acting release of anti-VEGF monoclonal antibody in a rabbit retinal vascular leakage model
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Abstract	Wet age-related macular degeneration (AMD) is a leading cause of vision loss among the elderly. In wet AMD, abnormal growth of blood vessels and leakage of fluid from those vessels under the retina are stimulated by overexpressed vascular endothelial growth factor (VEGF).[1,2] Accordingly, anti-VEGF therapy has emerged as a potent option to treat wet AMD. Administration of the anti-VEGF agents is accomplished by intravitreal injections typically every 4 weeks, but this injection frequency is problematic for patient convenience and compliance, and repeated injections increase the risks of infection, inflammation and hemorrhage. To reduce the frequency of intraocular injections, we developed injectable poly(lactic-co-glycolic acid) (PLGA) implants for controlled release of bevacizumab (Avastin®, anti-VEGF antibody). An antacid ($MgCO_3$) and trehalose were added to stabilize the encapsulated antibodies. However, the presence of water-soluble trehalose in the implants created high osmotic pressure, resulting in fast release of antibodies. To slow down the release, pure PLGA was coated onto the lateral side of core implants. The optimized implant formulation achieved high bevacizumab loading (8.2 % w/w) and displayed continuous in vitro release kinetics over six weeks with total cumulative release of 89 ± 4 %. Analysis of the released antibodies by size-exclusion high performance liquid chromatography, enzyme-linked immunosorbent assay, and circular dichroism spectroscopy showed little change in monomer content, immunoreactivity, and secondary structure during the 6-week release period. Anti-VEGF efficacy after injection of the optimized bevacizumab implant versus the free bevacizumab was compared in a rabbit VEGF-induced retinal leakage model (400 µg dose). Six weeks after injection of both formulations, only the bevacizumab implant protected retinal blood vessels while significant leakage was observed in the no-treatment control and free bevacizumab groups. The anti-VEGF efficacy of the implants was maintained over 8 weeks. Hence, this approach may be useful to realize long-acting anti-VEGF therapy.
References	[1] B. A. Syed, J. B. Evans, L. Bielory, *Nat. Rev. Drug Discov.* **2012**, 1–2. [2] A. D. Kulkarni, B. D. Kuppermann, *Adv. Drug Deliv. Rev.* **2005**, *57*, 1994–2009.