OPEN ACCESS
ARVO Annual Meeting Abstract | July 2018

Sustained release protein formulation for intraocular use

Sahar Awwad; Peng Tee Khaw; Steve Brocchini

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science July 2018, Vol.59, 5706. doi:

Abstract

Purpose : Anti-vascular endothelial growth factor (VEGF) antibody based medicines are administered by intravitreal (IVT) injection to treat wet age-related macular degeneration (AMD) every 1-2 months. Longer acting ocular formulations need to be developed to maintain a therapeutic dose of a medicine in the vitreous cavity. *In situ*-forming injectable gels are used to encapsulate drugs for sustained local release, drug delivery and tissue engineering. We prepared NIPAAM hydrogels in the presence of either bevacizumab or PEGylated ranibizumab (PEG_{10}-Fab_{rani}) to compare the release profiles in a two-compartment *in vitro* model called the PK-Eye™.

Methods : Both bevacizumab (1.0 mL; 25.0 mg/mL, Avastin®) and PEG_{10}-Fab_{rani} (0.5-2.0 mg) were separately mixed with NIPAAM monomer (40.0 mg) and ammonium per sulfate (APS, 4.0 mg). Poly(ethylene glycol) diacrylate (PEGDA) crosslinker were added (4, 8 and 12 µL), followed by *N*,*N*,*N*,*N*-tetramethylethylenediamine (TEMED) and incubated for ~24 hours at 4°C. Both sets of hydrogels were injected into the posterior cavity of the PK-Eye™ containing PBS (pH 7.4) with an inflow of 2.0 µL/min (37°C). Samples were collected at various time points and were analysed to calculate release profiles and *in vitro* half-lives ($t_{1/2}$s).

Results : Experiments were conducted in PBS to evaluate release kinetics more rapidly and it is expected that proteins will diffuse more slowly in a more viscous environment (such as simulated vitreous). The $t_{1/2}$ of bevacizumab (2.5 mg) was 2.0 ± 0.01, 3.7 ± 1.2 and 2.6 ± 0.03 days. Protein release was 74.2 ± 3.5, 87.6 ± 6.4 and 95.8 ± 2.3% in a month with the respective PEGDA amounts of 4, 8 and 12 µL. Bimodal release profiles with a first burst phase (60% of bevacizumab being cleared after 5 days) followed by a slower prolonged release phase are often observed with hydrogels. The $t_{1/2}$ of PEG_{10}-Fab_{rani} (2.0 mg) from the NIPAAM gel was 15.1 ± 0.6 days, which was significantly longer ($p<0.05$) than that of an injection (9.9 ± 1.1 days) of the same dose. The amount of the PEG_{10}-Fab_{rani} cleared by day 33 was 75.5 ± 5.9 and 92.3 ± 2.5% from the NIPAAM hydrogel and injection respectively.

Conclusions : PEG_{10}-Fab_{rani} loaded NIPAAM hydrogels displayed a longer clearance $t_{1/2}$ than free PEG_{10}-Fab_{rani} and bevacizumab loaded NIPAAM hydrogels. These results suggest that PEG entanglement within the PEGDA-NIPAAM hydrogel results in better mixing of PEG_{10}-Fab_{rani} than is possible for unmodified bevacizumab.

This is an abstract that was submitted for the 2018 ARVO Annual Meeting, held in Honolulu, Hawaii, April 29 - May 3, 2018.