Proceedings of the 8th International Conference on Theoretical and Applied Nanoscience and Nanotechnology (TANN 2024)
Chestnut Conference Centre - University of Toronto, Toronto, Canada – June 10-12, 2024
Paper No. 133
DOI: 10.11159/tann24.133

Vitreous Pharmacokinetic Of Anti-VEGF Mab Following the Intravitreal Injection of Drug Nanoparticles Embedded In Thermosensitive Sol-Gel

Reyhaneh Varshochian[1], Mohammad Riazi-Esfahani[2]
[1]Shahid Beheshti University of Sciences
Tehran, Iran.
varshochian@sbmu.ac.ir;
[2]University of California Irvine,
Irvine, CA 92697, USA
mriazies@uci.edu

Extended Abstract

Age-related macular degeneration (AMD) is a degenerative disease of the human retina and the leading cause of incurable blindness in individuals over 55 years worldwide. The prevalence of AMD is predicted to rise continuously and rapidly from about 2 hundred million in 2020 to near 3 hundred million by 2040. The intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs is currently the method of choice in age-related macular degeneration (AMD) treatment. However, the major restriction is the requirement of repetitive intraocular injections due to the short half-life of these drugs in vitreous which can lead to serious adverse effects. In addition to the difficulties and costs, there are serious concerns about the adverse effects of these injections including intravitreal haemorrhage, endophthalmitis, retinal detachment, and cataract [1,2]. To address this problem a new sustained release formulation containing bevacizumab was prepared and its vitreous pharmacokinetic was evaluated [3]. Bevacizumab is a monoclonal antibody (mAb) against VEGF and is widely used off-label by ophthalmologists for treatment of AMD [4].

The chitosan nanoparticles containing bevacizumab were prepared through ionotropic gelation method [5] and embedded in thermoresponsive PLGA-PEG-PLGA copolymer sol-gel obtained through the ring-opening polymerization. The prepared nanoparticles were characterized in terms of size, size distribution, zetapotential, entrapment efficiency and loading efficiency. The final sol-gel formulation was also characterized and the in-vitro drug release was evaluated. During the in-vivo investigations, following the single dose intravitreal injection of the formulation in rabbits, the vitreous concentration of the drug was assayed in defined time intervals using ELISA method and the intraocular pharmacokinetic parameters were determined.

CY5-antibody conjugate was employed in formulation to visualize the persistence of the drug in posterior segment tissues. Finally, in order to investigate the probable toxicity of the formulation two in-vivo studies were conducted.

According to the results the prepared formulation showed an appropriate sol-gel transition behavior in temperature change from 25 to 37°C and was able to extend the drug release time. The pharmacokinetic results showed that the bevacizumab vitreous concentration remained above 500 ng/ml (the minimum concentration required for the complete inhibition of VEGF function) more than 8 weeks in our formulation group, while, it fell below this value in less than 6 weeks in the control group treated with the free drug. According to the non-compartmental analysis, four times greater mean residence time (MRT) and halved clearance of bevacizumab was observed in rabbit treated with our formulation in comparison to the control rabbits which resulted in 14 days mean vitreous half-life, calculated through the terminal phase elimination rate, of the drug in our formulation group compared to that of the control group, 3.5 days.

The confocal microscopy images showed the red color of the labelled bevacizumab during the test span in retina and sclera. The histological evaluations and electroretinography outcomes following the intravitreal injections did not show a significant difference with the control rabbit and thus our formulation have no considerable toxicity.

Consequently, our results indicated the promising potentials of the designed formulation as a novel sustained release retinal drug delivery system.

References

[1] W.L. Wong, X. Su, X. Li, C.M.G Cheung, R. Klein, C. Cheng, T.Y. Wong, Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis, *Lancet Glob Healt,.* vol. 2, no. 2. pp. 106-16, 2014.

[2] M. Gałuszka, D. Pojda-Wilczek, I Karska-Basta, "Age-Related Macular or Retinal Degeneration?" *Medicina*, vol. 59, no. 5, pp. 920-933, 2023.

[3] A. Annala, B.C. Ilochonwu, D. Wilbie, A. Sadeghi, W.E. Hennink, and T. Vermonden, "Self-Healing Thermosensitive Hydrogel for Sustained Release of Dexamethasone for Ocular Therapy", *ACS Polym.*, vol. 3, no. 1, pp. 118–131, 2023.

[4] K. Berg, T.R. Pedersen, L. Sandvik, R. Bragadóttir, "Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration According to LUCAS Treat-and-Extend Protocol", *Ophthalmology*, Vol. 122, no. 1, pp.146-152, 2015.

[5] F. Chaharband, N. Daftarian, M. Rezaei Kanavi, R. Varshochian, M. Hajiramezanali, P. Norouzi, E. Arefian, F. Atyabi, R. Dinarvand, "Trimethyl chitosan-hyaluronic acid nano-polyplexes for intravitreal VEGFR-2 siRNA delivery: formulation and in vivo efficacy evaluation", *Nanomedicine: NBM*, vol 26, 2020, 102181.