Controlled Release Of Fenofibrate With Biodegradable Nanoparticles For Regulating Retinal Microvascular Dysfunction In Experimental Diabetic Retinopathy

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Abstract

Introduction: Fenofibrate is a peroxisome proliferator-activated receptor α (PPARα) agonist that has antiangiogenic and anti-inflammatory activities (1). Systemic administration of fenofibrate has robust therapeutic effects on diabetic retinopathy (DR) in animal model (2). However, the inefficient fenofibrate delivery to the eye limits its efficacy. We aim to explore the sustained therapeutic effects of fenofibrate loaded nanoparticles (Feno-NP) on DR.

Methods: Fenofibrate-loaded biodegradable PLGA nanoparticle were prepared and characterized on particle size, surface charge, drug loading, *in vitro* drug release, *in vivo* ocular pharmacokinetics. The efficacy of single intravitreal injection of Feno-NP in DR was investigated on streptozotocin (STZ)-induced rats. Therapeutic effects of Feno-NP were evaluated by retinal vascular leakage, retinal leukostasis, the expression of VEGF and ICAM-1 in the retina (3).

Results: Feno-NP were spherical with the particle size of ~250 nm (Fig A). Feno-NP (PLGA 34kDa) demonstrated a 6% drug loading and a sustained *in vitro* drug release up to 60 days (Fig B). Single intravitreal injection of Feno-NP in rat eyes maintained sustained fenofibric acid level in the eye for more than 60 days (Fig C). In STZ diabetic rats, Feno-NP reduced retinal vascular leakage, inhibited retinal leukostasis, downregulated the overexpression of VEGF and ICAM-1 at 8 weeks after IVT injection (Fig D~F).

Conclusion/Implications: Biodegradable NP platform with high drug loading and sustained fenofibrate release effectively attenuate retinal microvascular impairment, protects retinal dysfunction in DR. Compared with the i.p and oral administration, the single IVT injection of the nanoparticle reduced the total fenofibrate dose ~2000-times and ~40000-times respectively. Feno-NP displayed promising therapeutic potential for DR with sustained efficacy. Feno-NP were made from all Generally Regarded As Safe (GRAS) materials, facilitating the future translational use.

Acknowledgements: This study was supported by grants from National Institutes of Health. The travel grant is supported by “The Joseph B Schwartz Graduate Student Pharmaceutics Travel Fund at the Medical College of Virginica Foundation”.
References: (1) Chen, X.R, J. Neurotrauma. 2007:1119-31(2) Chen, Y. Diabetics. 2013: 261-72(3) Qiu, F. Mol Pharm. 2019: 1958-1970
Keywords: Route/target of delivery - Ocular, Type of delivery agent - Prodrug, Delivery vehicle - Biodegradable, Research approaches/methods/tools - Formulation development, Patient population/context - Translational, Focus groups - Ocular Delivery (OcD)
Learning Objectives:

- Explore biodegradable NP that can provide high fenofibrate loading and sustained in vitro drug release.
- Evaluate in vivo ocular pharmacokinetics of Feno-NP.
- Explore in vivo efficacy of Feno-NP on retinal leakage and retinal neovascularization in DR animal model.