Biodegradable β-Cyclodextrin-based Nanoparticles for Drug Delivery to Retina

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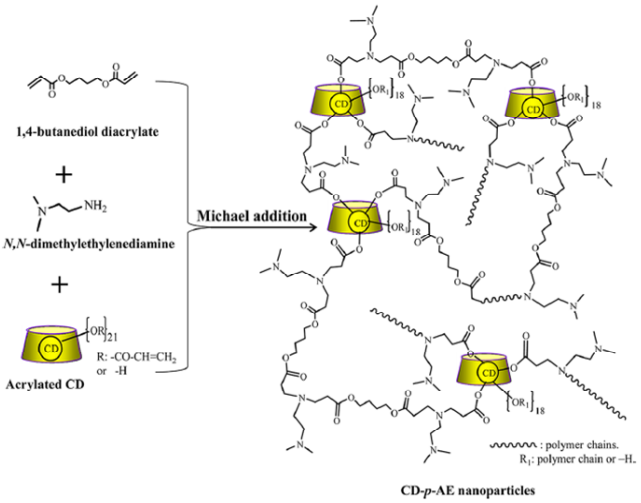
Statement of Purpose: Biodegradable β-cyclodextrin(CD)-based nanoparticles containing tertiary amine groups (CD-*p*-AE) have been developed in our lab via the Michael addition of acrylated CD macromer and 1,4-butanediol diacrylate with N,N-dimethylethyldiamine [1]. Our previous study has demonstrated that these nanoparticles are non-toxic and highly permeable to the *in-vitro* blood brain barrier (BBB) without disrupting the integrity of the BBB and could sustained release of doxorubicin for at least four weeks. In this current study, we further synthesized a serial of CD-*p*-AE nanoparticles by changing the precursor of amine groups. The feasibility of using these nanoparticles for drug delivery to the retina was investigated by *in-vitro* and *ex-vivo* methods.

Methods:

Synthesis of CD-p-AE nanoparticles

A serial of CD-*p*-AE nanoparticles were synthesized through Michael addition of Acrylated CD Macromer and 1,4-butanediol diacrylate with an amine molecule such as N,N-dimethylethyldiamine. The synthesized CD-*p*-AE nanoparticles were characterized using ^{1}H-NMR, dynamic light scattering, and atomic force microscope.



Scheme 1. Schematic structure of one of the serial of CD-*p*-AE nanoparticles synthesized.

In-vitro permeability of CD-p-AE nanoparticles across Human fetal retinal pigment epithelium (RPE) monolayers

All of the CD-*p*-AE nanoparticles were first labeled with dichlorotriazinylaminofluorescein (DTAF) for *in-vivo* and *ex-vivo* studies. Human fetal retinal pigment epithelium (RPE) monolayers were constructed on transwell inserts in the lab and used as the *in-vitro* blood-retina barrier (BRB) model to evaluate the permeability of the DTAF-labeled CD-*p*-AE nanoparticles. Permeability studies were conducted for 3 hours after the maximum transepithelial electrical resistance (TEER) was reached for the RPE monolayers.

Ex-vivo permeability of CD-p-AE nanoparticles across porcine sclera-choroid-RPE tissues

Ex-vivo permeability study is conducted using a side-by-side diffusion apparatus. Porcine sclera-choroid-RPE tissues were extracted from porcine eyeballs and mounted in the apparatus. DTAF labeled CD-*p*-AE nanoparticle solution was added into the donor cell while equal volume of transport buffer was added into the receiver cell. The fluorescence intensity in the receiver cell is monitored for 4 h.

Results:

^{1}H-NMR, dynamic light scattering, and atomic force microscope measurements confirmed the successful synthesis of the CD-*p*-AE nanoparticles. DLS and AFM analyses showed that the hydrodynamic diameters of the nanoparticles were around 20 to 400 nm. Permeability studies showed that the fluorescence-labeled CD-*p*-AE could more efficiently cross the REP monolayers than a control of dextran 4k. Currently, the *ex-vivo* permeability of CD-*p*-AE nanoparticles across porcine sclera-choroid-RPE tissues is under investigation. The *ex-vivo* permeability will provide information about how the chemistry of the CD-*p*-AE nanoparticles affects their permeability.

Conclusions:

The developed CD-*p*-AE nanoparticles have shown great potential for delivering drugs to retina.

References:

1. Gil, E.S.; L. Wu; L. Xu; T.L. Lowe. Biomacromolecules 2012, 13, 3533-3541.