β-Cyclodextrin-based Nanoparticles Containing Quaternary Amine for Drug Delivery to the Retina

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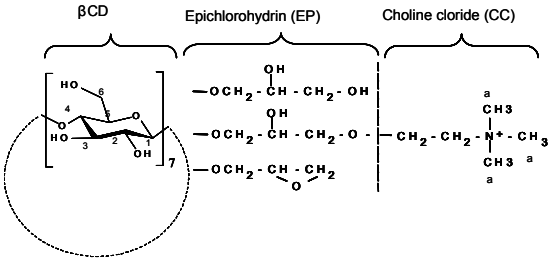
Statement of Purpose: β-Cyclodextrin-based nanoparticles containing quaternary amine groups (QA-β-CD) have been developed in our lab [1]. Our previous study [1] has demonstrated that these nanoparticles are non-toxic and highly permeable to the *in-vitro* blood brain barrier (BBB) without disrupting the integrity of the BBB, thus significantly enhancing the permeability of doxorubicin. The purpose of current work is to investigate the feasibility of using these nanoparticles for drug delivery to the retina through different administration methods.

Methods:

Synthesis of QA-β-CD nanoparticles

QA-β-CD nanoparticles were synthesized through one-step condensation polymerization by using β-cyclodextrin (β-CD), epichlorohydrin (EP) and choline chloride (CC) as the precursors. Scheme 1 illustrates the structures of the synthesized QA-β-CD nanoparticles. The synthesized QA-β-CD nanoparticles were characterized using ^{1}H-NMR, dynamic light scattering, atomic force microscope, and zeta potential measurements. QA-β-CD nanoparticles are denoted as 1-W-N, where W denotes the feeding molar ratio of CC to β-CD and N denotes the feeding molar ratio of EP to β-CD.



Scheme 1. Schematic structure of QA-β-CD nanoparticles.

Ocular bio-distribution of QA-β-CD nanioparticles

QA-β-CD nanoparticles were first labeled with dichlorotriazinylaminofluorescein (DTAF) for *ex-vivo* and *in-vivo* studies. DTAF labeled QA-β-CD PBS solutions (20mg/mL) were administrated into the rats through different routes (i.e. intravitreal injection at the right eye, subconjunctiva injection at the right eye, and topical application). After 1 day, the rats were sacrificed and both eyes were removed from the rats. The cornea, lens, vitreous and retina tissues were further separated and homogenized using standard procedures. The BSA protein and fluorescence intensity in these tissue samples were measured, respectively. The results were reported in fluorescence intensity per BSA protein (i.e. normalized fluorescence intensity).

Ex-vivo permeability of QA-β-CD nanoparticles across cornea and sclera tissues

Ex-vivo permeability study is conducted using a side-by-side diffusion apparatus. Either cornea or sclera is mounted in the apparatus. DTAF labeled QA-β-CD nanoparticle solution is added into the donor cell while equal volume of transport buffer is added into the receiver cell. The fluorescence intensity in the receiver cell is monitored for 4 h.

Results:

QA-β-CD nanoparticles 1-15-2, 1-15-4 and 1-15-6 were synthesized. The hydrodynamic radii and zeta potential of these QA-β-CD nanoparticles are summarized in Table 1.

Table 1. Hydrodynamic radii and Zeta potentials of QA-β-CD nanoparticles

Nanoparticles	Hydrodynamic Radius† (Rh)/ nm	Zeta Potential (ζ) / mV
1-15-2	81.0 ± 2.5	1.8 ± 2.3
1-15-4	65.3 ± 4.3	6.0 ± 2.9
1-15-6	88.0 ± 3.8	14.0 ± 3.8

In order to evaluate the feasibility of these nanoparticles for drug delivery to the retina, we conducted *in-vivo* ocular biodistribution study using DTAF labeled QA-β-CD (1-15-2) nanoparticles. Figure 1 showed that many QA-β-CD nanoparticles entered into the retina of the injected eye after intravitreal injection as compared with the other tissues in the same eye. More ocular biodistribution study is in progress in order to find the better administration route for drug delivery to the retina.

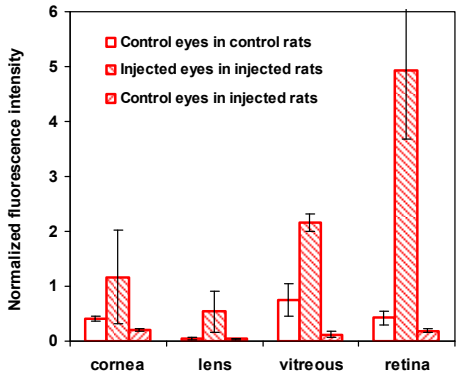


Figure 1. Ocular biodistribution of QA-β-CD (1-15-2) nanopartilces after intravitreal injection at the right eye.

The *ex-vivo* permeability will provide information about how permeable the QA-β-CD nanoparticles are to the cornea and sclera. So, the results will help us understand the ocular biodistribution of QA-β-CD nanoparticles via different administration routes.

Conclusions:

The developed QA-β-CD nanoparticles have shown great potential for delivering drugs to retina via intravitreal injection to treat retina diseases.

Acknowledgement

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References:

[1] Gil, E.S.; Li, J.S.; Xiao, H.N.; Lowe, T.L. *Biomacromolecules* 2009;10:505-516.