Oral Delivery Of Nanoparticles For Polycystic Kidney Disease

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Abstract

Introduction: Oral delivery is optimal for treating chronic diseases such as polycystic kidney disease (PKD), the most common genetic disease that lead to cyst formation and kidney failure [1]. Unfortunately, the only FDA-approved PKD drug, tolvaptan, resulted in a 23% dropout rate due to adverse side effects including liver toxicity [2]. To decrease toxicity, we developed self-assembling, kidney targeting micelles (KM) for targeted drug delivery [3]. To augment this system for oral delivery, herein, we load KMs with tolvaptan or metformin, a PKD drug under clinical trials, into chitosan nanocapsules. We test the hypothesis that chitosan nanocapsules can successfully deliver drugs and KMs across the GI tract and show therapeutic efficacy in PKD mice models.

Methods: Chitosan nanoparticles were synthesized via ionic gelation [4]. 2 mg/ml of chitosan (85% deacetylation) was added to a 1 mg/ml solution of poly-glutamic acid crosslinker. Drugs was loaded into our chitosan nanocapsules by mixing with the poly-glutamic crosslinker prior to ionic gelation. To assess oral drug delivery efficacy, 300 mg/kg of free drug or drug-KM loaded in CS-NP was orally gavaged to $Pkd1^{fl/fl}$;Pax8 rtTA;Tet-O cre mice every three days starting on P12, and euthanized on P22. Half-life and biodistribution were measured, and kidneys excised to assess kidney weight to total body weight ratio and stained with H&E to compare cystic index. Successful KM loading into chitosan nanocapsules was measured by dynamic light scattering (DLS).

Results: DLS and TEM of unloaded chitosan nanocapsules showed diameters of 148.5 ± 0.3 nm, while KMs are 14.9 ± 1.5 nm (Fig. 1 A(i, ii, v, vi)). DLS results of the mixed conditions shows both populations of particles (Fig. 1 A(iii)), whereas loading KMs within CS-NPs removes free KMs (Fig. 1 A(iv)), demonstrating they are encapsulated within CS-NPs. Half-life and biodistribution studies showed CS-NPs absorbed in the intestines to a greater extent than free drugs. H&E kidney sections from PKD mice orally gavaged show smaller cyst sizes in the CS-NP-drug group vs. free drug only (Fig. 1 C, D).

Conclusion/Implications: These initial studies show promise that KMs and PKD drugs can be loaded within CS-NPs and can function as an orally delivered targeted nanotherapeutic. The learning objectives include an understanding of 1) targeted delivery platforms for PKD, 2) developing chitosan nanocapsules as an oral delivery vehicle, and 3) the strategy of combining nanoparticles with oral biomaterials for chronic diseases. Our studies represent the first nanomedicine strategy for PKD therapy.

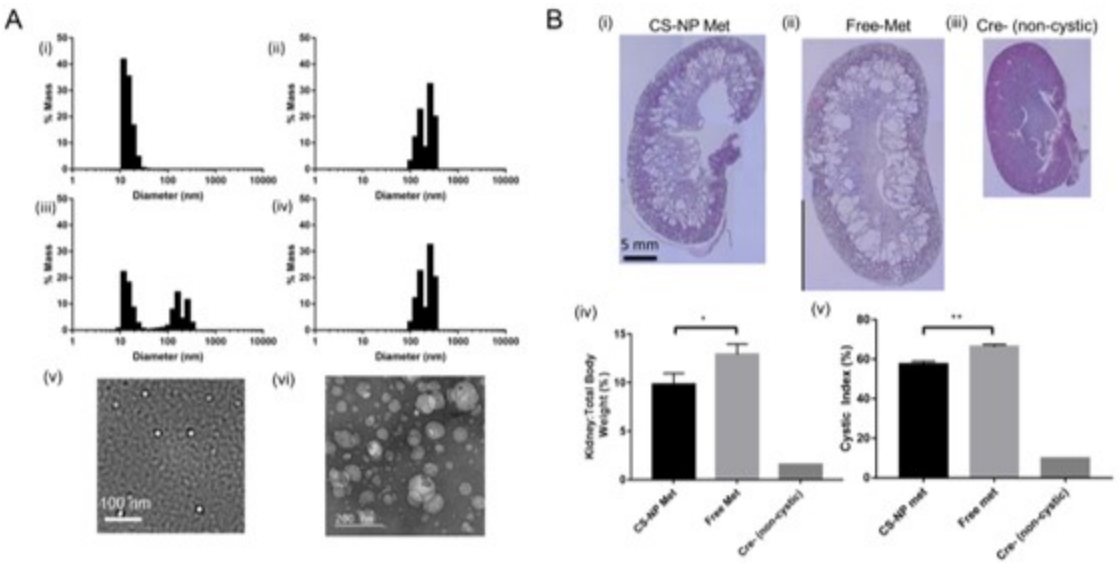

Figure 1. (A) DLS characterization of KM loading into chitosan nanoparticles: (i) KM only, (ii) CS nanocapsule only, (iii) KM and CS nanocapsule mixed, (iv) KM loaded into CS nanocapsules. TEM micrographs of (v) KM only and (vi) CS nanocapsule only. (B) H&E stained sections of kidneys from PKD mice pups orally gavaged with either (i) CS-NP-metformin or (ii) free met. (iv) Kidney weight to total body weight and (v) cystic index, given as the cystic area divided by total kidney area, of kidneys excised from CS-NP-met or free met treated mice (N = 3, * = $p < 0.05$, ** = $p < 0.01$).

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References: [1]Chapman AB et al., Kidney International. (2015)[2] Torres VE et al., N Engl J Med. (2017)[3]Wang J et al., Nano Research. (2018)[4]Lin YH et al., Biomacromolecules (2005)
Keywords: Route/target of delivery - Oral/Buccal/Gastrointestinal, Type of delivery agent - Small molecule, Delivery vehicle - Liposome/micelle/suspension, Delivery vehicle - Targeted, Focus groups - Nanomedicine and Nanoscale Drug Delivery (NND), Focus groups - Oral Delivery (OrD)
Learning Objectives:

- Discuss targeted delivery platforms for PKD
- Design chitosan nanocapsules as an oral delivery vehicle
- Demonstrate the strategy of combining nanoparticles with oral biomaterials for chronic diseases