Polysialic Acid-Based Nanoparticles for Systemic Drug Delivery

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Statement of Purpose: The use of polysialic acid (PSA) as the basis of nano-sized carriers for systemic drug delivery has been relatively unexplored. PSA is a non-immunogenic, highly hydrophilic, biodegradable polysaccharide, for which the body possesses no known receptors. Therefore, PSA is a potential alternative to poly(ethylene glycol) in preventing premature clearance through the ERS.[1] The goal of the current study was to generate PSA based nanoparticles via ionic complexation with chitosan in the presence of sodium tripolyphosphate (TPP). As a first step towards demonstrating the feasibility of using the developed nanoparticles for drug delivery, methotrexate (MTX) for the treatment of rheumatoid arthritis was entrapped within the PSA-based carrier systems.

Methods:

PSA nanoparticle preparation

Based upon a literature protocol,[2] ionic complexation of chitosan with TPP in the presence of PSA was used to prepare nanoparticles (Fig. 1). In brief, chitosan was dissolved at a weight percentage of 0.25% in 0.3% aqueous acetic acid. A solution of PSA and TPP together in DI water at concentrations of 0.25% and 0.1% respectively was also prepared. 1.5 ml of the PSA-TPP solution was added slowly to 3.0 ml of the chitosan solution to give a 0.5:1 weight ratio of PSA:chitosan, and the mixture was magnetically stirred for 30 minutes. Nanoparticles were isolated by centrifugation and re-suspended in DI water for characterization. Particle size and zeta potential were evaluated using Malvern Zetasizer Nano. AFM was used to verify the formation of spherical nanoparticles.

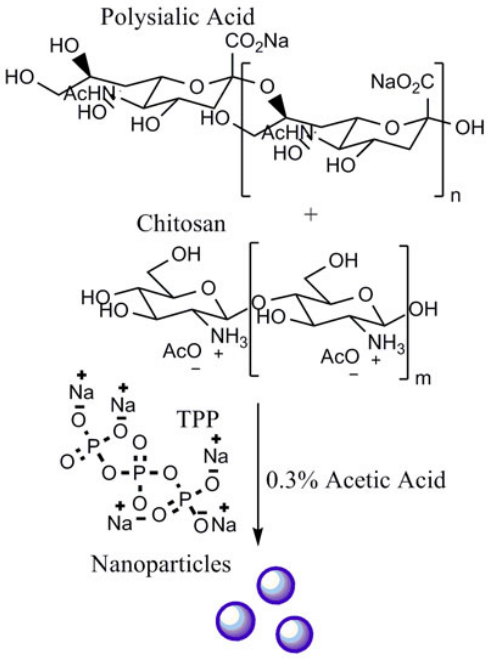

Fig. 1. Synthesis of PSA-based nanoparticles.

Entrapment of methotrexate within PSA nanoparticles

MTX was incorporated into the nanoparticles by adding MTX to the PSA-TPP solution at 25 wt. % relative to the total polysaccharide weight prior to nanoparticle formation, as described above. Analysis of the supernatant following centrifugation with UV-VIS spectroscopy was used to determine if MTX was entrapped within the nanoparticles.

Results: Particle size analysis and AFM confirmed the successful formation of nanoparticles via ionic complexation. (Figs. 2-3). The size of the particles was large enough to facilitate passive targeting if administered systemically.[3] AFM showed a spherical morphology, as expected; however, some particle aggregation occurred. The capacity of the particles to aggregate was confirmed by a zeta potential of only approximately -9 mV. MTX was successfully entrapped within the PSA-based nanoparticles.

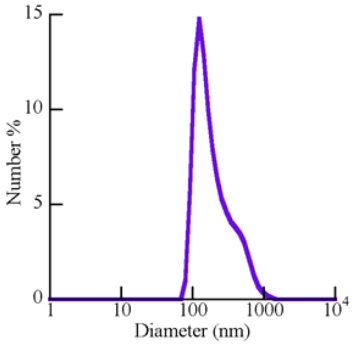

Fig. 2. Size distribution for PSA-based nanoparticles.

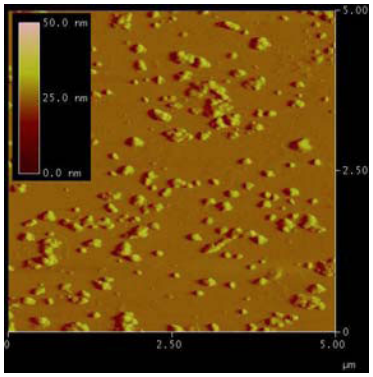

Fig. 3. AFM height image of PSA-based nanoparticles.

Conclusions: The results provide preliminary evidence that PSA can be used as the basis for nanoparticle drug carrier systems. Studies to optimize size/zeta potential and to quantify MTX entrapment and release are ongoing.

References:

1. Gregoriadis G. 2001. Int J Pharm. 2005;300:125-130.
2. De la Fuente M. Macromol Biosci. 2008;8:441-450.
3. Lee CC. Proc Natl Acad Sci U S A. 2006;103: 16649-16654.

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