Lipid-Enveloped Polymeric Nanoparticles For Delivery of Hydrophobic Drug

Chung-Fan Kuo[1], Andrew Leber[1], and Sheereen Majd[1,2]
Departments of Bioengineering[1], Engineering Science and Mechanics[2]
Pennsylvania State University, University Park, PA 16802

Statement of Purpose: Nanotechnology holds a great promise for the treatment of diseases, such as cancer and neurological disorders, by providing highly specific and efficient delivery vehicles for therapeutic agents. In this context, both polymeric nanoparticles and nano-scale liposomes have shown a great potential for carrying therapeutic molecules such as drugs and genes specifically to diseased cells. However, both approaches have disadvantages. For example, without surface modification, polymeric nanoparticles have poor colloidal stability in ionic solutions. On the other hand, low mechanical stability and poor hydrophobic drug loading efficiency limit the use of nanoliposomes for delivery purposes. Therefore, hybrid nanoparticles that combine the advantages of solid polymeric nanoparticles and biomimetic nanoliposomes present attractive delivery systems. In this study, we aim to develop and characterize nanoliposomes with polymeric cores that enable efficient and selective delivery of hydrophobic molecules to diseased cells.

Methods: We prepared nanoliposomes with a polymeric core of a FDA-approved biodegradable polymer, poly (lactide-co-glycolide) acid (PLGA), to encapsulate a water-insoluble cargo, curcumin. Curcumin possesses excellent anti-oxidatant, anti inflammatory, and anti-amyloidogenic properties, and has been employed to tackle cancer and amyloidogenic diseases such as Alzheimer's disease. The hydrophobicity of this compound has, however, made its delivery to desired sites challenging. To address this issue, we prepared curcumin-loaded PLGA nanoparticles using the nanoprecipitation technique and enveloped these nanoparticles in a lipid membrane decorated with PEGylated lipids. We characterized the resulting hybrid nanoparticles in terms of size, zeta potential, colloidal stability, loading efficiency, and release profile and compared these properties to those of PLGA nanoparticles. To optimize the particle size, we investigated the effect of several particle synthesis parameters including concentration of polymer, injection rate during nanoprecipitation, and polymer/drug ratio, on the size distribution of particles.

Results: Our results revealed that using high polymer concentrations (10 mg/ml), high polymer/drug ratio (1/0.3), and low injection rates (10 ml/hour) leads to production of larger particles (100-160 nm). Upon careful optimization of all parameters, we obtained particles with a mean diameter of ~ 75 nm. Loading the hydrophobic curcumin inside PLGA nanoparticles also resulted in much improved encapsulation efficiency of 88% compared to 4.44% in the case of crucumin-loaded nano-liposomes. To prove the success of lipid coating, we performed Dynamic Light Scattering (DLS) and colloidal stability test. Figure 1 shows the result of DLS; where the red curve shows the drug-loaded PLGA nanoparticles and the green curve represents the size distribution of empty liposomes mixed with PLGA particles, and the blue line represents the hybrid particle (lipid-enveloped PLGA) size distribution. Colloidal stability test, Figure 2, revealed that without a lipid membrane coating on the surface of nanoparticles, particles tend to aggregate in ionic strength of PBS. Presence of PEG chains on the surface of liposomes, however, led to much higher colloidal stability in case of liposomes and lipid-coated nanoparticles as there was no detectable aggregation after five days of incubation. Current studies are focused on comparison of the release profiles between the lipid-coated and bare curcumin-loaded PLGA nanoparticles, Cyro-TEM images of lipid-coated PLGA nanoparticles, and cell uptake of hybrid particles.

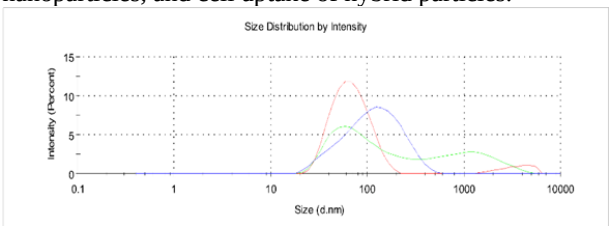

Figure 1: Size distribution of curcumin-loaded PLGA nanoparticles (red), curcumin-loaded PLGA particles mixed with empty liposomes (green), and lipid-coated curcumin-loaded PLGA nanoparticles (blue).

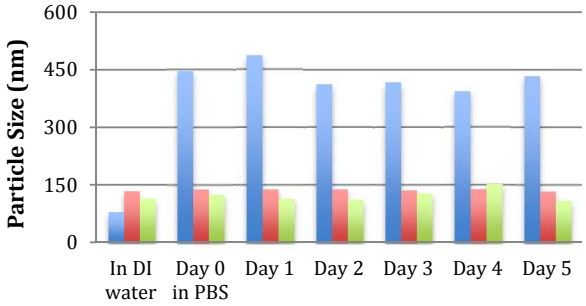

Figure 2: Colloidal stability test in PBS. Bare drug-loaded PLGA nanoparticles without lipid coating (blue), nanoliposomes (red), and lipid-coated drug-loaded PLGA nanoparticles (green).

Conclusions: Using a modified version of nanoprecipitation, we were able to fabricate polymeric nanoparticles with a homogeneous and narrow size distribution. Moreover, it is also possible to adjust the particle size during particle preparation. Using the optimized fabrication parameters, we have produced drug-loaded polymeric nanoparticles, which are around 75 nm in diameter, and the encapsulation efficiency of curcumin in these particles is around 88%. DLS and colloidal stability test have confirmed the presence of the lipid coating on particles, as the lipid envelop helps to improve electrostatic repulsions for stability in an ionic solution.