Optimization of modified poly (glycerol adipate) polymer nanoparticles for pulmonary drug delivery

Ramy Said-Elbahr[1, 2], Cynthia Bosquillon[1], Giuseppe Mantovani[1], Snow Stolnik[1]

[1] Division of Molecular Therapeutics and Formulation, School of Pharmacy, University of Nottingham, Nottingham NG7 2RD, United Kingdom; [2] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt

Background: Pulmonary drug delivery has attracted great interest especially in localized treatment of lung diseases. Polymeric nanoparticles could provide vast benefits in overcoming some of the challenges of that route. However, few polymers have shown suitability for the inhaled route. Poly (glycerol adipate) (PGA) has emerged as a green enzyme synthesized polyester polymer which is biodegradable, highly functionalizable, easily prepared in few steps and at low-cost. Therefore, we aim at testing the aptness of PGA polymer for pulmonary drug delivery application. However, modification of PGA polymer is required in order to obtain more solid polymer, elevate its glass transition temperature (T_g) and thus, enable future drying of its nanoparticles into inhalable powders.

Methods: PGA was synthesized from divinyl adipate and unprotected glycerol followed by modification with *N*-acetyl-tryptophan (NAT) using a simple Steglich esterification reaction. Polymers were characterized with Nuclear Magnetic Resonance and Differential Scanning Calorimetry to trace the effect of NAT % substitution on modified polymers T_g values. Moreover, PGA polymers were formulated into nanoparticles using nanoprecipitation technique and colloidally stabilized using different surfactants (Tween 80, Kolliphor HS 15 and Lecithin) followed by their characterization using dynamic light scattering.

Results: PGA polymer was successfully synthesized and coupled to *N*-acetyl-tryptophan (NAT) to obtain solid powder polymers demonstrating desired T_g values (40 – 62^{o}C) with a positive correlation between NAT % substitution and modified polymers T_g. The nanoparticles formulations showed small hydrodynamic diameter <120 nm, narrow size distribution (PDI <0.2) and negative zeta potential values. The highly substituted PGA-NAT polymers nanoparticles were sterically stabilized by the non-ionic surfactants which showed no significant changes in particle size and size distribution while significantly masked the nanoparticles surface charge. However, the phospholipid lecithin imparted electrostatic stabilization with significantly higher particle size, polydispersity index (PDI) and higher negative zeta potential values compared to the non-ionic surfactants.

Conclusions: Modification of PGA polymer with *N*-acetyl-tryptophan (NAT) dramatically elevated its glass transition temperature rendering it a promising candidate for pulmonary delivery of its dried nanoparticles. However, future work is needed to ensure preservation of its biodegradability upon modification and safety on lung cells.