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Nanocarriers Made of Amino Acid Based Biodegradable Polymers: Poly(Ester Amide) and Related Cationic and PEGylating Polymers

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Abstract : Polymeric nanoparticles-based drug delivery systems and therapeutics have a great potential in the treatment of a numerous diseases, due to they are characterizing the flexible properties which is giving possibility to modify their structures with a complex definition over their structures, compositions and properties. Important characteristics of the polymeric nanoparticles (PNPs) used as drug carriers are high particle's stability, high carrier capacity, feasibility of encapsulation of both hydrophilic and hydrophobic drugs, and feasibility of variable routes of administration, including oral application and inhalation; NPs are especially effective for intracellular drug delivery since they penetrate into the cells' interior though endocytosis. A variety of PNPs based drug delivery systems including charged and neutral, degradable and non-degradable polymers of both natural and synthetic origin have been developed. Among these huge varieties the biodegradable PNPs which can be cleared from the body after the fulfillment of their function could be considered as one of the most promising. For intracellular uptake it is highly desirable to have positively charged PNPs since they can penetrate deep into cell membranes. For long-lasting circulation of PNPs in the body it is important they have so called "stealth coatings" to protect them from the attack of immune system of the organism. One of the effective ways to render the PNPs "invisible" for immune system is their PEGylation which represent the process of pretreatment of polyethylene glycol (PEG) on the surface of PNPs. The present work deals with constructing PNPs from amino acid based biodegradable polymers – regular poly(ester amide) (PEA) composed of sebacic acid, leucine and 1,6-hexandiol (labeled as 8L6), cationic PEA composed of sebacic acid, arginine and 1,6-hexandiol (labeled as 8R6), and comb-like co-PEA composed of sebacic acid, malic acid, leucine and 1,6-hexandiol (labeled as PEG-PEA). The PNPs were fabricated using the polymer deposition/solvent displacement (nanoprecipitation) method. The regular PEA 8L6 form stable negatively charged (zeta-potential within 2-12 mV) PNPs of desired size (within 150-200 nm) in the presence of various surfactants (Tween 20, Tween 80, Brij 010, etc.). Blending the PEAs 8L6 and 8R6 gave the 130-140 nm sized positively charged PNPs having zeta-potential within +20 ÷ +28 mV depending 8L6/8R6 ratio. The PEGylating PEA PEG-PEA was synthesized by interaction of epoxy-co-PEA [8L6]0,5-[tES-L6]0,5 with mPEG-amine-2000 The stable and positively charged PNPs were fabricated using pure PEG-PEA as a surfactant. A firm anchoring of the PEG-PEA with 8L6/8R6 based PNPs (owing to a high afinity of the backbones of all three PEAs) provided good stabilization of the NPs. In vitro biocompatibility study of the new PNPs with four different stable cell lines: A549 (human), U-937 (human), RAW264.7 (murine), Hepa 1-6 (murine) showed they are biocompatible. Considering high stability and cell compatibility of the elaborated PNPs one can conclude that they are promising for subsequent therapeutic applications. This work was supported by the joint grant from the Science and Technology Center in Ukraine and Shota Rustaveli National Science Foundation of Georgia #6298 "New biodegradable cationic polymers composed of arginine and spermine-versatile biomaterials for various biomedical applications".

Keywords : biodegradable poly(ester amide)s, cationic poly(ester amide), pegylating poly(ester amide), nanoparticles
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