Biodegradable Nanoparticles Fabricated from Amino Acid-based Poly(ester amide)s for Drug Release

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Statement of Purpose: Micellar drug delivery systems self-assembled from amphiphilic copolymers have been extensively investigated because of the advantages, such as a prolonged circulation in blood, improved stability, and enhanced accumulation in tumor tissues. Owing to the undesirable side effects and systematical toxicity in cancer chemotherapy, drug-loaded micelles with active targeting property have become an attractive alternative. The biodegradable amino acid-based PEAs (AA-PEAs) [1] have recently been developed for their potentials in biomedical and biological fields because of their demonstrated biocompatibility, functionality, and versatility. In this abstract, a new family of multiblocks cationic AA-PEA based amphiphilic copolymers was designed and synthesized [2]. The resultant new AA-PEA amphiphilic copolymers can self assembled into micelle nanoparticles in water. The effect of trypsin enzyme on the biodegradation kinetics of these different types of cationic AA-PEAs micelles was studied. Doxorubicin drug was encapsulated within the micelles and the drug release profiles were examined.

Methods: The new cationic AA-PEA micelles were synthesized by first preparing Lys (lysine), Arg (arginine) and Phe (Phenylalanine) based diester monomers. These amino acid-based monomers then reacted with di-p-nitrophenyl adipate (NA) and di-p-nitrophenyl sebacate (NS) monomers via solution polycondensations. The zeta potential, size and size distribution of the self assembled micelles were determined. The critical micelle concentration (CMC) was determined by fluorescence spectra. The biodegradation of the AA-PEA micelles in the presence of trypsin was evaluated, and the morphology of the hydrogels was characterized by SEM. The cell cytotoxicity was tested by MTT assay of Hela cells. The Doxorubicin-impregnated AA-PEA nano micelles were fabricated and the release of Doxorubicin drug from the micelles in water was studied.

Results: A series of Lys-, Arg- and Phe- based biodegradable PEA amphiphilic copolymers was synthesized. These cationic AA-PEA copolymers can self-assemble into stable nano micelles in an aqueous medium due to the interaction between hydrophilic (Lys and Arg) and hydropholic (Phe) segments of the AA-PEAs. Scanning electron microscopic images showed that the self-assembled micelles had smooth spherical shape of diameter ranging from 131 nm to 200 nm. The diameter and Zeta potential increased with increasing the hydrophilic moiety, e.g., Lys or Arg segment, 134 nm for [2-Arg-4]0.25-[2-Lys-4]0.25-[2-Phe-4]0.5 and 201 nm for [2-Arg-4]0.33-[2-Lys-4]0.33-[2-Phe-4]0.33 micelles. The cumulative amounts of Doxorubicin released from these cationic AA-PEA micelles increased with a higher zeta potential of the AA-PEA solution. The effect of the trypsin enzyme (0.1 mg/mL) on the biodegradation property of these new AA-PEA micelles was examined. The biodegradation data of AA-PEA micelles showed that these AA-PEA micelles lost their spherical shapes after initial biodegradation, but the spherical micelles were restored after 12 hrs biodegradation, and the diameter of the micelles became less than 90 nm after 18 hours biodegradation. The Hela cell MTT data demonstrated that, when comparing with the blank control, there was virtually no reduction in cell viability when the concentration of the AA-PEA was below 1 mg/mL.

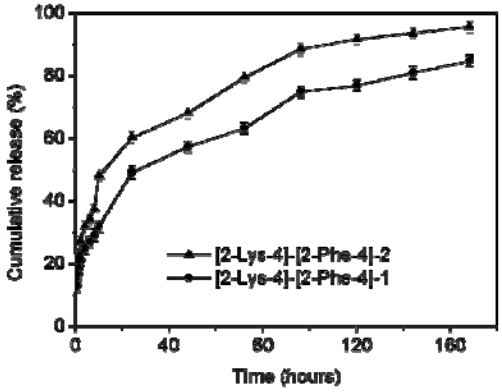

Figure 1. Doxorubicin released from the [2-Lys-4]-[2-Phe-4]. [2-Lys-4]-[2-Phe-4]-1 indicates [2-Lys-4]0.5-[2-Phe-4]0.5, [2-Lys-4]-[2-Phe-4]-2 indicates [2-Lys-4]0.67-[2-Phe-4]0.33.

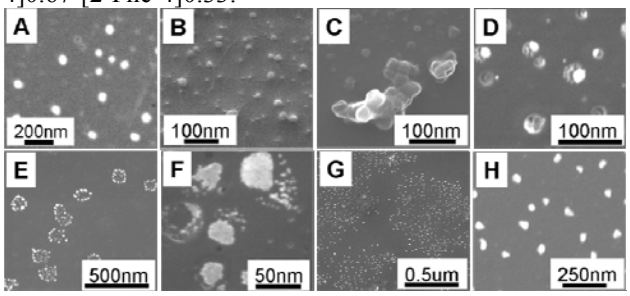

Figure 2. SEM of biodegradation of [2-Lys-4]0.5-[2-Phe-4]0.5 micelles under the enzyme trypsin concentration of 0.25mg/mg in PBS (pH 7.4, 0.1M) solution.

Conclusions: A new family of water soluble cationic AA-PEA amphiphilic copolymers based on Lys, Arg and Phe amino acids was successfully designed and synthesized; and these AA-PEAs can self-assembled into nano size micelles. Biodegradation study demonstrated that these AA-PEAs can be biodegraded in presence of trypsin. Doxorubicin drugs can be preloaded into these AA-PEA micelles for a controlled release. These cationic AA-PEA nano micelles may be the promising candidates for controlled drug release.

References:

[1] Deng, M. X.; Wu, J.; Reinhart-King, C. A.; Chu, C. C. Biomacromolecules 2009, 10, 3037.

[2] Jun Wu, D. W., Martha A. Mutschler, Chih-Chang Chu Advanced Functional Materials 2012.

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