Proceedings of the 5th International Conference on Nanotechnology: Fundamentals and Applications
Prague, Czech Republic, August 11-13, 2014
Paper No. 236

Controlling Interaction of Nanoparticles with Biological Media

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Extended Abstract

Non-specific protein adsorption from complex biological media, especially from blood plasma, is an urgent challenge for the application of nanoparticles as delivery systems, diagnostics, and other biomedical application. The surface modification of nanoparticles by physically anchoring hydrophilic biocompatible polymers is a simple and commercially attractive strategy to produce stealth drug delivery nanocarriers. We report the preparation, characterization and preliminary evaluation of the biological behaviour of several such systems.

Narrowly distributed sub-100 nm polymeric nanoparticles with stealth properties were successfully prepared by using a combination of interfacial nanoprecipitation and self-assembly using a biodegradable poly(butylene succinate-co-butylene dilinoleate) – PBS/PBDL – copolyester and a non-immunogenic and non-toxic hydrophilic N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer. The assemblies were characterized by using complementary scattering techniques and cryo-transmission electron microscopy. The dimension of the NPs was found to be in the proper range to avoid fast renal clearance (D_H > 10 nm) and still below the cut-off size of the leaky pathological microvasculature of hypervascular tumours (D_H < 200 nm), thus making them candidates for application in cancer therapy based on the EPR effect. The presence of PHPMA copolymer exposed at the surface of the nanoparticles was confirmed by scattering measurements. The stealth property of the biocompatible and biodegradable NPs is responsible for their remarkable in vitro stability monitored in a simulated physiological environment and increased stability in concentrated NaCl solutions compared to uncoated PBS/PBDL nanoparticles, making them an alternative to PEG-shielded particles.

The payload capability of the core-shell nanoparticles was confirmed since they can deliver high quantities of docetaxel and doxorubicin releasing the therapeutics at a sustained rate or *via* a pH-triggered pathway with *in vivo* efficacy in the treatment of mice bearing EL-4 T cell lymphoma. The multivalency of the HPMA copolymer in the NP shell enables further development of targeting strategies based on the use of cell membrane receptor-specific ligands attached to the NP surfaces for *in vivo* multi-target and combination therapies.

Nanocapsules (NC) prepared from FDA-approved degradable poly(ε-caprolactone) shell and Mygliol 812® oil in the core were coated with mono-methoxy terminated oligo(ethylene glycol) methacrylate (poly(MeOEGMA)) polymer brush layers with a well-controlled thickness at the nanometer scale up to 350nm using surface initiated atom transfer radical polymerization in water or phosphate buffered saline. Incubation of uncoated NC with human serum albumin solution, fetal bovine serum, or human blood plasma resulted in fast aggregation observed by dynamic light scattering as an increase in diameter of particles present in the solutions. Conversely, these biological fluids affected only marginally the size distribution of the NC coated with a 60 nm thick poly(MeOEGMA) layer. The high suspension stability of the coated NC in complex biological fluids was related to the suppressed deposition of proteins from these fluids observed by surface plasmon resonance (SPR) on analogous poly(MeOEGMA) layer prepared on flat surfaces of SPR chips.

Acknowledgements

Support by the Grant Agency of the Czech Republic (P208/10/1600) is gratefully acknowledged.