

SURFACE MODIFICATION OF PLGA MICROSPHERES

M. Müller¹, J. Vörös¹, G. Csúcs², E. Walter³, M. Textor¹, N. D. Spencer¹

¹ [Laboratory for Surface Science and Technology](#), ² [Laboratory for Biomechanics](#) and the ³ [Institute of Pharmaceutical Science and Technology](#), ETH Zürich, Switzerland

INTRODUCTION: Colloidal carriers such as micro- and nanospheres are regarded as a promising approach of drug targeting. Microspheres made of Poly (lactic-co-glycolic acid) PLGA are fully biocompatible and biodegradable, a prerequisite in micro-encapsulation of therapeutics. The adsorption of plasma proteins is regarded as the key factor for the rapid uptake of intravenously injected particulate drug carriers by the cells of the reticuloendothelial system (RES), which is a serious handicap for drug targeting. In this present work we focused on the polymer system PLL-g-PEG which is known from earlier investigation, performed on flat metal oxide surface, to drastically reduce the protein adsorption. PLL-g-PEG consists of a poly (L-lysine) PLL backbone, which is highly cationic at a physiological pH and interacts with the negatively charged PLGA microsphere surface by electrostatic forces. The PLL backbone is grafted with poly(ethylene oxide) PEG chains, which exhibit protein resistance. Of the many models proposed to explain this effect, steric stabilization and excluded-volume effects are the most commonly cited. Furthermore, graft copolymers of PLL and PEG have been evaluated for toxicity and biodegradation which render PLL-g-PEG coated PLGA microspheres a promising tool in the context of drug delivery.

METHODS: PLGA microspheres were prepared by spray-dry method. The coating process was carried out by mixing the coating solution with the microsphere dispersion followed by centrifugation and redispersion. Different polymer mixtures of PLL-g-PEG and PLL-g-PEG/PEGbiotin were mixed with PLGA microspheres. Fluorescently labelled streptavidin was added to test the functionality of PLL-g-PEG/PEGbiotin coated PLGA microspheres. The protein repulsion was investigated by exposing PLL-g-PEG coated PLGA microspheres to human proteins (human serum albumin, fibrinogen, fibronectin, immunoglobulin G), subsequently to the corresponding primary antibody and finally to the fluorescently labelled secondary antibody. For quantification the adsorbed amount of proteins, a new semi-quantitative method based on confocal

laser scanning microscopy (CSLM) was developed. Using this technique cross-section images from several microspheres at different heights were taken by CLSM and stacked up. The summed fluorescence intensity of the piled up single cross section images was quantified in arbitrary units.

RESULTS AND DISCUSSION: Figure 1 demonstrates a linear dependence of the measured fluorescent intensity, emitted by streptavidin Oregon-Green conjugate, on the concentration of biotin in the polymeric adlayer of the microspheres. This correlation confirms the feasibility to introduce functional groups to PLL-g-PEG coated PLGA microspheres while preserving the full biological functionality of the biotin-streptavidin system.

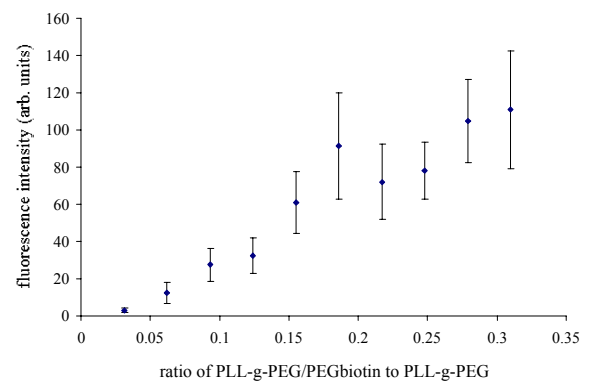


Fig.1: Fluorescence intensity as a function of the weight ratio of PLL-g-PEG/PEGbiotin to PLL-g-PEG.

PLL-g-PEG coated PLGA microspheres showed a drastic decrease of non-specific protein adsorption. The amount of proteins was reduced by two orders of magnitude in comparison to uncoated PLGA microspheres.

SUMMARY: In the present study we demonstrated the high efficiency of the protein-resistant character of PLL-g-PEG on PLGA microspheres and the feasibility to introduce functional groups on the PLGA microspheres via modified PLL-g-PEG.