Size dependent biodistribution of HPMA-based polymeric systems using ^{18}F-labeled polymers

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Introduction: During the last decades the development of polymeric nanomedicines for medical diagnosis and treatment is of increasing interest in pharmaceutical research.[1] Using synthetic polymers for therapeutic purposes offers the possibility of combining various functionalities among a single molecule e.g. for drug-targeting, solubility or modulation of bioavailability. In this respect, the biocompatible polymeric backbone N-(2-hydroxypropyl)methacrylamide (HPMA) is a promising candidate for applications in the field of nanoparticular drug-delivery systems and has already been extensively studied *in vivo*.[2] Such polymers accumulate in the diseased region due to an enhanced permeability and retention effect in tumor tissue. Nevertheless, detailed knowledge about the biodistribution of polymeric drug-delivery systems in living organisms are required to optimize polymeric systems for medical applications.
On this basis, a better understanding about biodistribution processes and also about the tumor accumulation *in vivo* can be realized by radioactive labeling in combination with non-invasive imaging techniques.

Experimental: Well defined HPMA-based random copolymers of different molecular weights (M_w=12 kDa and 77 kDa) synthesized via the RAFT polymerization technique[3] were labeled with the positron emitting isotope fluorine-18 using the secondary labeling synthon 2-[^{18}F]fluoroethyl-1-tosylate ([^{18}F]FETos). For labeling purposes the polymeric precursors were functionalized with ~ 4% tyramine moieties thus offering a reactive site for the prosthetic labeling procedure using [^{18}F]FETos. The radioactive coupling step was performed using a solution of 3 mg polymer, 1 µL 5N NaOH and [^{18}F]FETos in 1 mL of DMSO (figure 1). The clear solution was kept at 120 °C for 15 min. The reaction mixture was purified using size exclusion chromatography (HiTrap Desalting Column, Sephadex G-25 Superfine, column volume 5 mL; flow: 1 mL/min physiological saline) leading to a pure solution of the ^{18}F-labeled polymer. For biodistribution studies ~ 20 MBq of the purified polymer solution was injected intravenously via the tail vein in tumor bearing Copenhagen rats (R3327-AT1 dunning prostate carcinoma). At 2h after administration the rats were sacrificed and dissected. Samples of various organs were taken, weighted and their radioactivity was measured by a γ-counter.

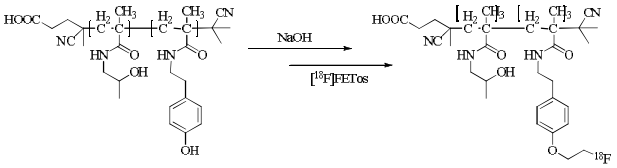

Figure 1. Radioactive labeling of polymers using [^{18}F]FETos.

Results: To understand how the molecular weight affects the biological uptake, different HPMA-based polymeric systems were ^{18}F-labeled successfully and evaluated *in vivo*. Biodistribution studies clearly showed higher renal clearance (kidney, urine) for lower MW polymer of 12 kDa (below the renal excretion threshold for HPMA copolymer) whereas higher MW polymer of 77 kDa showed increased accumulation in liver and spleen. Accumulation of both polymeric systems in lung, muscle, heart, intestines and testes is low. The uptake in tumor tissue is slightly higher for the polymer of 77 kDa (0.20% ID/g tissue). Better tumor accumulation might be achieved by the attachment of targeting vectors to the polymer backbone.

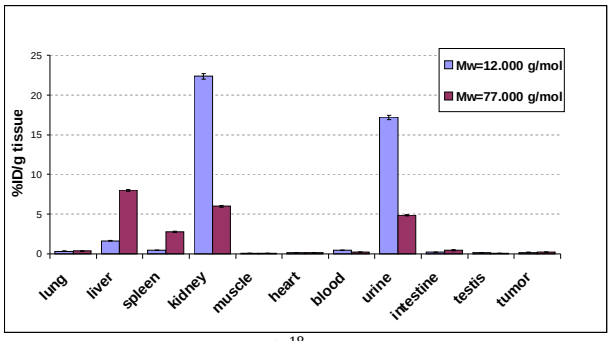

Figure 2. Biodistribution of ^{18}F-labeled HPMA-based polymeric systems (MW = 12 kDa and 77 kDa) in various organs 2h p.i.

References

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