Published in final edited form as:

Int Workshop Magn Part Imaging. 2015 March ; 2015: .

Tunable *in vivo* circulation characteristics of PEGylated MPI tracers

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Introduction

Understanding the pharmacokinetic (PK) properties of MPI tracers is necessary for enabling the wide spectrum of possible *in vivo* MPI applications. For intravenously administered tracers, blood half-life ($t_{1/2}$) is a critical PK property that will help determine the suitability and clinical readiness for applications such as cardiovascular and molecular imaging. Here we show the ability to tune the *in vivo* circulation characteristics ($t_{1/2}$) of polyethylene glycol (PEG)-coated (“PEGylated”) MPI tracers. PEG is a biocompatible polymer frequently used to enhance the circulation characteristics of nanoparticles and other macromolecules such as antibodies.

Methods

MPI tracers, composed of monodisperse and phase-pure magnetite nanoparticle cores, were coated with five variations of poly(maleic anhydride-alt-1-octadecene)-polyethylene glycol (PMAO-PEG) amphiphilic co-polymers (Table 1), with different PEG chain lengths and loading. Tracers were administered at 7 mgFe/kg dose as a bolus injection in the tail-vein of CD-1 female mice (~25-30 grams at 8 weeks old). Following the intravenous injection, blood samples were collected by retro-orbital bleeding at various time points to determine the active tracer content in the blood using our 25-kHz MPS, where active tracer is defined as circulating nanoparticles that still generate an unperturbed MPS signal.

Results

The circulation profile of MPI tracers following intravenous administration resembled a one-compartment PK model, which is characterized by a single elimination rate constant (Figure 1). Both PEG molecular weight and its loading percentage on the PMAO backbone – defined as the amount of PEG molecules relative to carboxylic acid groups in PMAO – appear to impact $t_{1/2}$. Specifically, increasing PEG molecular weight from 5 kDa to 20 kDa led to a near doubling in $t_{1/2}$; on the other hand, preliminary results suggest that around 18.8% PEG loading provided the longest $t_{1/2}$ (160 minutes) when using a 20 kDa PEG. For

comparison, independent pharmacokinetic studies with Resovist nanoparticles reported less than 5 minutes of blood half-life [1,2].

Conclusion

The blood half-life of PEGylated MPI tracers depends on the molecular weight and loading density of PEG. We show that the PMAO-PEG polymer is a versatile coating platform that gives the ability to modify and potentially tune the circulation characteristics of MPI tracers for for specific *in vivo* applications.

Acknowledgments

This work was supported by NIH grants 1R01EB013689-01/NIBIB, 1R41EB013520-01 and 2R42EB013520-02A1.

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Figure 1.

Blood half-life of PEGylated MPI tracers. For each averaged data point, $n = 3$. Blood half-life determined using single-compartment PK model: $t_{1/2} = -\frac{1}{R} \ln\left(\frac{1}{2}\right)$; where R is the elimination rate constant obtained from the fitting curves.

Table 1

Properties of MPI tracers used to evaluate blood half-life in female CD-1 mice

Sample ^a	PEG M _n [kDa]	%PEG loading ^b	VSM ^c dia. [nm] (σ); vol. wt.	DLS ^d dia. [nm] (PDI); z-average	$t_{1/2}$ [min]
A	5,000	8.8	17.0 (0.20)	86 (0.18)	4
B	5,000	13.1	21.0 (0.14)	42 (0.14)	18
C	20,000	12.5	27.6 (0.17)	67 (0.14)	35
D	20,000	18.8	27.0 (0.11)	78 (0.11)	160
E	20,000	25.0	27.0 (0.15)	89 (0.18)	80

^a Samples A and B coated with PMAO-*ester*-PEG(5kDa), while C, D and E coated with PMAO-*amide*-PEG(20kDa)^b % PEG loading is the amount of PEG groups for every 228 carboxylic acid groups per PMAO polymer (assuming PMAO M_n = 40 kDa)^c Core diameter determined by fitting M(H) curves measured using vibrating sample magnetometry (VSM)^d Hydrodynamic diameter measured using dynamic light scattering (DLS)