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Tuning magnetic relaxation properties of "hard cores" in core-shell colloids by modification of "soft shell"

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ABSTRACT

The present work introduces an impact of polyelectrolyte-based hydrophilic shell on magnetic relaxivity and luminescence of hard cores built from isostructural complexes of Tb(III) and Gd(III) in the core-shell aqueous colloids. Microscopic and scattering techniques reveal "plum pudding" morphology of the colloids, where polyelectrolyte-coated ultrasmall (<5 nm) hard cores form aggregates in aqueous solutions. Interaction of bovine serum albumin (BSA) with the colloids provides a tool to modify the polyelectrolyte-based shell, which is the reason for the improvement in both aggregation behavior of the colloids and their relaxivity. The modification of the hydrophilic polyelectrolyte-based shell enables to tune the longitudinal relaxivity from 5.9 to 23.3 mM^{-1} s^{-1} at 0.47 T. This tendency is the reason for significant improvement of contrasting effect of the colloids in T_1- and T_2-weighted images obtained by whole body scanner at 1.5 T. High contrasting effect of the colloids, together with low cytotoxicity towards Wi-38 diploid human cells makes them promising MRI contrast agents.

1. Introduction

Nanoparticulate contrast agents (CAs) are a top of current interest today due to great advantage of magnetic resonance imaging (MRI) as a powerful and noninvasive tool in medical diagnostics [1–3]. Gd(III)-based nanoparticles are highlighted in literature as most promising basis of positive contrast agents in MRI [4,5]. Most efforts in a development of nanoparticulate CAs are focused on core-shell morphology, where hard Gd(III)-based cores are stabilized by hydrophilic coating [6,7]. Although no theoretical framework is known for quantitative interpretation of relaxivities in Gd(III)-based colloids, main factors affecting the relaxivity have been highlighted on a qualitative level [8,9]. Restricted molecular motion of Gd(III)-centers in nanoparticles [10–12] as well as lowered toxicity [13,14] are main advantages of nanoparticulate CAs versus their molecular analogues. Nevertheless, size of hard Gd(III)-based cores is confined within 2–5 nm, since greater sizes restrict an accessibility of Gd(III)-centers to hydration, which in turn is a key reason for enhancing of water proton relaxation [15,16]. Thus, ultrasmall (2–5 nm) Gd(III)-based cores are ideal nanoparticulate CAs with high surface-to-volume ratio to provide an efficient access of water protons to Gd(III) paramagnetic center. In contrast, aggregation of nanoparticles is an unfavorable factor shortening longitudinal relaxivity of water protons due to restricted "active surface" of the nanoparticles, which in turn changes to worse a hydration of Gd(III)-centers at their surface [17]. It is also worth noting that an exchange of Gd(III) inner sphere coordinated water molecules with those in a bulk of solution requires their diffusion through a polymeric shell. The diffusion may be rate-determinative stage for magnetic relaxation in aqueous paramagnetic colloids. The latter tendency is well documented for silica coated Gd(III) complexes, although an effect of soft hydrophilic coating on longitudinal and transverse relaxivities of Gd(III) complex-based cores is not fully recognized [18,19].

Literature data indicate gadolinium oxides and salts, as a common basis for nanoparticulate MRI CAs [16,20,21], although plenty of reports published in recent decades highlight great impact of water insoluble Gd(III) chelates in development of nanoparticulate

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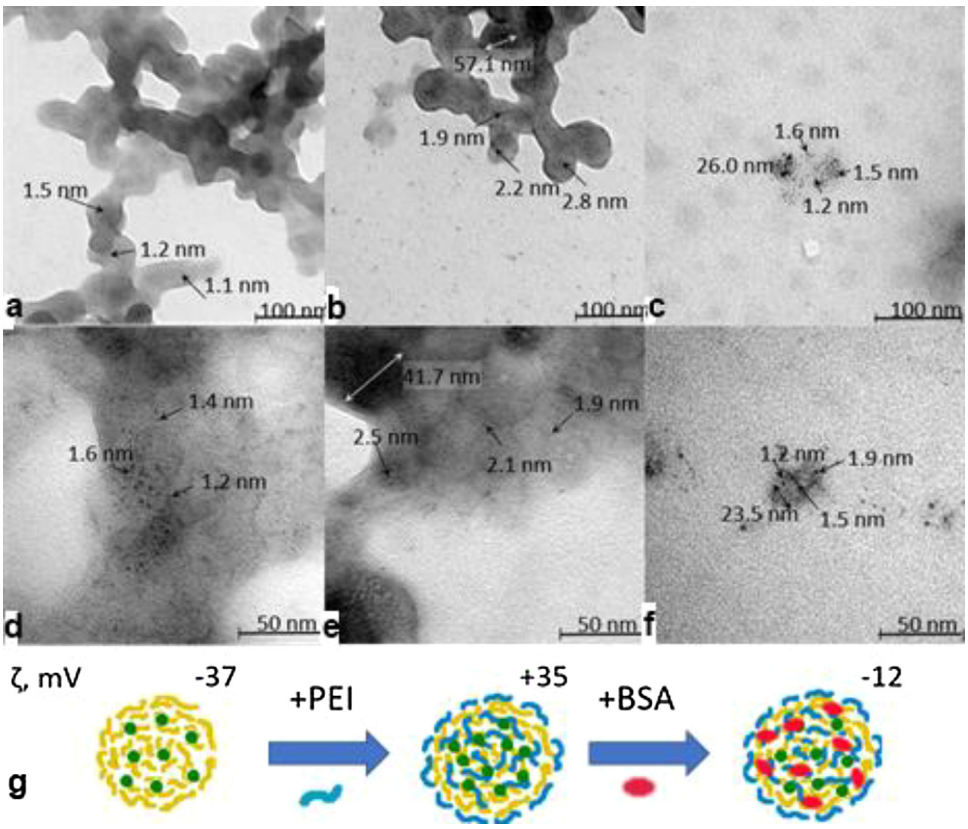

Fig. 1. TEM images of dried PSS- (a, d) and PEI-PSS- (b, c, e, f) [Ln_2L]-based colloids without (a, b, d, e) and at the presence of BSA (c, f; C_{BSA} = 0.9 g L^{-1}), where Ln = Tb (a–c), Gd (d–f). Schematic presentation of the [Ln_2L]-based colloids with different content of the hydrophilic coating (g).

CAs [22,23]. Our previous report represents facile one-pot synthesis of aqueous Gd(III)-based colloids with longitudinal and transverse relaxivity values (r_1 = 14.5 mM^{-1} s^{-1} and r_2 = 21.7 mM^{-1} s^{-1} at 1.43 T) [24] greater than those of the commercial mononuclear CAs [25]. The water insoluble Gd(III) complexes with macrocyclic tetra-1,3-diketones (Fig. S1) are highlighted as good basis for small (3–6 nm) hard cores, stabilized by polyelectrolytes. Nevertheless, the deeper insight into factors affecting the relaxivity values is required for their further improvement.

The present work is focused on a content of the multicomponent hydrophilic coating as a factor affecting the relaxivity of the aqueous Gd(III)-based colloids and reasons for the effect. The similar colloids based on Tb(III) counterparts are also studied in order to correlate luminescent and relaxivity responses with the type of multicomponent hydrophilic coating by using poly(sodium-4-styrenesulfonate) (PSS), polyethyleneimine (PEI) and bovine serum albumin (BSA) as the components. The relaxivity data at wide concentration range of the Gd(III)-colloids with different content of the multicomponent hydrophilic coating are analyzed in the correlation with dynamic light scattering (DLS) and small angle X-Ray scattering (SAXS) data with the aim to highlight the reasons for the hydrophilic coating effect on the relaxivity values. Interactions of the Gd(III)-colloids with blood proteins exemplified by bovine serum albumin is represented herein as a tool of the hydrophilic coating modification resulting in the higher relaxivity. The effect of the hydrophilic coating of the colloids on their ability to provide good positive contrast in T_1-weighted MRI at 1.5 T along with a cytotoxicity of the differently coated colloids are also introduced in the present work.

Table 1
DLS data of PSS (1.0 g L^{-1} in 0.5 M NaCl), BSA (0.9 g L^{-1}), PSS-, PEI-PSS- and PSS-PEI-PSS-Na[Ln_2**L**] colloids in aqueous and BSA solutions at 25 °C (C_{Ln} = 0.075 mM, Ln = Tb, Gd).

		$d_h \pm 10$, nm (PDI)		$\zeta \pm 2$, mV	
PSS (1.0 g L^{-1} in0.5 M NaCl)		505 ± 10 (0.59)		−16	
BSA (0.9 g L^{-1})		280 ± 50 (0.37)		−14.4	
Ln(III)		Tb(III)		Gd(III)	
Environment	Shell	$d_h \pm 10$, nm (PDI)	$\zeta \pm 2$, mV	$d_h \pm 10$, nm (PDI)	$\zeta \pm 2$, mV
Aqueous solution	–[a]	1170 (0.72)	+22	–	–
	PSS-	131 (0.17)	−37	137 (0.15)	−36
	PEI-PSS-	177 (0.14)	+35	188 (0.17)	+38
	PSS-PEI-PSS-	226 (0.15)	−37	226 (0.21)	−39
BSA solution (0.9 g L^{-1})	PSS-	139 (0.21)	−28	157 (0.18)	−29
	PEI-PSS-	206 (0.19)	−12	109 (0.24)	−13
	PSS-PEI-PSS-	236 (0.16)	−25	213 (0.17)	−28

[a] Aqueous colloids of [Tb_2**L**] with no polyelectrolyte coating.