Design of PLGA Based Nanoparticles for Imaging Guided Applications

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Supporting Information

ABSTRACT: An amphiphilic Gd(III) complex has been efficiently loaded in poly(lactic-co-glycolic acid) nanoparticles (PLGA-NPs) to yield a novel, high sensitive magnetic resonance imaging (MRI) contrast agent for imaging guided drug delivery applications. As the Gd(III) complex is soluble in organic solvents, the nanoparticles were prepared as oil/water emulsions. PLGA-NPs were stable, in buffer, for more than 1 week without any release of the incorporated agents. The millimolar relaxivity of the Gd(III) complex incorporated in the particles (140 nm diameter) was of 21.7 mM⁻¹ s⁻¹ at 21.5 MHz, a value that is about 5 times higher than that observed with the commercially available contrast agents used in clinic. The relaxometric efficiency of these particles resulted inversely proportional to the particle size measured by dynamic light scattering. The high stability and sensitivity of PLGA-NPs allowed their accumulation in vivo in murine melanoma xenograft as shown in the corresponding MR images. Once loaded with drug and contrast agents, PLGA nanoparticles can be proposed as efficient theranostic MRI agents.

KEYWORDS: poly(lactic-co-glycolic acid (PLGA) nanoparticles, MRI, Gd(III) complexes, imaging guided therapy, contrast agents

INTRODUCTION

Nanomedicine is the science and application of nanotechnology for diagnosis, monitoring, prevention, treatment, and understanding of disease to ultimately gain clinical benefit. One of the advantages on the use of nanoparticles is the possibility to generate imaging guided therapeutics whose biodistribution can be followed in real time after their in vivo administration. Furthermore, nanoparticles represent an important tool to improve the efficacy of drugs by increasing their bioavailability at the targeted area while decreasing undesired side effects compared to conventional drugs.1,2

Poly(lactic-co-glycolic acid) (PLGA) is one of the most widely used biodegradable polymers as it is able to form stable nanoparticles (PLGA-NPs) with a minimal systemic toxicity associated with their use for drug delivery or biomaterial applications.3 In fact, PLGA hydrolysis leads to lactic and glycolic acids, which are endogenous and easily metabolized molecules.4 PLGA is approved by the US FDA and European Medicine Agency (EMA) in several drug delivery systems for human use.5 The polymers are commercially available at different molecular weights and copolymer compositions. PLGA-NPs can be actively targeted to different epitopes expressed by the pathological tissue, by modifying the particle surface with proper ligands/vectors. Actively and passively targeted PLGA-NPs have been proposed as drug delivery systems for the treatment of a wide range of pathologies.6-9

Targeted delivery exploits tissue or cell specific phenotypic characteristics to accumulate an active agent at the desired location. Recently, actively and passively targeted PLGA-NPs have been proposed also for the delivery of magnetic resonance imaging (MRI) contrast agents for the detection of malignancies and for monitoring the effects of therapeutic agents.10-13 MRI offers a unique opportunity to obtain images characterized by superb anatomical resolution (0.1 × 0.1 mm) and simultaneously map function of soft tissues in vivo. The contrast agents that are routinely used in the clinical practice are mainly paramagnetic chelates of Gd(III) ions, which act by enhancing the longitudinal relaxation rate of water protons (1/T₁) in the tissues in which they are distributed. Moreover, the absence of radiation makes MRI safer than techniques based on the use of radioisotopes. However, MRI suffers from an intrinsic insensitivity with respect to the competing imaging modalities that has to be overcome by designing suitable amplification strategies based both on the development of Gd complexes endowed with a higher sensitivity and on the identification of efficient routes of accumulation of imaging reporters at the site of interest.14 In a MR image, there is a direct proportionality.
between the observed relaxation enhancement and the concentration of the paramagnetic MRI reporter. As far as it concerns cellular imaging, it has been shown that a given cell can be visualized when the number of Gd(III) complexes is on the order of \(1 \times 10^9\)–\(10^{10}\) per cell.\textsuperscript{15} In principle, PLGA-NPs can deliver a large payload of imaging agents to the site of interest that is sufficient to permit target cell MRI visualization. It has been recently reported that the use of commercially available hydrophobic contrast agents (i.e., Gd-DTPA, trade name Magnevist) entrapped in PLGA-NPs form a water-in-oil-in-oil (w/o/o) double emulsion.\textsuperscript{10,11} The disadvantage of the incorporation of these hydrophobic compounds is their fast release from the particle (few hours) with a consequent different biodistribution and clearance with respect to the intact particle. This is a crucial point in particular when target cells are located in tissues and not in the vascular system. In fact, nanoparticles of 100–200 nm size need many hours (up to 24 h) to extravasate in a sufficient concentration to obtain a detectable image contrast. Furthermore, the millimolar relaxivity and therefore sensitivity of these hydrophilic Gd complexes encapsulated inside PLGA-NP is relatively low and similar to that observed for the free complexes. In this study, an amphiphilic Gd based contrast agent (Scheme 1) has been

**Scheme 1. Schematic Representation of the Gd-DOTAMA Complex**

![Scheme 1](image)

entrapped in PLGA-NPs. The Gd complex is a DOTA- monoamide derivative (Gd-DOTAMA)\textsuperscript{16} functionalized with two steric chains that can form with PLGA an oil-in-water (o/w) emulsion. Gd-DOTAMA shows an extremely low solubility in water (<0.05 mg/mL). The highly hydrophobic steric chains are incorporated in the internal PLGA particle core, whereas the hydrophilic Gd coordination cage remains partly exposed on the external NP surface in direct contact with the aqueous solvent. The efficiency and stability of these Gd-loaded PLGA-NPs have been evaluated in buffer and in serum at 37 °C in the absence and in the presence of tumor cells that can catalyze the Gd complex release from the PLGA-NPs as a consequence of the membrane affinity for lipophilic compounds. The in vivo visualization of B16 melanoma xenografts has been finally evaluated by exploiting the passive tumor targeting ability of these nanoparticles (140 nm diameter).

**Experimental Section**

**Experimental Details.** Poly[(\(\alpha\)-lactide-co-glicolide) (PLGA)] 50:50 (Resomer RG 502 H), average molecular weight (Mw) 8650 Da, based on polystyrene was manufactured by Boehringer Ingelheim PharmaKG, Ingelheim (Germany). Poly(vinyl alcohol), Mw 31000–50000 Da (98–99% hydrolyzed) was provided by Sigma Chemical Co. DSPE-PEG(2000) \{1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-methoxy(polyethylene glycol)-2000\} ammonium salt was purchased from Avanti Polar Lipids. Gd-HPDOSA (Prohanse) was kindly provided by Bracco S.p.A. The lipophilic Gd-DOTAMA was synthesized according to a previously reported procedure.\textsuperscript{16}

**Synthesis of Microspheres and Nanospheres.** Microspheres and nanospheres were obtained using an oil-in-water emulsion solvent extraction method. For microspheres, the emulsion was prepared dissolving 320 mg of PLGA, 6 mg of DSPE-PEG(2000)methoxy, and 6 mg of Gd-DOTAMA in 1 mL of chloroform; this solution was called phase 1. Phase 2 consisted of 2% w/v PVA aqueous solution (8 mL). Phase 1 was added into phase 2 drop by drop, while phase 2 was being stirred at 10 000 rpm (Ika T-25 Ultra-Turrax Digital Homogenizer with an Ika Dispersing Tool S2SN-18G, Cole Parmer, Germany). After 10 min of homogenization, 10 mL of 0.5% w/v PVA aqueous solution was added to the emulsion and stirred at 8000 rpm for 10 min. The final emulsion was transferred to a 50 mL round-bottom flask and put into a rotary evaporator (at 740 mmHg and 30 rpm) for 150 min to remove the organic solvent. Gd-DOTAMA residual was removed by dialysis (molecular weight cutoff of 14 000 Da) carried out at 4 °C against water. The microspheres were centrifuged at 250 rpm, washed three times with 10 mL of water, and lyophilized for 24 h.

A sonication method was used for nanoparticles synthesis. PLGA (phase 1) and PVA (phase 2) concentrations, sonication power, and time were varied to control the nanoparticles sizes (see Table 1). As well as microspheres, PLGA, Gd-DOTAMA, and DSPE-PEG (2000)methoxy were dissolved in phase 1 (0.5 mL of chloroform). PVA aqueous solution formed phase 2 (3 mL). Phase 1 was added in phase 2 and sonicated according to conditions detailed in Table 1. Immediately, the emulsion was put into a rotary evaporator at the same conditions for microspheres to remove organic solvent. Nonentrapped Gd-DOTAMA was removed by dialysis (molecular weight cutoff of 14 000 Da) carried out at 4 °C against an isotonic NaCl/Hepes buffer (HBS). The excess of PVA was removed by washing the emulsion with vivaspin filters (Sartorius) (cutoff of 1 x 10\(^6\) Da) or by centrifugation. The amount of Gd-DOTAMA entrapped in PLGA-NP was determined by \(^1\)H nuclear magnetic resonance \(T_1\) measurement, at 21.5 MHz and 25 °C (Stellar Spinmaster, Mede, Italy), of the mineralized complex solution (in 6 mol/L HCl at 120 °C for 16 h). The hydrated mean diameter of PLGA-NPs was determined using a dynamic light scattering (DLS) Malvern Zetasizer 3000HS (Malvern, U.K.) All samples were analyzed at 25 °C in filtered (cutoff, 200 nm) HBS buffer (pH 7.4). Nanoparticles and microparticles were stored under dark at –20 °C until further analysis.

**Proton Nuclear Magnetic Relaxation Dispersion (NMRD) 1/T\(_1\) Profiles.** Data were measured at 25 °C over a continuum of magnetic field strengths from 0.00024 to 0.47 T.
(corresponding to 0.01–20 MHz proton Larmor Frequency) on a Stelar field-cycling relaxometer (Stelar, Mede, Italy), under complete computer control with an absolute uncertainty of 1%. Data points from 0.5 T (21.5 MHz) to 1.7 T (70 MHz) were collected on a Spinnmaster spectrometer (Stelar, Mede, Italy) working at variable field.

**Stability Test.** To perform the stability test, PLGA-NPs were diluted in HBS buffer and left at 37 °C, stirring, up to 15 days. The longitudinal water proton relaxation rate (1/T₁) of each PLGA-NP sample was monitored on a relaxometer operating at 21.5 MHz and 25 °C.

**Cell Lines.** Mouse melanoma (B16-F10) cell lines were purchased from the American Type Culture Corporation. B16-F10 cells were obtained by growing cells in a DMEM (Lonza) medium containing 4 mM glucose, 4500 mg/L glucose, 1 mM sodium pyruvate and supplemented with 10% (v/v) fetal bovine serum (FBS), 100 U/mL of penicillin, and 100 U/mL of streptomycin. Cells were incubated at 37 °C, 95% humidified atmosphere of 5% CO₂.

**Uptake Experiments.** For the in vitro uptake experiments, about 2.5 × 10⁶ B16-F10 were seeded in 6 cm diameter dishes. The day after, the cells were incubated for 24 h at 37 °C in the presence of PLGA-NPs at 50 μM Gd concentration. At the end of the incubation, the cells were washed three times with 5 mL of ice-cold PBS, detached with trypsin/EDTA, and transferred into falcon tubes. Cell samples were sonicated at 30% of power for 30 s in ice, and their protein concentrations were determined by a commercial Bradford assay (Biorad, Hercules, CA, USA). Sample digestion was performed with concentrated HNO₃ (70%, 1 mL) under microwave heating (Milestone MicroSYNTH Microwave labstation). The Gd content in the cell samples was determined by using inductively coupled plasma mass spectrometry (ICP-MS; element-2; Thermo-Finnigan, Rodano (MI), Italy).

**Experimental Mice and Induction of Transplantable Tumors.** Adult C57BL/6 mice were maintained in specific pathogen free conditions at both the animal facilities of the Department of Molecular Biotechnology and Health Sciences of the University of Turin, Italy, and at Charles River Laboratories (Calco, Italy). Handling and all manipulations have been approved by the Ethical Committee of the University of Turin. B16-F10 cells were cultured as described above and tumors were generated by subcutaneous injection in the mouse flank of 1 × 10⁶ cells in 0.2 mL of PBS. One week after B16 cell injection, mice developed solid tumors of 40–60 mm³ volume.

**MRI.** The MR images of 5 mm glass tubes containing PLGA-NP and Gd-HDPO3A (1) and in vivo MR images (2) were acquired at T1 with an Aspect M2-High Performance MRI System (Aspect Magnet Technologies Ltd., Netanya, Israel) consisting of a NdFeB magnet, equipped with a 35 mm solenoid T/R coil of inner diameter 35 mm. This system is equipped with fast gradient coils (gradient strength, 450 mT m⁻¹ at 60 A; ramp time, 250 μs at 160 V) with a field homogeneity of 0.2–0.5 gauss. (1) The MR image of glass tubes containing 0.4 mL of 140 nm PLGA-NPs and Gd-HDPO3A at different Gd concentrations (10–90 μM) was performed by using a T1-weighted protocol (TR/TE/NEX = 200:13:12; FOV = 3.5 cm). (2) Animals were anesthetized before MRI examination by injecting tiletamine/zolazepam (20 mg/kg; Zoletil 100, Virbac, Milan, Italy) and xylazine (5 mg/kg; Rompun, Bayer, Milan, Italy). For this study, a group of 4 mice (female) and one of 3 mice (female) were treated with PLGA-NPs (140 nm) and Gd-HDDO3A, respectively. Each mouse received in the tail vein a contrast agent dose corresponding to 33 μmol Gd/kg. MR images were acquired before and at 5, 24, and 48 h after contrast administration by using a T₁-weighted protocol (TR/TE/NEX = 250:8:10; FOV = 3.5 cm). The mean signal intensity (SI) values were calculated in the regions of interest (ROI) manually drawn on the whole tumor, on the muscle, liver, spleen, and kidneys. The mean measured SI was normalized by using a standard solution of Gd in 1% HNO₃. The mean SI enhancement (%) of target tissues (TT) was calculated according to the following equation: SI % enhancement = ((mean SI (TT) postcontrast − mean SI (TT) precontrast)/mean SI (TT) precontrast) × 100.

### RESULTS AND DISCUSSION

The selected methodology to obtain PLGA-NP was an o/w emulsion solvent extraction method. The organic phase was prepared dissolving PLGA RG 502H, Gd-DOTAMA, and pegylated phospholipid (DSPE-PEG(2000) methoxy) in chloroform. The water phase was a poly(vinyl alcohol) (PVA) aqueous solution. PVA is the most commonly used emulsifier for the preparation of PLGA-NPs because it yields particles that are relatively uniform, small sized, and easy to be redispersed in water. To obtain nanoparticles of 140 and 550 nm, the organic phase was added to the aqueous phase, while the mix was being sonicated. To control the size of the nanospheres, different PVA concentrations and sonication conditions have been used. To synthesize particles of 2000 nm, a homogenizer was used to obtain the o/w emulsion. In all cases the solidification of nanospheres was carried out by organic solvent evaporation from the o/w emulsion. Organic solvent was separated in a rotary evaporator under vacuum in 2.5 h. The Gd-DOTAMA encapsulation yields in PLGA-NPs were of 77%, 85%, and 48% for 140, 550, and 2000 nm particles, respectively. The nanospheres were stored in the dark at −20 °C before their use. The average hydrodynamic diameters of PLGA-NP have been obtained by dynamic light scattering (DLS) measurements, and they are reported in Table 2. DLS profiles are reported as Supporting Information (Figure S1). The millimolar relaxivity (21.5 MHz, 25 °C) of Gd complexes incorporated in the PLGA-NP with different sizes are reported in Table 2. Interestingly, the millimolar relaxivities are inversely proportional to the particle size measured by dynamic light scattering. This is in agreement with the PLGA-NP chemico-physical analysis reported by Choi and co-workers showing that the polymer–solvent interaction is inversely proportional to the particle size. The lower relaxivity measured in the largest particles is the consequence of the lower amount of Gd complexes exposed to the external surface with respect the total Gd loaded in the nanoparticle.

### Table 2. Hydrodynamic Particle Diameter Measured by DLS at 25 °C in HBS Buffer, Polydispersity Index (PDI), and Millimolar Relaxivities (mM⁻¹ s⁻¹) of PLGA-NPs

<table>
<thead>
<tr>
<th>particle diameter (nm)</th>
<th>polydispersity index measured by DLS</th>
<th>relaxivity (mM⁻¹ s⁻¹) at 21.5 MHz and 25 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>140 ± 5</td>
<td>0.106</td>
<td>21.7</td>
</tr>
<tr>
<td>550 ± 40</td>
<td>0.482</td>
<td>5.3</td>
</tr>
<tr>
<td>2000 ± 90</td>
<td>0.413</td>
<td>0.27</td>
</tr>
</tbody>
</table>
In the particles with a 2 μm diameter, most of the complexes are distributed in the internal hydrophobic core of the particle and can not interact with the solvent water molecules. In fact, the dipolar interaction between the paramagnetic ion and water protons is the basic requirement to induce a significant increase of water proton relaxation rate.

By decreasing the particle size, the relaxation rate of the solvent water protons increases exponentially as a consequence of the increased solvent contact surface of the smaller particles. This observation was confirmed by analyzing nuclear magnetic resonance dispersion (NMRD) profiles (Figure 1) that show a relaxivity hump at about 30 MHz, typical of slowly moving systems. The relaxivity enhancement of the surface exposed complexes observed, with respect to the free complex, is quite high (more than three times) also if it is partially quenched by the relatively long exchange time τM of the water directly coordinated to the metal ion (inner sphere water) as previously shown for several Gd complexes of DOTA-monoamide ligands. The relaxation enhancement is the consequence of the strong interaction of the lipophilic chains of the Gd complexes with the hydrophobic PLGA polymer that causes a strong reduction of the reorientational time of the paramagnetic complex. This was not observed in the case of hydrophilic Gd complexes already reported in the literature because they are usually a very low concentration.

The capacity to enhance the efficiency of Gd-loaded PLGA-NPs with respect to a standard clinically used contrast agent (Gd-HPDO3A commercial name prohance) has been carried out by acquiring MR images at 1 T (Figure 3). The capillaries contain the same Gd concentration of the two contrast agents in a range from 10 to 90 μM. The highest sensitivity of the Gd-DOTAMA stably incorporated in the PLGA-NPs permits to obtain a well detectable signal intensity enhancement also in the specimen containing the lower Gd concentration (10 μM). High sensitivity is a primary imaging probe property in particular for molecular imaging applications where target receptors to be visualized and detected have usually a very low concentration.

PLGA-NPs were coated with a pegylated phospholipid in order to reduce (i) the in vivo macrophage uptake that causes a too-fast elimination by the bloodstream and (ii) the interactions with cell surface that can cause nonspecific PLGA-NP distribution. The presence of PEG chains on the particle surface creates a hydrophilic protective layer around the nanoparticles that is able to avoid the absorption of opsonin proteins via steric repulsion forces, thereby blocking and delaying the first step in the opsonization process. PEG modification reduces serum-dependent phagocytosis, mainly by inhibiting IgG adsorption and complement activation on nanoparticles surfaces resulting in a marked increase in the blood circulation half-life of the particles. The absence of the nonspecific binding to the cell surface was checked by incubating mouse melanoma B16-F10 cells for 24 h at 37 °C in the presence of PLGA-NP of 140 nm (50 μM in Gd). The amount of cell-associated Gd, measured by ICP/MS after washing with PBS, was <6 × 10⁻¹¹ Gd mol/mg protein. Such a

![Figure 1](image1.png)  
**Figure 1.** Profiles of 1/T1, 1H-NMRD (pH 7.4, 25 °C) of PLGA-NPs with different diameters measured by DLS: 2 μm ( ), 550 nm ( ), and 140 nm ( ).

![Figure 2](image2.png)  
**Figure 2.** PLGA-NP stabilities in HBS (PLGA-NP 2000 nm ( ), 550 nm ( ), and 140 nm ( )).
low value appears consistent with the macropinocytosis activity of cells, and it is significantly lower than the minimum Gd amount necessary for cell visualization.

Next, Gd-loaded PLGA-NPs were tested on mouse models bearing a tumor xenograft obtained by subcutaneous injection of ca. 1 million B16-F10 melanoma cells. After 8–10 days, the tumor volume was between 40 and 60 mm$^3$. Pegylated PLGA-NPs were able to accumulate in solid tumors as a consequence of microvascular permeability increase (EPR effect) and defective lymphatic drainage. The extent of passive extravasation is directly dependent on the prolonged residence time of the particles in the bloodstream.

PLGA-NP biodistribution (Figure 4A,C), measured by MRI, showed that, 5 h after the injection (33 μmol Gd/kg dose), the highest nanoparticle amount was localized in the spleen, whereas 24 h after, signal intensity (SI) enhancements (40–50%) measured in the tumor, liver, and spleen were similar. The %SI enhancement recorded on mice treated with Gd-HPDO3A (as control) at the same Gd dose (Figure 4B,D) was markedly lower in tumor and in other organs. Figure 5 shows the corresponding MR images of the tumor region (abdominal) recorded before and 24 h after the PLGA-NP (A,B) and Gd-HPDO3A (C,D) injection, respectively.

The amount of the Gd delivered by PLGA-NPs to the tumor is high enough to be detected in the $T_1$-weighted spin–echo

Table 3. PLGA-NP Diameter (nm) Measured by DLS at 25°C in HBS and in Human Serum

<table>
<thead>
<tr>
<th>particle size</th>
<th>time = 0 days</th>
<th>time = 14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBS SERUM</td>
<td>HBS SERUM</td>
</tr>
<tr>
<td></td>
<td>diameter (nm)</td>
<td>% PDI</td>
</tr>
<tr>
<td>140</td>
<td>140 ± 5</td>
<td>100</td>
</tr>
<tr>
<td>550</td>
<td>550 ± 40</td>
<td>100</td>
</tr>
<tr>
<td>2000</td>
<td>2000 ± 90</td>
<td>100</td>
</tr>
<tr>
<td>138 ± 7</td>
<td>100</td>
<td>0.234</td>
</tr>
<tr>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>257 ± 166</td>
<td>27</td>
<td>0.833</td>
</tr>
</tbody>
</table>

Figure 3. MRI at 1 T of 5 mm glass tubes containing solutions of PLGA-NPd (140 nm) and GdHPDO3A at the same micromolar concentrations 90 (A,E), 50 (B,F), 20 (C,G), and 10 (D,H).

Figure 4. MRI percentage signal intensity enhancement measured on the regions of interest, which were manually drawn on different organs (tumor, muscle, liver, spleen, and cortical regions of kidneys) 5 and 24 h after the injection of PLGA-NPs (140 nm) (A,C) and Gd-HPDO3A (B,D) at a Gd dose of 0.033 mmol/kg. Error bars indicate standard deviation of the means.

Figure 5. Results of MRI of a mouse treated with PLGA-NPs (140 nm) (A,B) and Gd-HPDO3A (C,D) injection, respectively.

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image, and it can be exploited to follow the biodistribution of the nanoparticle. This is an important characteristic of the PLGA-NP that can be proposed as a highly sensitive MRI theranostic agent for monitoring, in real time, the accumulation at the target site when coloaded with a hydrophobic antitumor drug dissolved in the organic phase of the PLGA emulsion. The high spatial resolution of MRI allows to detect with higher spatial precision the local drug concentration at the pathological site with respect to techniques based on the use of radiolabeled compounds and once the stoichiometric ratio between drug and Gd-complex is known. Furthermore, PLGA-NPs with a diameter >500 nm can be proposed to monitor drug release because, as shown in Figure 2, their relaxivity is dependent on particle degradation.

Forty-eight hours after the administration, the tumor SI enhancement decreases at about 20% as a consequence of the particle clearance from the tumor environment by the bloodstream.

CONCLUSIONS

PLGA-NPs can efficiently be loaded with Gd-DOTAMA complexes. The formed adducts appear quite stable and are characterized by a marked relaxation enhancement with respect to the previously reported PLGA-NPs loaded with Gd-DTPA. The size of the NPs can be suitably modulated, and in the case of systems with a diameter of 140 nm, they proved to work well in the visualization of mice bearing tumor models.

ASSOCIATED CONTENT

Supporting Information

Figure S1 shows DLS profiles of PLGA-NPs in HBS buffer at day 0. Figure S2 shows DLS profiles of PLGA-NPs in serum at day 14. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES


