Aluminium hydroxide stabilised MnFe$_2$O$_4$ and Fe$_3$O$_4$ nanoparticles as dual-modality contrasts agent for MRI and PET imaging

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1. Introduction

Superparamagnetic nanoparticles (NPs) have been intensively investigated due to their potential applications in biosensors [1–3], targeted drug delivery [4–7], MRI [8,9] and localised hyperthermia induction [10,11]. An obstacle to application of these NPs is that they tend to aggregate and form larger secondary particles, in order to minimise their surface energy. Moreover, magnetic NPs are most often synthesised in organic solvents and coated with an inorganic shell material that introduces stability, functionality and biocompatibility. In biological environments, many methods have been developed to obtain stable colloids of magnetic NPs, reviewed by Laurent et al. [12]. Amongst them, coating with polyethylene glycol (PEG) [8] or Dextran [13] has been widely used, as these hydrophilic and biocompatible materials not only provide a steric barrier against aggregation, but also make them hardly recognised by the macrophage-monocytic system [14]. To avoid desorption of the polymeric coating by heating or dilution, one or more functional groups, such as carbonate or phosphonate, are necessary to bind with the NPs. Such polymers, however, involve a complicated multi-step synthesis approach [8,15]. Therefore the use of an inorganic shell material that introduces stability, functionality and water-solubility is desirable.

Herein, we report a simple approach to stabilise magnetic NPs by coating them with an Al(OH)$_3$ layer. The aluminium hydroxide layer of oleyamine or oleic acid rendering them soluble only in non-polar solvents. On the other hand, medical or bio-applications require colloidal stability and dispersibility in water and biological environments. Many methods have been developed to obtain stable colloids of magnetic NPs, reviewed by Laurent et al. [12]. Amongst them, coating with polyethylene glycol (PEG) [8] or Dextran [13] has been widely used, as these hydrophilic and biocompatible materials not only provide a steric barrier against aggregation, but also make them hardly recognised by the macrophage-monocytic system [14]. To avoid desorption of the polymeric coating by heating or dilution, one or more functional groups, such as carbonate or phosphonate, are necessary to bind with the NPs. Such polymers, however, involve a complicated multi-step synthesis approach [8,15]. Therefore the use of an inorganic shell material that introduces stability, functionality and water-solubility is desirable.

Herein, we report a simple approach to stabilise magnetic NPs by coating them with an Al(OH)$_3$ layer. The aluminium hydroxide
coating was selected, due to its high affinity with fluoride anions [16] and bisphosphonate groups [17], which allow easy radio- labelling and functionalisation, and its biocompatibility as shown by its application in vaccine adjuvants [18].

2. Experimental section

2.1. Materials and general characterisation

All chemicals were used as purchased without further purification. Deionised water was obtained from an ELGA Purelab Option Q system. Bisphosphonate poly- methylenglycol (BP-PEG) polymers were synthesised in house according to published methods [9]. X-Ray powder diffraction (XRD) measurements were recorded at room temperature on a PANalytical X’Pert PRO diffractometer using Cu Kα radiation (λ = 1.540598 Å) at 40 kV, 40 mA, a scan speed of 0.02°/s and a step size of 0.02° in 2θ, at Nottingham University. X-Ray photoelectron spectra were recorded using a Thermo Fisher ESCALAB 250 X-ray Photoelectron Spectrometer with a hemispher- ical sector energy analyser at Aston University. Monochromatic Al Kα X-ray source was used at excitation energy of 15 kV and an emission current of 6 mA. The analyser pass energy of 20 eV with step size of 0.1 eV was used throughout the experiment. Transmission electron microscope (TEM) images were taken on a Tecnai FEI T20 at Centre for Ultrastructural Imaging, King’s College London. Attenuated total reflectance infrared (ATR-IR or IR) spectra were recorded on a Perkin Elmer spectrum 100. Dynamic light scattering (DLS) experiments were carried out on Zetasizer Nano ZS from Malvern Instruments with a measure angle 175° and a 632.8 nm laser. Zeta potential for all samples was measured in neutral aqueous solution with a pH value = 7.

2.2. Synthesis

2.2.1. Synthesis of MnFe2O4 and Fe3O4

Magnetic NPs were obtained via a method reported previously [19,20]. Typically, 6 mmol 1,2-hexadecanediol was added to a 100 ml flask containing 20 ml phenyl ether, 5 ml oleic acid and 5 ml oleic acid at 120 °C, and the resultant solution was kept at this temperature under vacuum for over 30 min to remove water in the solvent. To this light yellow solution, 1 mmol Mn(acac)2 and 2 mmol Fe(acac)3 (or 2 mmol Fe(acac)3 for Fe3O4) was added under N2, and then temperature was increased to 270 °C at a rate of 10 °C/min with magnetic stirring. After 30 min, the flask was cooled to room temperature by removal from the hotplate. To precipitate out the NPs, 40 ml ethanol was added. The particles were collected by centrifugation (Jouan CR312, at a speed of 3000 rpm for 30 min) and washed with ethanol/hexane twice.

2.2.2. Synthesis of MnFe2O4@Al(OH)3 (1)

MnFe2O4 (80 mg, 0.33 mmol) was dissolved in 30 ml diethyl ether by sonication for 20 min to form a dark brown solution, and then 10 ml of a diethyl ether solution containing AlCl3 (144 mg, 1 mmol) was added dropwise. The mixture was sonicated for 2 min before the addition of 500 μl water (27.8 mmol). The subsequent addition of 10 ml acetone led to a brown suspension. The product was collected by centri- fugation and then dried in a stream of N2 to remove ether and acetone, and re-dispersed in water.

2.2.3. Synthesis of Fe3O4@Al(OH)3 samples (2–4)

In the case of Fe3O4@Al(OH)3 (with a precursor molar ratio of Fe3O4 to AlCl3 of 1:3) (4), a faster uncontrolled hydrolysis method was used. Fe3O4 (82 mg, 0.33 mmol) was dissolved in 30 ml diethyl ether after sonication for 20 min to form a dark brown solution, and then 10 ml diethyl ether solution containing AlCl3 (144 mg, 1 mmol) was added dropwise. The mixture was sonicated for 2 min before the addition of 10 ml acetone leading to a brown suspension. The product was collected by centrifugation and then dried with a stream of N2 to remove ether and acetone, and re-dispersed in water.

2.2.4. Filtration of MnFe2O4@Al(OH)3 (M = Mn or Fe)

The Al(OH)3@MnFe2O4 solution prepared as described in Section 2.2.2 (200 μl) was diluted with water (1 ml) to form a transparent brown solution, and then transferred to a 1 ml centrifuge tube with a filter inside (Nanosep, cut-off-molecular size, 30 K). Brown NPs were obtained on the filter by centrifugation at 5000 rpm for 20 min.

2.2.5. Preparation of Fe3O4@Al(OH)3–BP-PEG(5K)

Bisphosphonate polyethylenglycol (prepared as described elsewhere [8]) (5 mg) was added to the aqueous solution of Fe3O4@Al(OH)3 (5 ml, ca. 4 mg/ml), followed by a sonication treatment for 10 min.

2.3. Radio labelling with 18F and radiochemical stability in water

18F labelling of MnFe2O4@Al(OH)3 (M = Mn, or Fe, 1–4) was measured in triplicate at different concentrations. Typically, 50 μl aqueous [18F]fluoride solution containing ca. 5 MBq radioactivity was added to a 450 μl solution of varying concentrations of MnFe2O4@Al(OH)3 in NanoSep with a cutoff size of 30K. After 10 min incubation with continuous shaking at room temperature, labelled NPs were sepa- rated from the supernatant and particles by centrifugation (Eppendorf centrifuge 5424) for 20 min. The radioactivity of the supernatant and particles (on the filter) was measured separately using a gamma counter. The labelling efficiency was given by the following equation (1):

\[
\text{Labelling efficiency (}%) = \frac{\text{Activity of NPs}}{\text{Activity of NPs} \times \text{Activity of supernatant}} \times 100 \%
\]

Triplet samples of 18F labelled NPs were separated as described above. The NPs retained on the filter were re-suspended in deionised water in the inner NanoSep tube and then centrifuged at 5000 rpm for 20 min. This step was repeated three times. The percent binding retained after each washing step was calculated using equation (1). The correction for cumulative loss of label for the second and third washing steps was performed as exemplified by the following equation (2):

\[
\text{Cumulative Binding} = \frac{\text{Activity in NPs} \times \text{Activity in NPs prewash}}{\text{Activity in NPs} \times \text{Activity in NPs prewash}}
\]

2.4. Radiochemical stability of 18F-labelled 1, 2, 3, 4 in serum

Triplet samples of labelled NPs were prepared on a NanoSep membrane as described above. The NPs retained in the filtrate were re-suspended in 25% serum in water (v/v), incubated at 37 °C for a period of up to 6 h, and then centrifuged at 10,000 rpm (Eppendorf centrifuge 5424) for 30 min. The cumulative binding was calculated using equation (2) as described previously.

2.5. Adsorption of non-radioactive 18F

5 mg NP I was dissolved in 5 ml freshly prepared NaF solution with concen- trations of 0.01 mmol/L, 0.1 mmol/L, 1 mmol/L and 10 mmol/L. The suspensions of NPs were sonicated with the laboratory sonicator bath for 1 h, and then left over- night. The samples were centrifuged for 30 min at 3000 rpm (Jouan CR312) and 4 ml of supernatant was then withdrawn from each sample. The concentrations of fluoride anions in supernatant and corresponding particle-free NaF solution were measured with an Orion Star 214 bench-top meter with a fluoride combination electrode (from Fisher Scientific). Duplicate samples were prepared for each concen- tration. Adsorption percentage was obtained by dividing the concentration differ- ence between the supernatant and the initial particle-free solution by the initial concentration.

2.6. [18F]fluoride radiolabelling of washed Fe3O4@Al(OH)3 samples

500 μl of 1.34 mg/ml suspension of 2 in water (or 2 mg/ml 3 NPs, or 2.35 mg/ml 4 NPs) was placed in a NanoSep tube with omega membrane (molecular weight cutoff, 30 KDA). The tubes were centrifuged at 5000 rpm (Eppendorf centrifuge 5424) for 20 min, and then these NPs were re-dissolved in 450 ml water. 50 μl [18F]fluoride (ca. 5 MBq) was added to these NPs solutions in the NanoSep tubes. After 10 min incubation by continuous shaking at room temperature, the tubes were centrifuged at 5000 rpm for 20 min. As described before, the activities in the filtrate and remaining on NPs (on the filter) were separately measured with a gamma counter, to produce a labelling efficiency for the 1st washed Fe3O4@Al(OH)3. Samples to measure the labelling efficiency for 2nd washed NPs, the washing step was repeat twice before incubation with [18F]fluoride radioactivity.

2.7. Radiolabelling of 1 with 64Cu

1 mg bis(dithiocarbamate) bisphosphonate (DCTCPB) [15] was dissolved in 100 mM Na2CO3 buffer (pH 9). 200 μl of the above solution was added to 200 μl 64CuCl2 radioactivity (ca. 20 MBq) solution that was buffered to pH 5 with sodium acetate. It is essential to maintain the solution at neutral pH, since Al(OH)3 is not stable either in acidic or in basic solution. After 5 min, 200 μl 0.5 mg/ml MnFe2O4@Al(OH)3 solution containing 0.2 mg/ml PEG-5K was added and the mixture was incubated at room temperature for another 5 min. The radiolabelled NPs were isolated by filter centrifugation at speed of 5000 rpm for 15 min, using a NanoSep with a cutoff size of 30 K. There was no radioactivity observed in the filtrate, and all radioactivity remained on the NPs in the filter. The 64Cu radiolabelled NPs were re-dissolved in 100 μl saline for injection.

2.8. T1, T2 and T2′ relaxation measurement

MR imaging of all particles was performed with a standard extremity flex coil on a clinical 3T Philips Achieva MRI scanner (Philips Healthcare, Best, The Netherlands). T1 mapping was obtained by a 2D sequence that employed two non-selective inversion pulses with inversion times ranging from 20 to 2000 ms, followed by eight segmented readouts for eight individual images [21]. The two imaging trains resulted in a set of 16 images per slice with increasing inversion times (FOV = 200*200 mm, matrix = 200*179 mm, in-plane resolution = 1.12 mm, measured slice thickness = 3 mm, slices = 46, TR/TE = 3.2/1.6 ms, FA = 10°). T2 was
determined with a 2D multi-spin-echo sequence (FOV = 200 × 200 mm, matrix = 200 × 200, measured slice thickness = 3 mm, ETL = 5, TE = 10 ms, TR = 725 ms, FA = 90°). The acquired imaging data were transferred to a computer running Matlab and analysed using an in-house Matlab tool to receive the relaxation times $T_1$ and $T_2$ for each NP concentration (in terms of [Fe] or [Fe] + [Mn]). Excel was used to plot the relaxation rates against concentration and the relaxivity (i.e. gradient of linear fit) determined from a least squares fit.

2.9. In vivo PET/MR imaging

A 6–7 weeks old female C57 black mouse with a weight of 20–21 g was used. Animal experiments were carried out at the Nanobiotechnology & In Vivo Imaging Center, Semmelweis University in Hungary, with permission from the local institutional animal ethics committee and in compliance with the relevant European Union and Hungarian regulations. PET/MRI images were recorded on a nanoScan (r) integrated PET/MRI system (Mediso, Budapest, Hungary), in which the MR is a preclinical 1T MRI scanner (M2, Aspect Imaging) with horizontal bore magnet, solenoid coil (diameter of 35 mm) and 450 mT/m gradients. Mice were anaesthetised with isoflurane and placed in prone position on the MRI bed. After the pre-contrast MR scan, 85 μl 18F-labelled (as described above, Section 2.3) NPs solution in saline containing 0.95 MBq fluoride radioactivity and ca. 60 μg Fe was injected via the tail vein. PET scanning was commenced immediately after injection of NPs using a NanoPET/CT scanner from Mediso, with PET acquisition time 120 min with a coincidence mode 1–5 and energy window 400–600 keV. CT scans were performed immediately after PET. Adjoint Monte Carlo was used for reconstruction, while the detector model and the number of iterations/subsets were LOR filter and 5/6, respectively.

3. Results and discussion

Typically, MnFe$_2$O$_4$@Al(OH)$_3$ NPs (1) were obtained by adding a diethyl ether (Et$_2$O) solution of AlCl$_3$ to a Et$_2$O solution of MnFe$_2$O$_4$ NPs, at the selected mole ratios, whilst stirring. After 10 min, the black mixture was treated with water (500 μl) to induce controlled hydrolysis and stirred for a further hour. The particles were precipitated out by the addition of 10 ml acetone, and then isolated by centrifugal filtration, washed with ethanol and re-dispersed in water. Fe$_3$O$_4$@Al(OH)$_3$ samples with different Fe:Al ratios (2–4)
were obtained via a quick hydrolysis process, where no water was added prior to the addition of acetone and AlCl₃ was hydrolysed rapidly when the NPs were dispersed in water, rather than by addition of a small amount of water in Et₂O. Two weak peaks around 21°/C₁₄ in the XRD pattern appeared after coating and were associated with the nordstrandite phase of Al(OH)₃ (Fig. 1a) [22].

The infrared spectrum of all Al(OH)₃ coated samples showed the disappearance of adsorption peaks of CeH at 2845 cm⁻¹ and 2950 cm⁻¹ after coating with Al(OH)₃, confirming that oleylamine had been removed, and the appearance of three absorption peaks at 842 cm⁻¹ and 1645 cm⁻¹ and a broad band from 3000 to 3500 cm⁻¹, corresponding respectively to the Al=O stretching [23], the deformation vibration of water, and O=H stretching mode (Fig. S1). Nanoparticulate MnFe₂O₄ is soluble in hexane but insoluble in water due to the organic layer (oleylamine and oleic acid) on the surface. Once coated with Al(OH)₃, the NPs become soluble in water but insoluble in hexane (Fig. 1b). All these features suggest a coating of Al(OH)₃ replacing the oleylamine on the iron oxide NPs. Transmission electron microscopy (TEM), however, revealed no obvious difference size or morphology before and after coating with Al(OH)₃ (Fig. 1c–d, Fig. S2). This could be attributed to the poorly crystalline and low-density nature of shell, indicated by the weak and broad diffraction peak on XRD pattern in Fig. 1a and Fig. S3.

X-Ray photoelectron spectroscopy (XPS) spectrum and inductively coupled plasma mass spectrometry (ICP-MS) both indicated that the content of Al in the shell increased with increasing ratios of AlCl₃ to magnetic NPs (Table S1, Figs. S4 and S5). NPs with insufficient Al(OH)₃, for example 2 tended to aggregate strongly in water, as indicated by TEM images (Fig. S2) and exhibited large hydrodynamic size (hydrodynamic diameter, Dₜ) up to 400 nm as measured by dynamic light scattering (DLS) experiments (Table S2). This suggested the important role of Al(OH)₃ in stabilising iron oxide NPs in water by converting the hydrophobic surface of oleylamine-coated Fe₃O₄ NPs into a hydrophilic surface, as well as offering a highly positive surface potential to protect them from aggregation. DLS experiments confirmed that NPs 3 exhibited a highly positive zeta potential up to +70 mV, and a small Dₜ of 21 nm, reduced from 43.8 nm for Fe₃O₄ in hexane (as measured by DLS). These coated NPs were stable in water with no obvious changes in Dₜ for over 12 months.

Another benefit of the Al(OH)₃ coating is its high affinity to fluoride ions and bisphosphonate groups [16,17], which allows a simple and easy approach for radiolabelling with [¹⁸F]-fluoride or metallic radionuclides conjugated with bisphosphonate. Indeed, a nearly 100% labelling efficiency (LE) was achieved by simply mixing a solution of NPs 1 with radioactive ⁶⁴Cu(DTCBP)₂ solution (Fig. 4a) [15] at room temperature for no more than 5 min, and no radioactivity was observed in the supernatant. Moreover, NPs 1 exhibited a high labelling efficiency (LE) with no-carrier-added [¹⁸F]-fluoride of up to 97% using as little as 10 μg NPs (Fig. 2). The adsorption of fluoride ions by Al(OH)₃-coated NPs was further confirmed using a fluoride selective electrode, with cold NaF instead of tracer level radioactive [¹⁸F] (Fig. S6). The binding capacity
was measured to be up to 44.45 mg (fluoride)/g (NPs) (10 times higher than 4–7 mg/g observed for hydroxyapatite [16,25]). The kinetic stability of $^{18}$F binding to NPs (0.34 mg and 0.68 mg) was investigated in water and in serum. The results demonstrated that over 99.8% $^{18}$F remained on the NPs even after washing with water three times (Fig. 2b). However, the stability appeared to become diminished with a smaller sample of NPs (0.07 mg). This may be simply a result of mechanical losses due to manipulation of the very small sample. Studies on the dynamic stability in human serum indicated that there was a slow release of $^{18}$F from radiolabelled NPs 1 over a period of 4 h, with ca. 40% $^{18}$F remaining on NPs after 4 h incubation and no obvious further release of $^{18}$F-fluoride afterwards. The release of $^{18}$F into serum could be a combination of the dissociation of loosely bonded $^{18}$F from the surface, the substitution by other anions in serum, interaction with proteins in serum via hydrogen bonding or ion pairing, and the dissolution of a labile fraction of the Al(OH)$_3$ layer.

Interestingly, initial results suggested that Fe$_3$O$_4$@Al(OH)$_3$ samples (2–4), prepared by a fast, uncontrolled hydrolysis process, are much less efficient in radiolabelling with $^{18}$F than their analogues 1 prepared by controlled hydrolysis (Fig. S7). Moreover, NPs coated with a thicker Al(OH)$_3$ layer, for example NPs 3 and 4,
showed a worse LE, less than 10%, but higher colloidal stability. NPs 2 have a thinner shell and correspondingly lower colloidal stability. These phenomena lead to the hypothesis that a quick hydrolysis with large amount of water resulted in an unstable Al(OH)3 layer on the NPs (2–4) whereas a slow hydrolysis with a small amount of water in Et2O led to a stable layer (1). An external unstable Al(OH)3 layer would be washed into the supernatant during the separation process, resulting in a low value of LE. By monitoring the Al concentration in the supernatant after washing and comparing to the initial solution by ICP-MS, we found that almost half of the aluminium was washed out at the first wash for samples 3 and 4 which were synthesised by the quick hydrolysis process. The aluminium remaining on the NPs after washing was stable since no Al was detected in the supernatant after further washing (Table S3). Correspondingly, these NPs 2–4 displayed a high affinity to 18F-fluoride after washing, of up to 94.9%. Only trace amounts of Al were detected in the supernatant of 1, which suggested a stable layer of Al(OH)3 consistent with the excellent radiolabelling results above.

As expected, these Al(OH)3-coated NPs displayed essentially the magnetic properties of the cores and were active as contrast agents in MR imaging, showing a darkening contrast on the T2 or T2* weighted MR images of solutions of NPs as a result of shortening transverse relaxation time of water molecules (Fig. 3). The transverse relaxivity property (r2) of the NPs strongly depends on the shell thickness, weakening dramatically as the Al(OH)3 shell thickness increases (3 and 4), consistent with previous reports that relaxivity is proportional to the volume fraction of magnetic materials [26]. Fe3O4@Al(OH)3 samples 3 and 4 displayed higher relaxivities (r1 and r2) after washing off the unstable layer; for example, r2 was improved from 81.6 to 121.9 mm−1 s−1 for NPs 3, and from 60.5 to 116.6 mm−1 s−1 for NPs 4 at 3T magnetic field (Fig. 3, Table S2). For the samples with a stable layer (1), no obvious improvement was observed on the relaxivity properties after washing.

In vivo PET/CT and PET/MR imaging results showed that both 1 and 3 labelled with 18F-fluoride exhibited a quick uptake, seen by PET imaging, in the spleen and liver after intravenous injection via tail vein, despite their small hydrodynamic size of 21 nm in saline solution. Accumulation of NPs in the spleen and liver was evident also by MR, in a significant darkening contrast in the corresponding areas on MR images in Fig. S8. The combined images show that the magnetic cores and the radioactivity co-localise in the early period after injection but separate with time. Due to the unstable aluminium hydroxide shell, [18F]-fluoride radioactivity was gradually released from NPs 1, 2 and 3 showing a significant bone uptake increasing with time. Consistent with in vitro studies presented above, 1 NPs showed a better in vivo stability and slower, but still significant, release of [18F]-fluoride radioactivity (Fig. S9). By contrast, intravenously injected free [18F]-fluoride, without NPs, is immediately accumulated in bone and not in liver and spleen. PET/CT imaging a normal mouse with 64Cu@Al(OH)3 showed a similar biodistribution to that of 64Cu radiolabelled NPs (Fig. 4). All intravenously administered NPs were taken up by the spleen and liver within 2 h post-injection, and showed no sign of efflux of radio-label from these organs, in contrast to the 18F-labelled particles. By comparison, PET/CT using 64Cu@Al(OH)3 (Fig. S10) showed uptake dominated by liver and kidneys but not spleen. This confirms that 64Cu radioactivity attached to NPs via bisphosphonate groups co-localises with the magnetic cores and is not rapidly detached from the NPs. The quick clearance of 1 NPs by the liver and spleen was not unexpected, as the in vivo behaviour is determined not only by their hydrodynamic size but also by surface properties (surface chemistry and potential) [27,28], generally, intravenously administered NPs over 100 nm are readily cleared by the reticuloendothelial system (RES) through opsonisation, whilst small particles (10–100 nm) tend to stay in the blood pool longer [27]. Thus, although their hydrodynamic size as measured in saline or in water was sufficiently small, to achieve stealth features, the Al(OH)3-coated NPs needed further surface modification to neutralise the surface potential. We found that in this case, polymers with anionic functional groups bound to the NPs via bisphosphonate groups, such as bisphosphonate polyethylene glycol (BP-PEG), could be used to modulate the surface potential of particles (Fig. S11), and protect them from opsonisation and aggregation in serum.

4. Conclusions

In summary, we have presented a simple approach to convert hydrophobic iron oxide-based magnetic NPs into hydrophilic particles stabilised by an Al(OH)3 shell. The features of this system, including high efficiency on 18F or 64Cu labelling, excellent colloidal stability, small hydrodynamic size, good transverse relaxivity and controllable surface potential, suggest that materials based on Fe3O4@Al(OH)3 have potential applications as bimodal contrast agents in PET/MRI imaging. A slow release of 18F from NPs was observed in vivo, whereas PET imaging with 64Cu radiolabelled NPs showed no loss of radioactivity from the initially targeted organs (liver, spleen). The ability to derivatise the surface with radiolabels and bisphosphonate groups suggests applications in molecular imaging. Barriers to in vivo use due to toxicity should be low, because of the established use of Al(OH)3 as adjuvants in vaccines. The high affinity to bisphosphonate groups for Al(OH)3 allows us to conjugate these NPs with a range of imaging and therapeutic radionuclides which may be used in conjunction with magnetic imaging and therapy.

Acknowledgements

Authors thank Drs Alice Varley and Gana Vizcay, at Centre for Ultrastructural Imaging, King’s College London for TEM, and Mr Andrew Cakebread at King’s College for ICP-MS measurements. RTMR and DM would like to thank EU COST action (BM1102) for Ultrastructural Imaging, King’s College London. We acknowledge the financial support from the European Research Council under the European Union’s Seventh Framework Programme (FP7/2007-2013)/ERC Grant agreement no 279251 (EUCAIMM) and from the Engineering and Physical Sciences Research Council (EPSRC) (grant number EP/I02921X/1). We would like to acknowledge the financial support from the National Institute for Medical Research (NIMR) under contract number WT088641/Z/09/Z, and the King’s College London and UCL Comprehensive Cancer Imaging Centre funded by the CRUK (C1519/A10331) and EPSRC in association with the MRC and DoH (WT088641/Z/09/Z (England), and by the National Institute for Health Research Biomedical Research Centre at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London. PET and SPECT scanning equipment at KCL was funded by an equipment grant from the Wellcome Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.biomaterials.2014.04.004.

References


