Carbon coated microshells containing nanosized Gd(III)-oxidic phases for multiple bio-medical applications

E. Gianolio[1], A. Arrais[2], S. Avedano[3], G. Giovenzana[4], E. Boccaleri[2], M. Botta[3], P. Staghellini[2], and S. Aime[1]

[1]Chemistry IFM, Università di Torino, Torino, Italy, Italy, [2]Scienze e Tecnologie Avanzate, Università del Piemonte Orientale A. Avogadro, Alessandria, Italy, Italy, [3]Scienze dell'ambiente e della vita, Università del Piemonte Orientale A. Avogadro, Alessandria, Italy, Italy, [4]Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università del Piemonte Orientale A. Avogadro, Novara, Italy, Italy

Purpose

To generate inhert particles endowed with a high payload of Gd-oxide to be applied as T2-susceptibility agents in MRI, X-ray scattering material in CT and activable substrates for Neutron Capture Therapy.

Introduction

The outstanding achievements in many fields of Bio-medicine prompt chemists to develop new micro-nano sized particles endowed with peculiar characteristics. Cell-targeting, cell-tracking and cell-therapy are issues that often require the use of micro- or nano-sized carriers for efficient visualization and treatment. Furthermore there is an increasing attention to the possibility (that only these systems may offer) of developing multi-modal agents that tackle simultaneously diagnosis and therapy. Being in tight association or even entrapped by cells the particles must not release any toxic substance during the time they stay in living organisms. The inhertness toward biological molecules is therefore a primary requisite.

Herein we report our results on the preparation of an agent based on Gadolinium that may find applications as diagnostic tool in MRI and X-ray techniques as well as in therapy as Neutron Capture agent.

Methods

The composite Gd@C material has been very simply and cheaply prepared via precipitation of saturated hydrophilic humic acids (HAs) acqueous solutions with $GdCl_3$ and successive pyrolitic thermal treatment in tubular oven under inhert N_2 conditions. The obtained Gd@C material has been purified from extra-carbon shells gadolinium by successive washings/dialisis against concentrated HCl and with DTPA solutions. The full removal of not-encapsulated Gd has been assessed by the lack of water proton relaxation enhancement of the suspensions of Gd@C in the presence of the sequestering agent. In order to improve the water suspendability of Gd@C material, the particles have been functionalized with arene sulphonic groups:

$$Gd@C + {}^{+}{}_2N\text{-}Ar\text{-}SO_3^{-}{}_{(aq)} \ (THF, r.t.) \rightarrow Gd@C(\text{-}OH)_n(\text{-}Ar\text{-}SO_3^{-})_n + nN_2 + nH^{+}$$

The obtained material, salified with NaOH, yielded sufficiently stable suspensions at the concentration of ca. 1.5 mg/ml.

The metal content varies from 40 to 50% w/w according to the conditions of the of the thermal treatment. The particles have been characterized by TGA, IR, Raman, SEM-EDAX, TEM and X-ray powder diffraction. The magnetic properties have been evaluated on an NMR spectrometer operating at 9.4T and 7T.

Discussion

The several different combined techniques of characterization were consistent in assessing a micrometrical, nearly spherical, capsular multilayered carbon coating in which nanometric Gd-oxide particles are embedded. The obtained capsular systems are featured with enhanced thermal and chemical stability and inherteness. No release of Gd(III) ions was detected upon suspending the particle in 10 mM solution of DTPA. As shown in Fig. 1, the particles appears as grossy spheroidal objects with diameters in the order of 1 µM.

The presence of Gd-oxide core endows the particles with a large magnetic susceptibility (r_2* (per Gd) ~ 40$mM^{-1}s^{-1}$ at 7T). As each particle contains ca. 2-5×10^{10} Gd, one particle is sufficient for the MR visualization of a cell. Furthermore such electron-dense material appears well suitable for X-ray detection. Finally, these Gd@C particles may find application in Neutron Capture Therapy (NCT) as Gd-157 (15% natural abundance) shows an excellent abiliy to capture neutrons (its cross section is 66 times larger than the standard NCT Boron-10 nucleus).

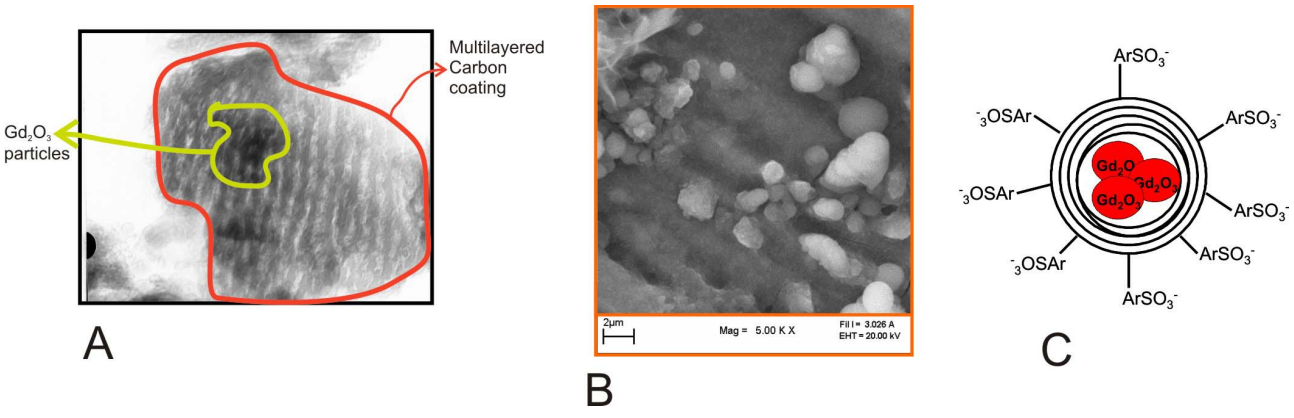

Fig.1: Images of Gd@C particles acquired on TEM (A, single particle) and SEM(B, ensemble of capsules); (C) graphical representation of the graphenic micro-particles.