ZIF-8 and maghemite based nanoparticles as radionuclide carriers and hyperthermia agents in bi-modal cancer therapy

Bratislav Antic[1], Biljana Dojcinovic[2], Milos Ognjanovic[1], Sladjana Novakovic[1], Tatjana Stanojkovic[3], Drina Jankovic[1], Sanja Vranjes-Đuric[1]
[1]VINČA Institute of Nuclear Sciences-National Institute of the Republic of Serbia, University of Belgrade, Mike Petrovića Alasa 12-14, Belgrade, Serbia
[2]Institute of Chemistry, Technology and Metallurgy, National Institute of the Republic of Serbia, University of Belgrade, Njegoševa 12, Belgrade, Serbia
[2]Institute for Oncology and Radiology of Serbia, Pasterova 14, Belgrade, Serbia

bantic@vin.bg.ac.rs

This study focuses on developing novel nanoplatforms for therapy in cancer. We investigated the radiolabeling of ZIF-8 (a metal-organic framework) and Zn/Mn-substituted γ-Fe_2O_3 nanoparticles. Using polyol synthesis, we produced flower-like γ-Fe_2O_3 nanoparticles with multicore structures (23–67 nm), Figure 1.

The $Zn_{0.098}Mn_{0.447}Fe_{2.455}O_4$ nanoparticles exhibited moderate antiproliferative activity against tumor cell lines HeLa, LS174 and A375, while showing no activity against A549 and normal MRC-5 cells (IC_{50} > 200 μg/mL). After coating the nanoparticles with citric acid (CA), they were inactive against all cell lines. he cytotoxicity was linked to the high concentration of Fe ions on the surface área [1].

Investigating the changes in heating efficiency due to the partial substitution of iron ions with Zn and Mn in the parent compound while preserving the flower-like morphology and maghemite structure revealed significant variations in the ILP (Intrinsic Loss Power) values. ILP varied from 0.34 to 5.77 nH·m²/kg. The high ILP value for the $Zn_{0.098}Mn_{0.447}Fe_{2.455}O_4$ sample suggests its potential as an agent for applications in magnetic hyperthermia (both *in vitro* and *in vivo*). Our ongoing work focuses on *in vitro* magnetic hyperthermia studies.

The coated sample, $Zn_{0.098}Mn_{0.447}Fe_{2.455}O_4$@CA, was labeled with the therapeutic radionuclide ^{177}Lu. The maximum labeling yield of ^{177}Lu-$Zn_{0.098}Mn_{0.447}Fe_{2.455}O_4$@CA achieved was 89%, as determined by ITLC-SG. After 72 hours of incubation in saline and human serum, the labeled nanoparticles demonstrated very high stability.

The results show that ZIF-8 metal-organic frameworks are an effective potential carrier of the therapeutic radionuclide ^{177}Lu for nuclear medicine (cancer therapy). The maximum labeling yield was 92%. Stability testing over 72 hours showed 100% stability of the labeled ZIF-8. Zeta potential measurements show that the surface of ZIF-8 is positively charged at pH 7.

In order to identify the relevant binding sites within the porous framework of ZIF-8, the electrostatic potential distribution was calculated on the basis of periodic DFT methods implemented in CRYSTAL code. The analysis of the electrostatic potential mapped on an electron density isosurface (0.001 au) reveals well defined regions of negative potential located within the four- and six-membered apertures of ZIF-8 (red regions in Figure 2). These nucleophilic zones originate from the electron cloud density of the 2-methylimidazole linkers and can serve as main adsorption sites for Lu^{3+} ions, primarily by strong electrostatic interactions.

The results indicate that magnetic nanoparticles can be used in bi-modal therapy (magnetic hyperthermia and radionuclide therapy), while ZIF-8 has potential for use in radionuclide therapy.

Funding

The research was financially supported by the Science Fund of the Republic of Serbia, Program PRISMA, Grant No. 4961, Design of radioactive magnetic nanoconstructs for tumour therapy by synergy of nanobrachytherapy and magnetic hyperthermia—RADIOMAG.

References

[1] M.A. Abakumov, A.S. Semkina, A.S. Skorikov, D.A. Vishnevskiy, A.V. Ivanova, E. Mironova, G.A. Davydova, A.G. Majouga, V.P. Chekhonin, J. Biochem. Mol. Toxicol., 32 (2018) e22225.

Figures

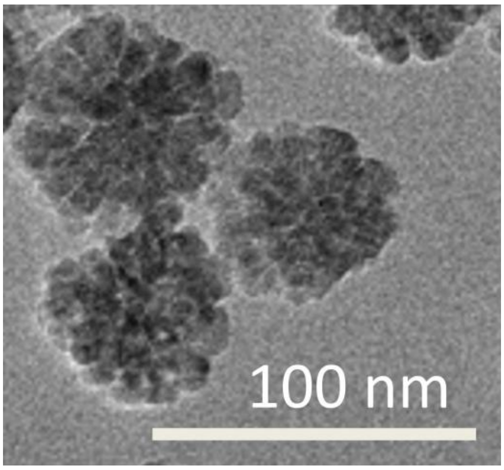

Figure 1. TEM micrograph of particles with flower-like morphology.

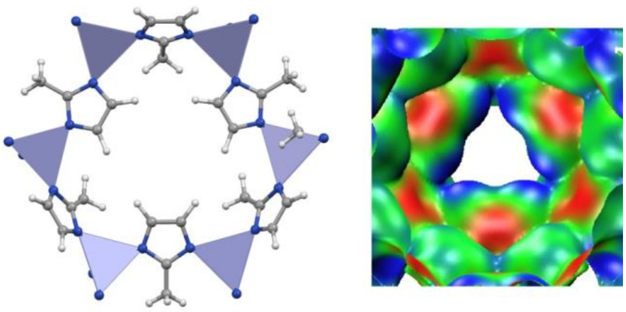

Figure 2. Six-membered aperture of ZIF-8 (left); Electrostatic potential mapped on the charge density isosurface (right). Red, green, and blue regions indicate negative, zero, and positive values of electrostatic potential.