

Nanocargo-Delivery Platform for Targeted Drug Delivery in Biomedical Applications: Magnetic Gd₂O₃ Nanoparticles in Porous SiO₂

L. ŽID^{a,*}, V. ZELENÁK^a, A. BERKUTOVA^b, J. SZŮCSOVÁ^b AND A. ZELENÁKOVÁ^b

^aPavol Jozef Šafárik University in Košice, Department of Inorganic Chemistry, Košice, Slovakia

^bPavol Jozef Šafárik University in Košice, Department of Condensed Matter Physics, Košice, Slovakia

We investigated nanocargo-delivery magnetic platform composed of spherical Gd₂O₃ particles, loaded together with cytostatic drug 5-fluorouracil (5-FU) in periodic mesoporous silica matrix. The system under study combined the advantages of high surface area and pore volume of mesoporous silica cargo with the advantages of magnetic separability and targeted drug delivery, provided by magnetic Gd₂O₃ nanoparticles. The sample was characterized by HRTEM (High-Resolution Transmission Electron Microscopy), PXRD (powder X-ray diffraction), elemental analysis, and magnetic measurements by MPMS apparatus. A conventional paramagnetic response was observed in the whole 5–330 K range with high magnetization about 90 emu/g at 50 000 Oe. Effective magnetic moment per formula unit 7.88 μ_B obtained at room temperature is close to theoretical value 7.94 μ_B . The released amount of 5-FU represented more than 90% of the loaded one.

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PACS/topics: mesoporous silica, Gd₂O₃ nanoparticles, drug delivery, 5-fluorouracil, magnetic susceptibility

1. Introduction

In recent years, the use of nanomaterials in medicine, especially in diagnostics and therapy has received a lot of attention [1]. The systems, which combine therapy with diagnostics (so called theragnostic) are emerging for example in biomedical science and medicine. Among the various systems that acquire the ability to diagnose and administer therapy in one package are mesoporous silica systems loaded with magnetic nanoparticles. Mesoporous silica is one of the promising nanomaterials which can carry the molecules of drugs and overcome many problems linked to drug delivery. Mesoporous silica as a drug delivery system can significantly improve the solubility of the hydrophobic drugs [2], release them at a prolonged time [3], or cargo molecules of the drug to the time when they reach the target tissue [4]. Moreover, when magnetic nanoparticles are embedded in mesoporous silica, then such systems can be used as contrast agents in MRI [5].

In our work we loaded magnetic Gd₂O₃ nanoparticles into pores of mesoporous silica of SBA-15 type together with anticancer drug 5-fluorouracil (5-FU). Gadolinium-based systems were in 1988 approved as MRI contrast agents for clinical use [6]. Gadolinium is paramagnet with strong relaxation effect owing to seven unpaired electrons in the 4f shell [7]. Therefore, gadolinium is a unique element that can be applied in the form of its oxide as a contrast agent [8]. Furthermore, gadolinium oxide can be used simultaneously in X-ray tomography,

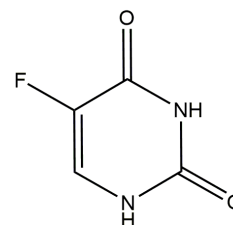


Fig. 1. Molecule of 5-fluorouracil.

neutron capture therapy, and magnetic resonance imaging. In addition, magnetic properties of Gd₂O₃ / mesoporous silica systems have a promising feature thanks to which one can track their movement in the body directly to the targeted tissue using external magnetic field [9]. For our purpose, we have prepared mesoporous silica SBA-15 loaded with Gd₂O₃ nanoparticles as a nanocargo-delivery magnetic platform (NDMP) for anticancer drug 5-FU (Fig. 1). This drug 5-FU belongs to the antimetabolite and pyrimidine family of drugs for several cancers including esophageal, stomach, pancreatic, colon, cervical and breast cancer. Moreover, 5-FU has hydrophilic character [10].

2. Experimental

To prepare the mesoporous silica SBA-15, the sol-gel process used by Zhao et al. [11] have been applied. The obtained Gd₂O₃/SBA-15 nanocargo-delivery platform was synthesized by the nanocasting method. Typically, the 1 g of dry SBA-15 was impregnated with 20 ml of 0.5 M solution of Gd(NO₃)₃. Subsequently, the product was filtered off, and left to dry at 323 K for 2 h. The final product Gd₂O₃/SBA-15 was obtained by thermal treatment at 773 K for 3 h. Then, 5-fluorouracil

*corresponding author; e-mail: lukas.zid@student.upjs.sk

was loaded into the pores of $\text{Gd}_2\text{O}_3/\text{SBA-15}$ by wet-impregnation method. The 100 mg of $\text{Gd}_2\text{O}_3/\text{SBA-15}$ was immersed in 10 ml of 10 mg/ml 5-FU aqueous solution. The mixture was stirred at laboratory temperature for 24 h in open beaker to promote the slow evaporation of solvent resulting in a higher loaded amount of 5-fluorouracil. Prepared nanomaterial was denoted as $\text{Gd}_2\text{O}_3/\text{SBA-15}/5\text{-FU}$.

The release study was performed in simulated body fluid with pH 7.4. The experiment started by mixing 45 mg of $\text{Gd}_2\text{O}_3/\text{SBA-15}/5\text{-FU}$ with 5 ml of physiological saline solution. The sample was stirred by a rotator at 25 rpm at laboratory temperature of 24 °C. This sampling made for concentration change analysis was performed at predetermined time intervals from 10 min to 48 h. The change in concentration was analyzed by UV-VIS spectroscopy at $\lambda = 266$ nm. Temperature and field dependence of magnetization was obtained by SQUID based magnetometer MPMS 5XL (Quantum Design) in the temperature range 1.8–300 K in both regimes ZFC/FC (zero field cooled and field cooled regimes) in magnetic fields up to 5 T. The signal contribution of the empty gelcap and the straw was subtracted from the total signal. Additionally, the obtained data were corrected for the diamagnetic contribution using Pascal's constants.

3. Results and discussion

The structural characterization of prepared $\text{Gd}_2\text{O}_3/\text{SBA-15}$ nanocargo-delivery platform and phase composition of magnetic nanoparticles inside mesoporous silica have been provided by high energy X-ray diffraction (HE-XRD) measurements using synchrotron radiation (see Fig. 2). Measurements were carried out with synchrotron radiation energy of 60 kV and wavelength $\lambda = 0.0207$ nm, on accelerator PETRA III in DESY, Hamburg. The large full width at half maximum of diffraction peaks that were recognized in the patterns, indicates the nanocrystalline character of the Gd_2O_3 particles. Broad peaks at around $2\theta = 3.98^\circ$ and $2\theta = 6.2^\circ$, can be assigned to amorphous SBA-15 silica matrix, which overlap almost whole diffraction peaks from gadolinium oxide nanoparticles. In spite of this, there is still clear evidence of Gd_2O_3 presence in the XRD spectra of nanoparticles in porous silica matrix (space group Ia3 (No. 206), JCPDS No. 43-1014), with major diffraction peaks at 2θ values. These are 3.84° , 4.43° , 6.25° , and 7.33° , that correspond to (2 2 2), (4 0 0), (4 4 0), and (6 2 2) reflections. Overlapping of diffraction peaks from amorphous silica and gadolinium oxide nanoparticles also suggests that Gd_2O_3 particles are encapsulated inside of SBA-15 porous system, and not on the surface.

The presence of 5-FU in the $\text{Gd}_2\text{O}_3/\text{SBA-15}$ nanocargo was confirmed by IR spectra (not shown). The SBA-15 silica matrix was represented by: (i) broad and strong asymmetric Si–O–Si stretch $\nu_{\text{as}}(\text{Si-O-Si})$ observed

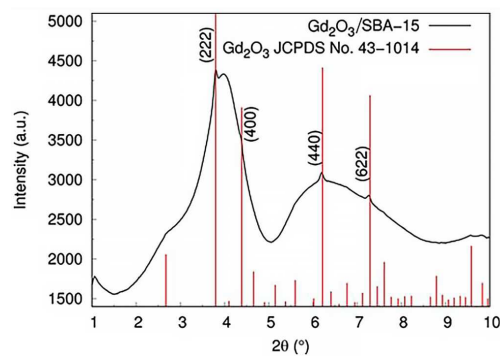


Fig. 2. Diffraction pattern of $\text{Gd}_2\text{O}_3/\text{SBA-15}$.

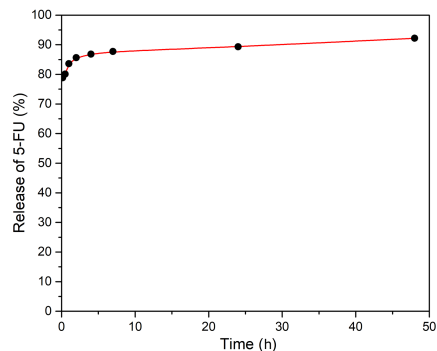


Fig. 3. Cumulative release of 5-FU from $\text{Gd}_2\text{O}_3/\text{SBA-15}/5\text{-FU}$ nanocargo-delivery platform.

at around 1100 cm^{-1} , (ii) the symmetric Si–O–Si stretch $\nu_{\text{s}}(\text{Si-O-Si})$ observed at 790 cm^{-1} , and (iii) the bending vibrations $\delta(\text{Si-O-Si})$ observed at 460 cm^{-1} . In addition to SBA-15 spectrum, the presence of 5-FU in the pores of SBA-15 was reflected by the stretching $\nu(\text{C=O})$ vibrations at 1720 cm^{-1} , while the presence of C–H was in plane vibrations $\nu(\text{C-H})$ at 1243 cm^{-1} . The amount of 5-FU in the pores of $\text{Gd}_2\text{O}_3/\text{SBA-15}/5\text{-FU}$ was determined by elemental analysis. As a result, sample contains 21.93 wt% of carbon and 12.49 wt% of nitrogen. Based on these data, the amount of loaded 5-FU per gram of $\text{Gd}_2\text{O}_3/\text{SBA-15}/5\text{-FU}$ material was calculated to be 580 mg/g by using nitrogen wt%, or to be 593 mg/g by using carbon wt%. Slight difference in calculated values can be ascribed to unburned traces of surfactant (carbon) in calcination step. Therefore, for further the 5-FU release study amount calculated on the N content was used. The release of 5-FU from $\text{Gd}_2\text{O}_3/\text{SBA-15}/5\text{-FU}$ was investigated in physiological saline solution with pH 7.4. The profile of cumulative release of 5-FU is shown in Fig. 3. The 5-FU release profile from $\text{Gd}_2\text{O}_3/\text{SBA-15}/5\text{-FU}$ exhibited fast release in an initial stage and slower release in a later stage. This behavior is in accordance with other studies of 5-FU release from mesoporous silica nanomaterials [2, 12]. However, it is still much faster than observed for non-steroidal anti-inflammatory drugs (NSAID) [13]. The difference between kinetics of the release of 5-FU and NSAID might be due to different polarity of the molecules.

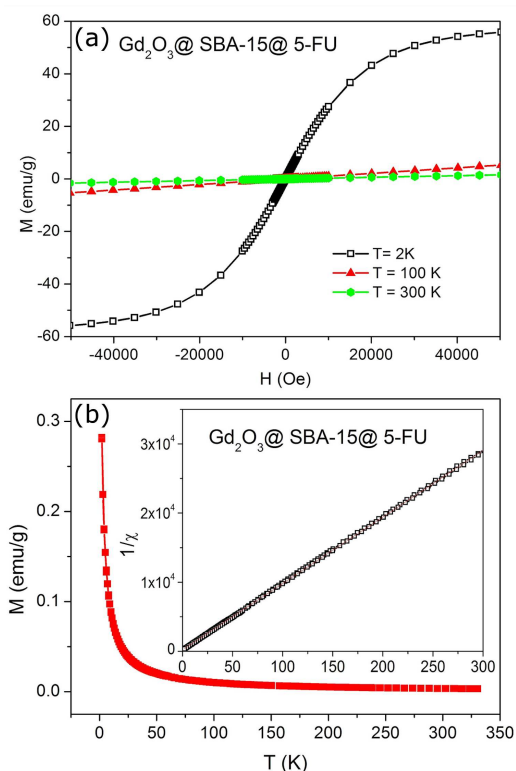


Fig. 4. (a) Magnetization dependence on magnetic field at 2, 100, 300 K. (b) Magnetization dependence on temperature. Inset shows the reciprocal value of magnetic susceptibility with a linear fit according to the Curie–Weiss law.

To study the magnetic properties of nanocargo system $Gd_2O_3/SBA-15/5-FU$, the molar magnetic susceptibility of complexes was measured in the range of 1.8–300 K in the magnetic field of 100 mT.

Magnetic susceptibility data recorded in both ZFC and FC regimes are shown in Fig. 4b. The temperature dependence of inverse magnetic susceptibility (inset of Fig. 4b) perfectly follows the Curie–Weiss law. Linear fit for temperature 10–300 K gives values of $\Theta = -2.04\text{ K}$, confirming the presence of antiferromagnetic exchange interaction between Gd(III) ions.

The theoretical effective magnetic moment was calculated using formula

$$\mu_{\text{eff}} = \sqrt{J(J+1)}\mu_B g_J, \quad (1)$$

where μ_B is Bohr magneton, J is atom magnetic moment, and g_J is theoretical Landé factor for inner-transition metals. The effective magnetic moment per formula unit was calculated with

$$\mu_{\text{eff}} = \sqrt{\frac{3Ck_B}{N_A}}, \quad (2)$$

where C is Currie constant, k_B is Boltzmann constant, and N_A is Avogadro constant. Effective magnetic moment per formula unit $7.88\ \mu_B$ obtained at room temperature is close to theoretical value $7.94\ \mu_B$. The magnetization versus external magnetic field plots

at temperatures 2 K, 100 K, and 300 K (Fig. 4a) show paramagnetic behavior. Saturation magnetization decreases from 1.3 to $0.22 \times 10^3\text{ emu/mol}$, and it is in accordance to calculated effective magnetic moment $\mu_{\text{eff}} = 7.94\ \mu_B$.

4. Conclusions

Nanocargo-delivery magnetic platform composed of spherical Gd_2O_3 particles loaded was prepared and characterized. The platform showed high uptake of anticancer drug 5-FU, and its fast and nearly quantitative release. The magnetic properties of composite $Gd_2O_3/SBA-15/5-FU$ are determined by the paramagnetic properties of Gd_2O_3 nanoparticles loaded within nanopores, exhibiting a large value of magnetic moment with suitable response to the gradient of the external magnetic field. The investigated system has shown to combine magnetic separability and targeted drug delivery, provided of drugs with low solubility.

Acknowledgments

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