MAGNETIC PROPERTIES OF NOVEL DRUG DELIVERY SYSTEM CONTAINING FINE Fe_2O_3 NANOPARTICLES AND NAPROXEN IN MESOPOROUS SILICA

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1. Introduction

Over the past few years have been studied several nanodevices, based on nanoparticles, which are important in the delivery of drug into a biological system [1]. The reason for the further study of nanoparticles is that delivery of the drug is not appropriate due to the impaired absorption of the drug or the tissue non-specific delivery. This is a disadvantage in the treatment of cancer. Therefore, development of new functional materials for the delivery, targeting and release of drug, and review of conditions of this process is necessary [2]. The principle of drug delivery is based on a multi-component system comprising a drug and magnetic nanoparticles, which enable the control of drug delivery with the assistance of a magnetic field. There are several ways to control the delivery and targeting of the drug. Mesoporous silica nanoparticles (MSN) appear to be one of the preferred methods for drug delivery system. A small pore size of the mesoporous silica is preferred because it controls the size of the nanoparticles. Other advantages are the large pore volume, surface area, biocompatibility, high temperature and chemical stability [3, 4]. Slowing et al. [5] studied the biocompatibility of mesoporous silica MCM-41 with the use of Fe_2O_3 nanoparticles (NPs) and investigated penetration of the various cell membranes of animal and plant cells. Mesoporous silica was used to regulate the encapsulation and release of drug molecules. Vivero-Escoto et al. [6] have dealt with studying the system AuNPs-MSN using MCM-41, where NPs served as a capping mechanism. Song et al. [7] used a mesoporous SBA-15, which was investigated as matrixes for controlled drug delivery. Ibuprofen and bovine serum albumin was used as model drugs. Mesoporous silica nanoparticles impregnated with zero-valent Fe in MCM-41 examined Shevtsov et al. [8] as nanocarrier system for drug delivery into tumor cells. Magnetization study confirm the superparamagnetic behavior at room temperature and the saturation magnetization Ms with value of 7.4 emu/g. In our previous paper, we have studied a stimuli-responsive drug delivery system consisting of mesoporous silica MCM-41 with surface modified by coumaric acid derivatives (CA) as photo-switchable ligands for the delivery of the non-steroidal anti-inflammatory drug (NSAID) naproxen. Our results shows that the reversible photo-reaction of CA attached on the surface of MCM-41 can be applied to the controlled storage/release of drug molecules and the release can be driven by UV light as a physical stimulus [9].

In this article, we have focused on studying drug delivery system consisting of mesoporous silica MCM-41 anchored with magnetic nanoparticles Fe_2O_3 (sample MCM-41@Fe_2O_3) and naproxen (sample MCM-41@naproxen). The structural characteristics of silica were evaluated by TEM and dynamic light scattering method and magnetic properties were studied by SQUID magnetometer in temperature range from 2-300 K in external magnetic field up to 5T.

2. Experimental

MCM-41 mesoporous silica matrix was synthesized according to Qiang et al. [10] in the molar ratio 1/0.12/0.33/601.3 of TEOS/CTAB/NaOH/H_2O. The hematite containing nanocomposite material was prepared by filling of the pores of mesoporous matrix MCM-41 by the 4 M solution of $Fe(NO_3)_3.9H_2O$, followed by thermal treatment at 773 K for 6 h and decomposition of the nitrate to the iron oxide. For the loading of mesoporous support with naproxen, 200 mg of modified mesoporous silica MCM-41 with hematite was added into the solution of naproxen in ethanol (1 mg/ml) and stirred for 24 hat a laboratory temperature. The obtained products were filtered off, gently washed with ethanol and dried at laboratory temperature.

The TEM micrographs were taken with a JEOL 2100 microscope. Copper grid coated with holey carbon support film was used to prepare samples for the TEM observation.

The particle size distribution was measured by dynamic light scattering (DLS) using Zetasizer Nano S, Malvern Instruments. The powder sample was dispersed in deionized water and homogenized by ultrasonic breaker for 5 minutes.

The magnetic measurements were performed on a commercial SQUID-based magnetometer (Quantum Design MPMS 5 XL) over a wide range of temperatures (2-300 K) and applied DC fields (up to 50 kOe). The magnetic properties of the powder sample were changed by dispersing the powder in deionized water. Powder and samples were encapsulated into plastic capsule and into plastic sample holder. Diamagnetic contribution of empty capsule and plastic holder was subtracted from the total magnetization data.

3. Results and discussion

Structural characterization of prepared samples by TEM (Transmission Electron Microscopy) is presented on Fig. 1 and show the size and shape of the blank mesoporous silica MCM-41, sample MCM-41 with Fe_2O_3 nanoparticles inside the pores (MCM-41@Fe_2O_3) and MCM-41 with drug naproxen inside the pores (MCM-41@naproxen), respectively. Blank MCM-41 silica exhibit the regular porous system with hexagonal symmetry with the size of pores around 7 nm, see Fig. 1a. The total size of blank mesoporous silica particles was around 320 nm, see Fig.1b. After loading of Fe_2O_3 nanoparticles inside the porous system, the regular hexagonal symmetry of MCM-41 silica is retained. Iron oxide magnetic nanoparticles embedded inside MCM-41 matrix are visible as dark area in the center of matrix (Fig. 1c). It is obvious that silica matrix control the growth of Fe_2O_3 MNPs and serve as nanoreactor for preparation of superparamagnetic iron oxide nanoparticles (SPIONs) with very low particle size distribution.

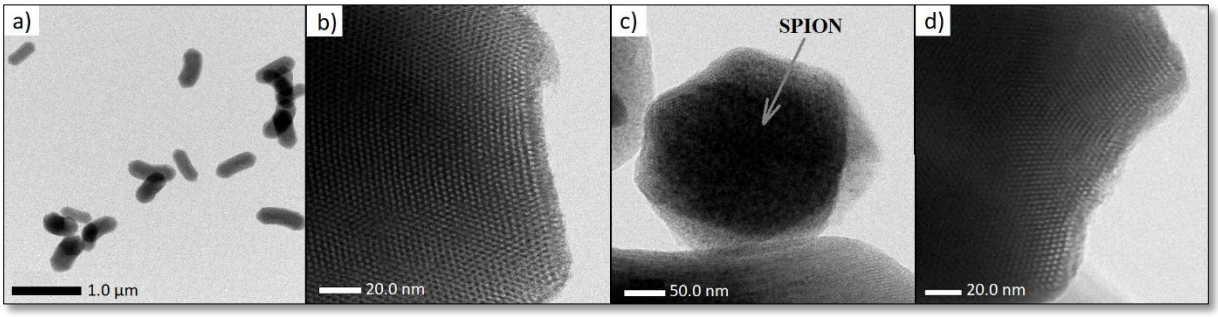

Fig. 1: a) mesoporous silica MCM-41; b) a blank mesoporous silica MCM-41 higher resolution; c) mesoporous silica containing iron oxide nanoparticles MCM-41@Fe_2O_3; d) mesoporous silica with drug MCM-41@naproxen.

After impregnation of blank MCM-41 by drug naproxen (Fig. 1d) a regular hexagonal symmetry of matrix was slightly disturbed and the total size of composites increases from

320 nm to 450 nm after impregnation. These results are in agreements with results of particle size obtained from DLS method. On the Fig. 2 are documented that size of mesoporous silica MCM-41 after modification of naproxen increases from 314 nm to 449 nm.

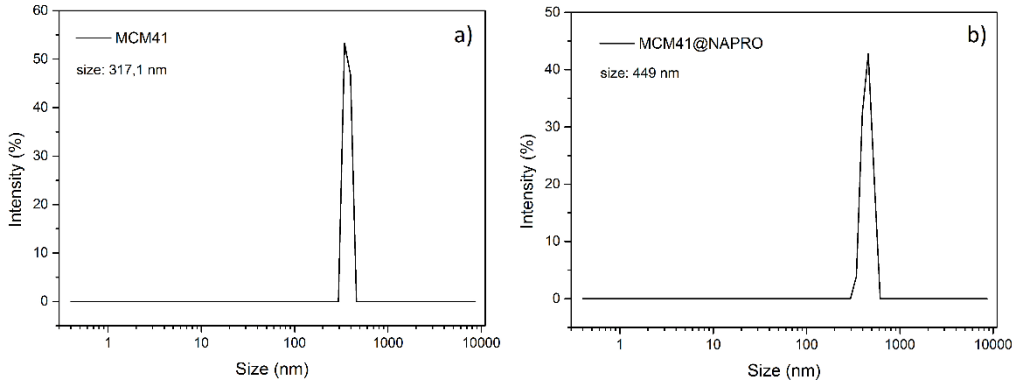

Fig. 2: Particle size distribution of the samples from DLS: a) blank mesoporous silica MCM-41; b) mesoporous silica with drug naproxen MCM-41@naproxen.

Fig. 3 presents the temperature dependence of magnetization recorded in both ZFC/FC protocols (Zero-Field-Cooling/Field Cooling)) at different DC fields of 50 Oe, 100 Oe and 500 Oe. On ZFC curve was observed maximum at temperature associated with blocking temperature (T_B). At temperature above to T_B ($T>T_B$) the particle`s magnetic moments can freely fluctuate through the energy barrier of magnetic system leading to superparamagnetic state. In opposite, below T_B ($T<T_B$) the magnetic moments are blocked to the external magnetic field direction what is documented by high irreversibility of ZFC and FC curves below T_B. Identical behavior of powdered MCM-41@Fe_2O_3 and MCM-41@Fe_2O_3@naproxen samples confirm that magnetic properties are determined by the properties of Fe_2O_3 nanoparticles loaded within nanopores. Moreover, the magnetic properties of liquid sample (sample MCM-41@Fe_2O_3@naproxen in physiology solution with pH=7**)** are very similar to powdered sample showing that relaxation process is caused by Neel relaxation with very small contribution of Brown relaxation.

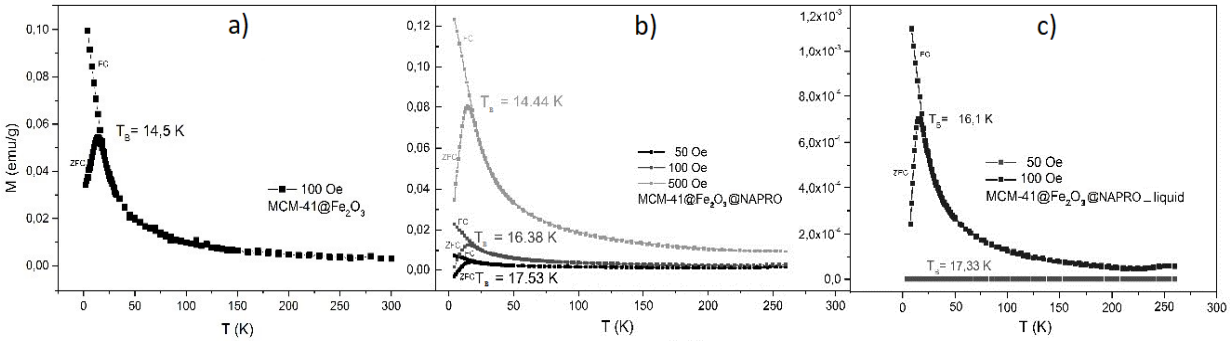

Fig. 3: ZFC and FC magnetization of the samples a) MCM-41@Fe_2O_3; b) MCM-41@Fe_2O_3@naproxen; c) MCM-41@Fe_2O_3@naproxen_liquid.

Dependence of magnetization versus an external magnetic field (M(H) loops) are shown in Fig. 4. These results confirm the existence of superparamagnetic behavior at 300 K in all studied sample. At temperature 2 K (below TB) a blocking process was confirm by existence of hysteresis loops with coercivity about 2000 Oe.

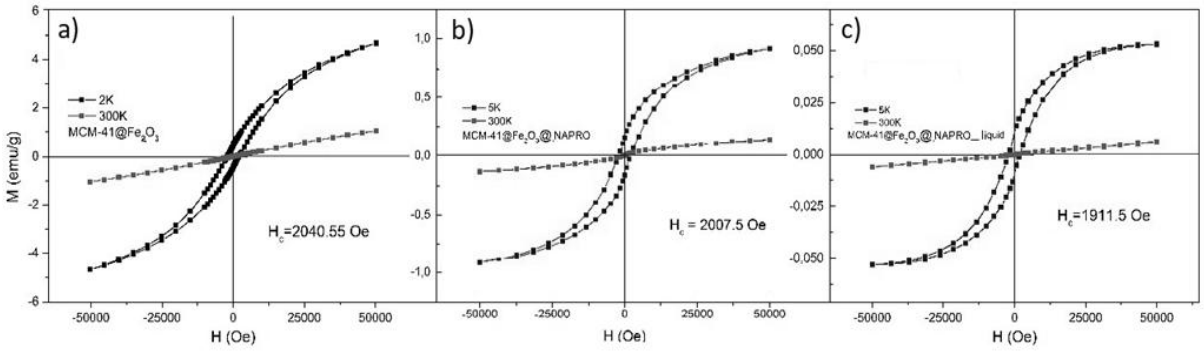

Fig. 4: Magnetization on magnetic field dependence measured at various temperatures for a) MCM-41@Fe_2O_3; b) MCM-41@Fe_2O_3@naproxen; c) MCM-41@Fe_2O_3@naproxen_liquid;

4. Conclusions

In our work, we used MCM-41 silica with hexagonal porous system modified with iron oxide nanoparticles as a drug delivery system for drog naproxen. The magnetic properties of composite MCM-41@Fe_2O_3@naproxen are determined by the properties of Fe_2O_3 nanoparticles loaded within nanopores. After encapsulation of the magnetic nanoparticles into the mesoporous silica the particles keep their superparamagnetic behaviour and could be used for vectored drug delivery using magnetic field and preparation of smart drug delivery systems. Magnetic properties of liquid sample (sample MCM-41@Fe_2O_3@naproxen in physiology solution with pH=7) are very similar to powdered sample showing that relaxation process is caused by Neel relaxation with very small contribution of Brown relaxation.

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