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Microwave Synthesis of Core–Shell Nanosize Materials on the Basis of Magnetite Functionalized with Gold and Doxorubicine

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Abstract—A method for the microwave synthesis of multifunctional magnetic nanomaterials with a “core–multilayered shell” structure is proposed. The optimal conditions for the step-by-step synthesis of a material on the basis of magnetite Fe_3O_4 (“core”) modified by silicon-containing polymers (TEOS + MPTMS), gold nanoparticles, and immobilized antineoplastic drug doxorubicine (DOX) (“shell”) are found. Using instrumental techniques, the composition of the prepared nanomaterials (Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX) is investigated and the sizes of particles synthesized at different temperatures and reagent ratios are determined. The sorption processes involving DOX and synthesized nanomaterials are studied at different phase contact times, doxorubicine concentration, and pH of the medium. The possibility of controlled release of DOX from the nanoparticle surface upon changing the pH value is demonstrated. The synthesized hybrid nanoparticles could be promising for different biomedical applications, in particular, for targeted drug delivery and local hyperthermia.

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INTRODUCTION

Studies on the synthesis and practical application of different nanomaterials with magnetic properties are attracting the growing interest of researchers [1]. Magnetic nanomaterials occupy a special place in biotechnology and medicine [2, 3]. These materials are used in medicine for the controlled delivery of drugs to target organs [4, 5], visualization of objects by the method of magnetic resonance [6], and also hyperthermia of malignant neoplasms [7]. Nanoparticles with several functions are of particular interest [8]. As a rule, such hybrid magnetic nanoparticles (MNPs) have a core–multilayered shell structure.

Each type of shell (covering) in such hybrid MNPs plays a certain function. Thus, the silicon dioxide layer provides better stability to MNPs in a solution and has excellent biocompatibility; in addition, the surface of silica gel undergoes further chemical modification to a larger extent owing to a higher surface concentration of silanol groups, which is revealed in an approximately twofold increase in the specific surface charge as compared to pure magnetite (Fig. 1) [9]. This property is used for the more complete surface immobilization of chemical drugs designed for their address delivery to diseased organs. The additional coating of MNPs with a shell composed of noble metal nanoparticles allows one to provide them with the capability of point heating upon irradiation with IR radiation of a certain frequency and of fluorescence in the visible optical range. In practice, these properties are used for the synthesis of multifunctional nanomaterials, for therapeutic procedures, immunoassay analysis, design of biosensors, etc. [10, 11]. Hence, the development of synthetic paths for the preparation of MNPs that possess a combination of the necessary properties combining different required functions is a first-priority task.

For the synthesis and subsequent surface modification of MNPs, we used the method of microwave (MW) heating, i.e., heating in a microwave electromagnetic field. Owing to the rapid volume heating of the reaction medium, the conditions for the fast and reproducible formation of particles with a high degree of dispersion are created at MW heating. In recent times, MW heating is widely used for the synthesis of various nanoparticles [9, 12–15]; however, there are only a few examples of using the MW radiation for the synthesis of different kinds of nanocomposites in the domestic literature [16, 17].

In the present work, a method for the MW synthesis of MNPs with a core–multilayered shell structure is developed and physicochemical and sorption properties of the synthesized particles are investigated. We used Si-containing hydrolysis products of TEOS as components for a multicomponent shell of MNPs and then gold nanoparticles synthesized in a separate syn-

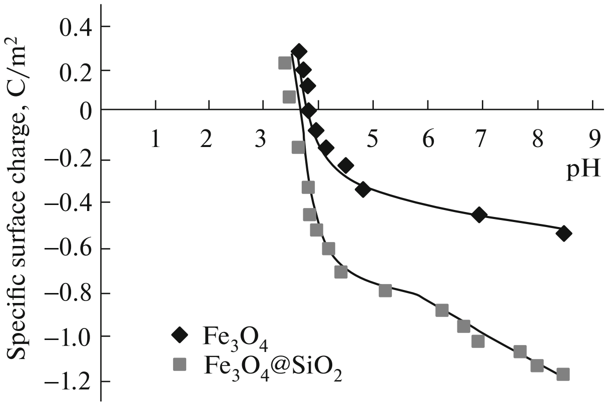


Fig. 1. Specific surface charge of Fe_3O_4 and $Fe_3O_4@SiO_2$ particles as dependent on pH.

thesis step. The drug doxorubicine (DOX) was used as a final modifying agent for MNPs.

DOX is an effective but highly toxic antibiotic of the anthracycline series. Its overall toxicity can be decreased by the targeted delivery of this drug with the use of magnetic biocompatible nanocomposite materials as carriers [18, 19]; the possibility of the release of DOX in weakly acidic media is important in this case, since tumor tissues are characterized by a lower level of extracellular pH [20].

The objectives of the present work were (1) to select conditions for the MW synthesis of a nanosized magnetic multifunctional material with the composition $Fe_3O_4@TEOS/MPTMS@Au_{coll}$, which is used then as a carrier for DOX; (2) to study the composition and properties of the products in different synthesis steps; and (3) to study the behavior of DOX in the presence of synthesized nanoparticles at different acidities of the medium (simulation of the processes of immobilization and release of DOX molecules).

Thus, the main purpose of these studies is to show, using the development of a method for the fast and effective preparation of hybrid MNPs with a core–shell structure by the MW synthesis as an example, the prospects of application of the proposed approach for the synthesis of magnetic nanosized materials that could serve as a prototype of a new class of chemotherapeutic drugs.

EXPERIMENTAL

Reagents and Materials

All the reagents were of a purity at least equal to chemically pure and analytical grades. Iron salts $FeSO_4 \cdot 7H_2O$ and $Fe_2(SO_4)_3 \cdot 9H_2O$ (Khimmed, Russia) and aqueous ammonia (25–28 wt %, special purity grade, Khimmed, Russia) were used for the synthesis of magnetic nanoparticles. Tetraethoxysilane (TEOS, Reakhim, Russia) and Z-mercaptopropyltrimethoxysilane (MPTMS, Reakhim, Russia) were used for the stabilization and modification of nanosized magnetite. Medical ethanol (ZAO Farmatsevticheskiy kombinat, Russia) and bidistilled water were used for washing the synthesized nanoparticles.

One-percent NH_4OH and H_3PO_4 solutions and a 0.001 M NaOH solution (in the synthesis of colloidal gold) were used to correct pH. A series of experiments on the adsorption of DOX were carried out in a phosphate buffer medium (1.44 g/L of sodium hydrophosphate, 0.24 g/L of potassium dihydroorthophosphate, 8 g/L of sodium chloride, and 0.2 g/L of potassium chloride; pH 7.2).

A solution of chloroauric acid $HAuCl_4$ in 10% hydrochloric acid (c = 3000 mg Au/L) and sodium citrate $Na_3C_6H_5O_7 \cdot 2H_2O$ (a 1% aqueous solution) were used for the preparation of colloidal gold nanoparticles.

Lyophilized DOX (ZAO Ferein, Russia) was used for the biofunctionalization of the obtained composite. A starting DOX solution (100 mg/L) was prepared every 2 weeks with the use of distilled water; it was stored in a fridge. Working solutions were prepared right before the experiment by appropriate dilution of the starting solution with bidistilled water.

HPLC-gradient grade acetonitrile (Panreac, Spain) was used for high-performance liquid chromatography (HPLC).

Equipment

The synthesis of nanoparticles was carried out in a Discover SP-D microwave system with a focused radiation beam (CEM Corp., United States; a frequency of 2.45 GHz; a maximum magnetron capacity of 300 W; and the programmed control of current parameters, namely: temperature and its rise rate, pressure, time, and capacity). The optical density is measured on a UV-1800 spectrophotometer (Shimadzu Corp., Japan). An Ekotest-120 pH/ion meter (Russia) supplied with an ESK-10601 combined pH electrode was used for the measurements of pH. Magnetite particles were separated from a solution by using a Nd-Fe-B magnet with $(BH)_{max}$ = 40 MG Oe. The size distributions of particles in solutions were studied by the method of dynamic light scattering (DLS) with the use of an ARN-2 particle size analyzer (Russia). The mixing was carried out using an MST magnetic stirrer (Velp Scientifica, Italy) and an LOIP LS-120 shaker (ZAO Laboratornoe oborudovanie i pribory, Russia).

Elemental analysis for the gold and sulfur content in the samples of $Fe_3O_4@TEOS/MPTMS@Au_{coll}$ (after their treatment with aqua regia at heating and subsequent dilution with a 1 M HCl solution) was performed on an IRIS Intrepid Duo atomic emission spectrometer with inductively coupled plasma (ICP-AES) (Thermo Electron Corp., United States).

The concentration of DOX in solutions was determined on an LC-20 Prominence liquid chromatograph (Shimadzu Corp., Japan) equipped with a Luna C-18(2) chromatographic column (50 mm × 4.6 mm, Phenomenex Corp., United States) and using the mixture of acetonitrile and 0.1% H_3PO_4 as a mobile phase (gradient elution from a the 15 : 85 to 100 : 0 ratio in 15 min). A column was thermally equilibrated at 45°C. The flow of eluent through a column was 1 mL/min and the volume of a dosing loop was 50 μL. DOX was detected spectrophotometrically (480 nm).

The synthesis of magnetic nanoparticles (Fe_3O_4) was described in [13] and consisted of the following procedures. In order to obtain nanosized magnetic particles, the weighed samples of $FeSO_4 \cdot 7H_2O$ (0.0424 g) and $Fe_2(SO_4)_3 \cdot 9H_2O$ (0.0873 g) were dissolved in 10 mL of bidistilled water deaerated by blowing argon through it for 10 min. The resulting solution was poured into a thick-walled glass vessel containing about 10 mL of bidistilled water deaerated as well, and then 1 mL of aqueous ammonia was added dropwise to the obtained solution of salts and stirred for 2 min with a magnetic stirrer. The vessel with the obtained suspension was subsequently placed into a microwave system and heated according to the preset program given in Table 1. After cooling the reaction mixture, a precipitate was isolated using magnetic separation and washed with bidistilled water three times.

Table 1. Conditions of the MW synthesis of hybrid magnetic nanoparticles

Nanoparticle type/MW synthesis parameters	
Fe_3O_4	
Temperature, °C	90
Capacity, W	300
Temperature rise time, min	0.5
Heat duration, min	10
Fe_3O_4@TEOS/MPTMS	
Temperature, °C	90
Capacity, W	300
Temperature rise time, min	2.5
Heat duration, min	15
Au_{coll}	
Temperature, °C	100
Capacity, W	200
Temperature rise time, min	5
Heat duration, min	5
Fe_3O_4@TEOS/MPTMS@Au_{coll}	
Temperature, °C	60–100
Capacity, W	200
Temperature rise time, min	5
Heat duration, min	5

Modification of Fe_3O_4 by Tetraethoxysilane (Preparation of Fe_3O_4@TEOS/MPTMS by Described Method [9])

For the surface modification, the synthesized particles were dispersed in a mixture of 16 mL of ethanol, 4 mL of distilled water, and 0.2 mL of aqueous ammonia solution with the subsequent addition of 60 μL of TEOS and 20 μL of MPTMS. The suspension was stirred with a magnetic stirrer for 2 min at ambient temperature. Further, a thick-walled glass vessel with its content was placed into a microwave system and heated according to the preset program given in Table 1. After cooling the reaction mixture, the product (Fe_3O_4@TEOS/MPTMS) was isolated using magnetic separation and twice washed with ethanol and twice with bidistilled water; the nanoparticles were left in 20 mL of bidistilled water. The final concentration of the product in the obtained suspension was 1 mg/mL as recalculated to the content of Fe_3O_4.

Synthesis of Colloidal Gold Particles (Au_{coll})

Gold colloid particles were synthesized using the reaction of a solution of $HAuCl_4$ in hydrochloric acid with sodium citrate. A 10-mL volume of distilled water was mixed with 120 μL of an $HAuCl_4$ solution (c = 3000 mg Au/L) and 0.7 mL of a sodium citrate solution in a thick-walled glass vessel. Then pH of the system was measured and corrected to a value of 5.5. Next the vessel with the obtained suspension was placed into a microwave system and heated using the preset program (Table 1) [15]. The typical appearance of the gold nanoparticles obtained using the MW heating and their electronic absorption spectra are shown in Fig. 2. The final concentration of gold (according to ICP-AES) in the colloidal solution was 13 μg Au/mL. According to the calibration dependence of the effective diameter of colloidal gold particles on λ_{max} [21], the mean size of particles in this case is 30 nm, which is also confirmed by the electron microscopy data.

Synthesis of Fe_3O_4@TEOS/MPTMS@Au_{coll} Nanoparticles

A suspension of Fe_3O_4@TEOS/MPTMS (3 mL) and colloidal gold nanoparticles (3 to 20 mL) were mixed in a thick-walled glass vessel and placed into a microwave system for heating according to the preset schedule given in Table 1. After cooling the reaction mixture, the product was isolated using magnetic separation, washed with bidistilled water three times, and then either used for the sorption experiments with DOX or dissolved in aqua regia under heating for carrying out the elemental analysis.

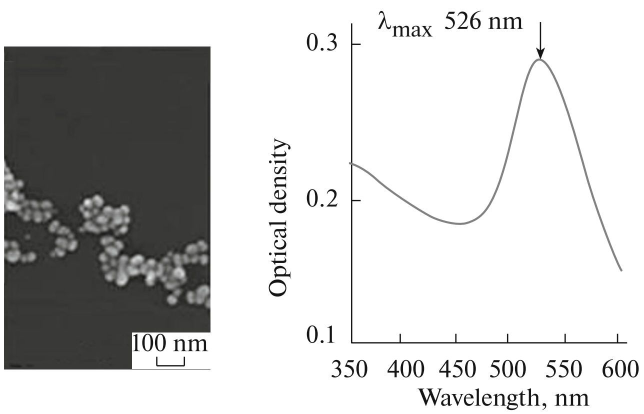


Fig. 2. Electron microphotographs of nanosized gold particles and their absorption spectrum in the visible range.

Study of DOX Soprtion Kinetics

The sorption for 3 mg (recalculated to the content of magnetite) of Fe_3O_4@TEOS/MPTMS@Au_{coll} and 3 mL of a DOX solution with a concentration of 2 mg/L was performed in 50-mL plastic centrifuge tubes at ambient temperature under strong stirring with a magnetic stirrer. The sorption of DOX in each version was carried out for 5, 10, and 15 min. After completion of the sorption process, the filtrates obtained after the magnetic separation of Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX were analyzed using the HPLC method for the presence of residuals of DOX. The data were used for calculating the amount of adsorbed antibiotic (in mg/g Fe_3O_4).

Construction of DOX Adsorption Isotherm Plot

The experiment was carried out in 50-mL plastic centrifuge tubes with screw caps. A 3-mg (recalculated to the content of magnetite) sample of Fe_3O_4@TEOS/MPTMS@Au_{coll} and 3 mL of an aqueous DOX solution with a concentration of 0.5, 1.0, 1.5, 2.5, 4.0, 7.0, 10.0, or 12.0 mg/L were placed in each centrifuge tube. Then pH was measured and corrected to a value of 7.0. After equilibration for 5 min, the filtrates were separated from particles by magnetic separation and analyzed using the HPLC method for the presence of a residual concentration of DOX; the data were used for the calculation of the adsorption value.

Study of DOX Desorption

In order to study the desorption of DOX from the surface of Fe_3O_4@TEOS/MPTMS@Au_{coll}, the sorption under the conditions corresponding to the maximum adsorption value (i.e., the initial DOX concentration was 12 mg/L, the pH value was corrected to 7.0, and the sorption duration was 5 min) was first carried using the method given above. After completion of the sorption process, the obtained Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX particles were washed once with bidistilled water and the precipitate was left in the centrifuge tube.

The desorption of DOX from the obtained precipitates was carried out into distilled water (3 mL) with a given pH value of 3.0, 4.0, 5.0, or 7.0. The desorption process in each case was carried out for 10, 20, and 30 min. After completion of the desorption process, the filtrates obtained after the magnetic separation of Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX particles were analyzed by the HPLC method. Using the data, the amount of desorbed antibiotic in percentage to the amount of adsorbed DOX was calculated.

RESULTS AND DISCUSSION

Details of the Synthesis of Nanomaterials under the Influence of MW Radiation

We demonstrated the efficiency of the application of the MW radiation for the practical synthesis and chemical modification of the surface of different nanoparticles by the examples of the synthesis of nanomagnetite [13], its subsequent modification by surfactants [13, 14] and tetraethoxysilane [9], and the synthesis of a colloidal gold sol [15]. In the same works, optimal conditions for the MW synthesis (heating time, temperature, and component ratios) were determined. It was established that high volume and time gradients of the MW heating give rise not only to a significant decrease in the synthesis duration, but also allow one to obtain monodisperse particles [12]. The aligning action of the electromagnetic field in combination with the dielectric characteristics of magnetite leads to the formation of more ordered (in comparison with the usual conditions) layers of surfactants and polymers on the surface. These factors indicate the advantage of the application of the MW synthesis for the preparation of materials with specified properties; however, this approach is only rarely applied in the domestic literature, for example, in [16, 17].

The following synthesis scheme was used in the present work for the preparation of magnetic nanocomposites [22]: (1) the preparation of an aqueous suspension of magnetite nanoparticles, (2) building up a silica-gel shell with the use of TEOS and MPTMS, (3) the preparation of a colloidal gold suspension, and (4) the sorption of colloidal gold through the formation of sulfur–gold covalent bonds. Each stage was carried out under the conditions of MW heating. Conditions for the stepwise preparation of the materials are described in the experimental part and given in Table 1.

Modification of the Fe_3O_4@TEOS/MPTMS Surface by Gold Nanoparticles

The Fe_3O_4@TEOS/MPTMS magnetic carrier consists of particles of the core–shell type. The magnetic core can play the role of a contrasting agent in the MRT studies, while the silicon-containing shell protects the magnetite core from oxidation and provides better biocompatibility and aggregate stability. The additional introduction of sulfur-containing silane (MPTMS) into the composition of a silicon-containing shell is intended to provide stronger (covalent) attachment of gold nanoparticles on the shell surface by means of Au–S bonds; in turn, gold nanoparticles in MNPs bring additional fluorescent properties (preparation of fluorescent markers) and the ability to transform the near-infrared radiation energy to the thermal energy (phototherapy).

The study of immobilized colloidal golf on Fe_3O_4@TEOS/MPTMS particles included the synthesis of Fe_3O_4@TEOS/MPTMS@Au_{coll} samples at different processing temperatures and component ratios and the determination (after appropriate sample preparation) of the content of gold and sulfur in them (the sulfur content in MNPs is determined from the amount of immobilized MPTMS). The results are given in Fig. 3. The initial $Fe_3O_4 : Au_{coll}$ ratio in the experiments remained the same with the variation of temperature and equaled 1 : 0.013 (mg/mg). As is seen from the data, the amount of colloidal gold immobilized on the surface of Fe_3O_4@TEOS/MPTMS particles is maximum and equal to 7.8 μg/mg magnetite (or 60.2% from the taken amount) in the investigated temperature range from 75 to 85°C. Since it is assumed that gold nanoparticles are fixed on the surface of Fe_3O_4@TEOS/MPTMS particles primarily through the formation of covalent Au–S bonds, we also calculated the Au/S molar ratios. The fact that the largest ratio (0.69) in the investigated particles is observed at 75°C can be explained by the maximum degree of formation of these bonds in the above conditions.

Varying the initial magnetite : gold ratio, it is established that the largest amount of colloidal gold is adsorbed at a Fe_3O_4 : Au ratio of 1 : 0.13 mg/mg, specifically, 18.5 μg Au/mg Fe_3O_4 (14.2% from the initial amount); the gold/sulfur molar ratio is also maximum (1.205) at the chosen ratio of the initial components.

Based on the results of the performed experiments, the following conditions of the MW modification were chosen for further studies on the DOX sorption properties: a temperature of 75°C and a Fe_3O_4 : Au ratio of 1 : 0.13 mg/mg.

Characteristics of Modified Magnetic Nanoparticles Sizes of Synthesized Fe_3O_4@TEOS/MPTMS@Au_{coll} Particles as Dependent on the Method of Synthesis and the Initial Ratio of Components

According to the data of electron microscopy and powder X-ray diffraction analysis [13], the microwave synthesis of magnetite nanoparticles yields large aggregates composed of particles with a diameter of about 10 nm. The aggregation degree significantly decreases in the presence of any stabilizers (oleic acid, mercaptopropyionic acid, etc.), so particles with a size from several tens to hundreds of nanometers are formed. The hybrid nanomaterial prototypes on the basis of magnetite, which are described in the literature and successfully applied for therapeutic purposes (in vivo as well), have final sizes in the range from 8–10 [18] to 150 [13] and 200–400 nm [10]. The results of our studies of the Fe_3O_4@TEOS/MPTMS@Au_{coll} particles by the DLS method, which were synthesized using a Discover SP-D microwave system and differed by the content of colloidal gold, show that a significant fraction of the particles has a size in the range from 100 to 1000 nm (Fig. 4), i.e., a quite suitable particle size for testing them as drug-carrier models. As is also seen from Fig. 4, the maximum of the corresponding distribution curves is shifted to smaller particle sizes in the Fe_3O_4–Fe_3O_4@TEOS/MPTMS–Fe_3O_4@TEOS/MPTMS@Au_{coll} sequence, and peaks become higher and narrower; i.e., the additional modification of magnetite nanoparticles gives rise to the production of particles with a smaller size and narrower distribution. The preparation of less aggregated monodisperse MNPs is of crucial importance for further in vivo experiments.

Interaction of Fe_3O_4@TEOS/MPTMS and Fe_3O_4@TEOS/MPTMS@Au_{coll} with Constant Magnetic Field

A constant magnetic field imposed on aqueous dispersions of the synthesized MNPs samples gives rise to their motion. The full separation of particles from a solution under the influence of a magnet is shown in Fig. 5, which requires about 1 min and proves the preservation of magnetic properties after the building up of a multilayered shell on the surface of magnetite. The efficiency of the separation of particles from a filtrate does not depend on the content of gold or on the storage time of the sorbent (up to 3 months at room temperature).

Immobilization of DOX onto the Fe_3O_4@TEOS/MPTMS@Au_{coll} Particles

Dependence of the DOX Immobilization (Adsorption) Degree on the Phase Contact Time and Solution pH

The experimental data on the DOX adsorption degree on the phase contact time and pH are given in Fig. 6. As is seen from the results, the equilibrium in the entire range of the investigated pH values is reached as soon as after 5 min; accordingly, the phase contact duration in the further experiments was 5 min. The largest amount of DOX bound on the surface of Fe_3O_4@TEOS/MPTMS@Au_{coll} nanoparticles is observed at pH 7 (85.0 to 88.5% of the taken amount), while the adsorption significantly decreases at pH 3.1 (21.0 to 27.5%).

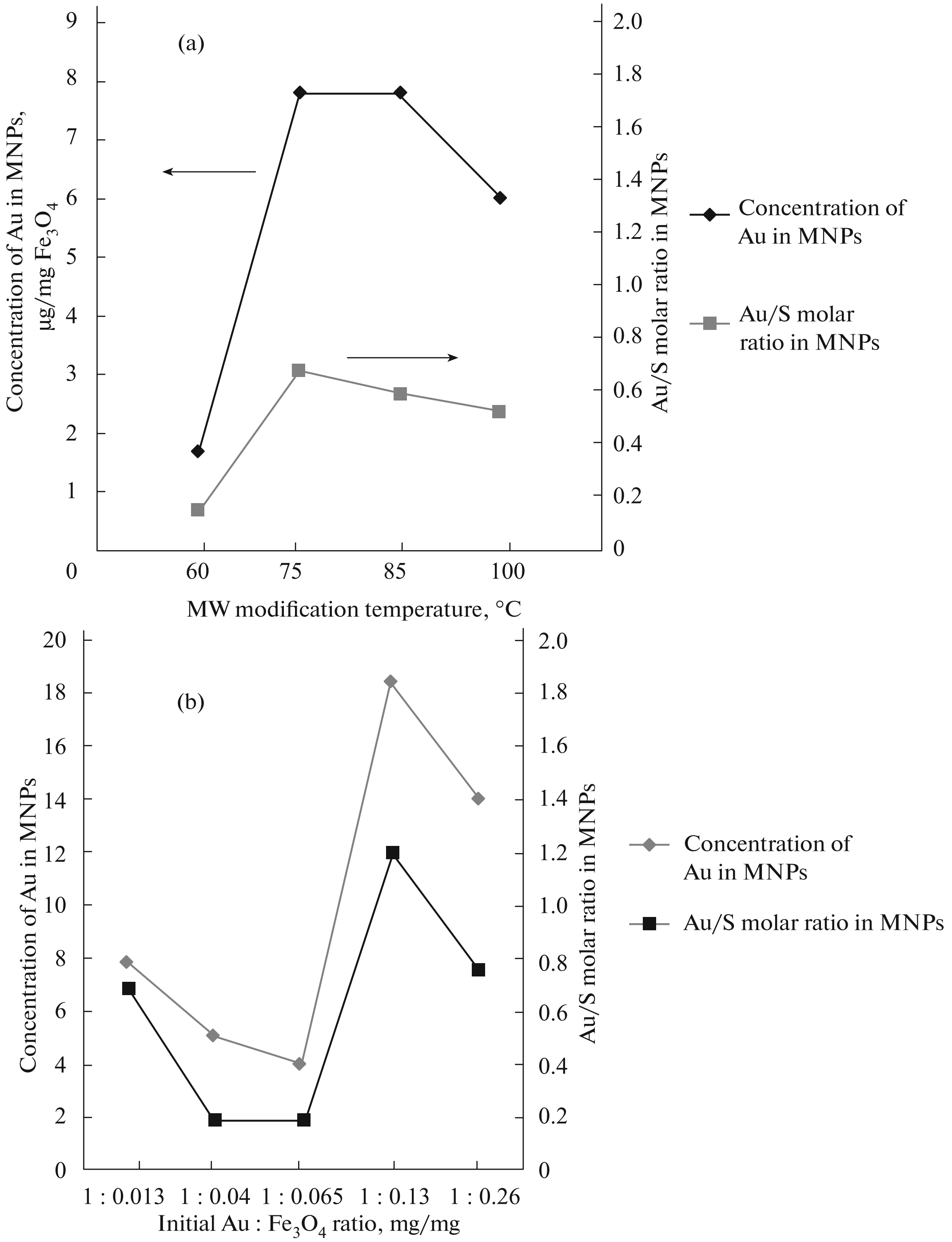


Fig. 3. Concentration of immobilized gold and the gold–sulfur ratio in the synthesized hybrid nanoparticles at different (a) temperatures of the MW modification and (b) reagent ratios.

Isotherms of the Sorption of DOX on Fe_3O_4@TEOS/MPTMS@Au_{coll} and Fe_3O_4@TEOS/MPTMS

In order to evaluate the DOX sorption capacity of the nanomaterials and to understand a possible DOX sorption mechanism, the sorption isotherm for the Fe_3O_4@TEOS/MPTMS@Au_{coll} nanoparticles synthesized under the optimal conditions (see above) was constructed. As is seen from Fig. 7, the isotherm is of the Langmuir type, i.e., describes the process of gradual filling of the sorbent surface with the formation of a saturated monomolecular sorbate layer at the limit. The limiting capacity of the adsorptive monomolecular layer in our case was about 8 mg DOX/g Fe_3O_4 or

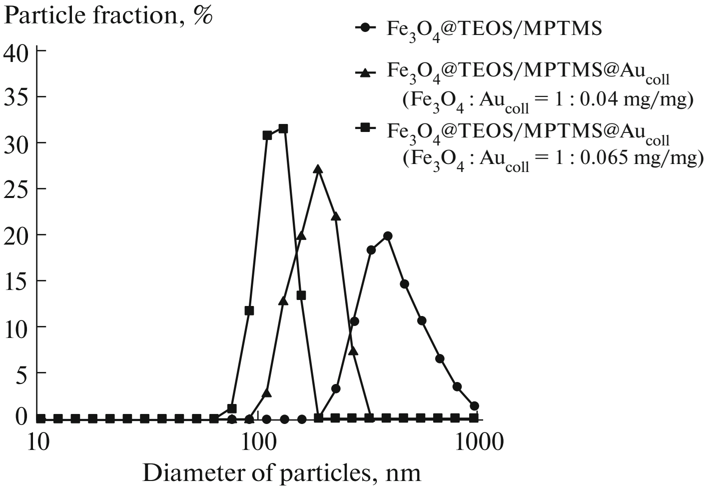


Fig. 4. Size distribution of Fe_3O_4@TEOS/MPTMS and Fe_3O_4@TEOS/MPTMS@Au_{coll} particles according to the dynamic light scattering data.

0.015 mmol DOX/g Fe_3O_4. Taking into account the available data on the specific surface area of silica-gel-coated nanosized magnetite prepared in a similar way (168 m^2/g) [23], the area occupied by one molecule upon the DOX sorption can be estimated (1855 A^2/molecule or 11.1 $m^2/\mu mol$).

A study of the adsorption of DOX on Fe_3O_4@TEOS/MPTMS showed that the isotherms are quite similar. This allows one to assume that both immobilized gold nanoparticles and hydroxyl groups of the silica-gel shell can serve as adsorption sites for DOX molecules.

Desorption of DOX from the Surface of Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX Nanoparticles

As was noted above, the drug-use efficiency is basically determined by the possibility of the targeted drug delivery into the focus of the pathological process; therefore, the aim of this experiment was to demonstrate in vitro that a controlled process of the release of DOX from the surface of the synthesized

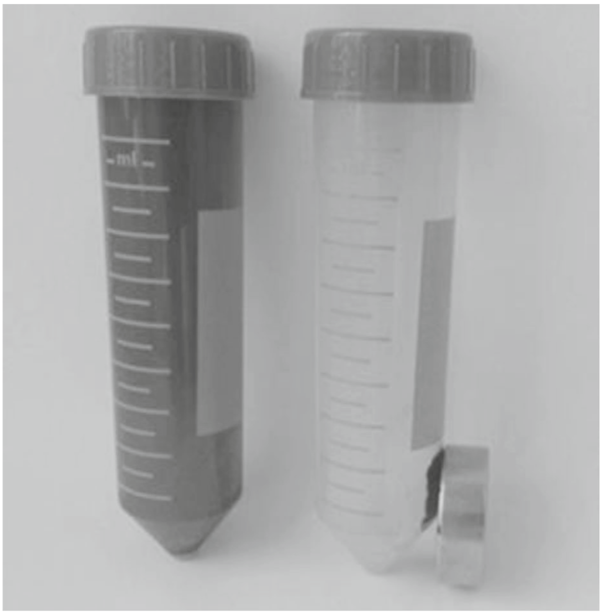
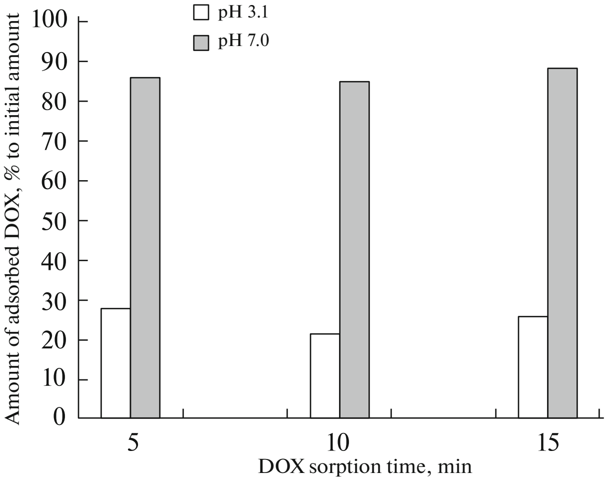
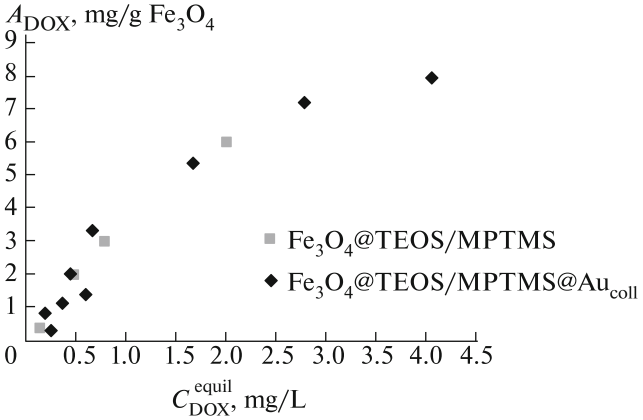


Fig. 5. Illustration of the action of a constant magnetic field on an aqueous Fe_3O_4@TEOS/MPTMS@Au_{coll} dispersion.



The initial concentration of DOX is 2 mg/L
The DOX solution volume is 3 mL
The sorbent sample weight recalculated to the amount of Fe_3O_4 is 3 mg

Fig. 6. Dependence of the adsorption degree of DOX on Fe_3O_4@TEOS/MPTMS@Au_{coll} particles on the contact time of phases and on pH of a solution.



Sorption pH is 7.0
The sorption duration is 5 min
The sorbent sample weight recalculated to the amount of Fe_3O_4 is 3.0 mg
The DOX solution volume is 3.0 mL

Fig. 7. Sorption isotherms of DOX on Fe_3O_4@TEOS/MPTMS and Fe_3O_4@TEOS/MPTMS@Au_{coll} particles.

Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX nanoparticles, depending on the system pH value, is possible. The desorption values of DOX from Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX nanoparticles at different pH are given in Table 2. As is seen from the data, the DOX desorption degree significantly increases (to 35–36% in average) upon lowering the pH value to the acidic region; at the same time, the following dependence is clearly traced: the desorption degree sharply increases below a certain pH value and almost does not change upon further lowering of the level of pH while the DOX desorption is nearly absent at pH 7.

Table 2. Kinetics of the process of DOX desorption from the surface of Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX particles at different pH

pH	Desorption time, min	C^{desorp}_{DOX}, mg/L (at $C^{init}_{DOX} = 12$ mg/L)	DOX desorption degree, % of the adsorbed amount
7	20	0.01	<0.1
	30	<0.001	<0.1
5	20	4.04	37.4
	30	2.48	32.9
4	20	4.18	38.7
	30	3.40	33.5
3	20	3.96	36.7
	30	3.94	36.5

The desorbing solution volume is 3 mL.

In summary, we have experimentally confirmed the assumption about a reversible mechanism of the interaction of DOX with the MNPs surface and showed that pH plays the role of a sort of switch initiating the desorption process. Thus, these preliminary in vitro experiments have a significant potential for the design of multifunctional nanomaterials and for understanding the mechanisms of their action.

CONCLUSIONS

A method for the microwave synthesis of magnetic materials with a magnetic core–multilayered shell structure is proposed, and the advantage of this approach for the fast and simple preparation of nanosized composites is demonstrated by the example of the preparation of Fe_3O_4@TEOS/MPTMS@Au_{coll}@DOX nanoparticles. The nanosized magnetite core was modified layer by layer using the TEOS + MPTMS mixture and colloidal gold. Particles with such a structure are potentially capable of serving as new multifunctional materials for MRT diagnostics, hyperthermia, and targeted drug delivery.

Based on the data concerning the content of gold and sulfur in the synthesized Fe_3O_4@TEOS/MPTMS@Au_{coll} samples, we have optimized the conditions for the microwave modification with colloidal gold (temperature and reagent ratios). The results allow one to evaluate the efficiency of the proposed procedure.

The processes of the immobilization of DOX onto the synthesized MNPs are studied at different phase contact times, DOX concentrations, and pH of media. The possibility of the controlled release of DOX from the surface of Fe_3O_4@TEOS/MPTMS@Au_{coll} particles depending on the medium acidity is shown, and the common possibility of the targeted delivery of immobilized chemotherapeutic drugs and their release in the conditions of the changed medium acidity is thereby demonstrated by the example of DOX.

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