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SYNTHESIS AND PROPERTIES OF MAGNETICALLY SENSITIVE NANOCOMPOSITES BASED ON MAGNETITE AND GEMCITABINE

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The aim of the work is synthesis of new polyfunctional magnetosensitive nanocomposites (NC) capable of the targeted delivery in the tumors of hepatocellular carcinoma and intrahepatic cholangiocarcinoma of a drug with chemotherapeutic mechanism of action – gemcitabine (GC), and deposition with the help of magnetic field, investigation of the basic physico-chemical properties of NC. Research direction includes synthesis of nanosized one-domain magnetite as a magnetically sensitive carrier, modification of its surface by carbon covering with the aim of stabilization and chemical functionalization, biofunctionalization of NC by GC immobilization.

For investigation the following samples of NC were synthesized: Fe_3O_4, Fe_3O_4/HA, Fe_3O_4/C. The choice of samples is explained by the necessity to obtain a protective biocompatible cover with high adsorptive properties on a surface of magnetosensitive carrier. Carbonization of Fe_3O_4 surface and obtaining of Fe_3O_4/C NC was realized with the help of an organic substance – CS polygel (Carbomer 934).

Adsorption of GC on a surface of magnetite and Fe_3O_4/HA, Fe_3O_4/C NC was carried out in aqueous medium in the concentration range C_0 = 0.2–0.8 mg/L (g = 0.03 g, V = 5 mL, pH = 7.0) for 2 h in dynamic regime at room temperature. Amount of the adsorbed substance on a surface of NC was determined with the help of a spectrophotometer at λ = 268 nm from a calibration graph.

Adsorption characteristics were studied for surfaces of the synthesized NC with respect to GC. The results obtained show the dependence of adsorption capacity of the investigated samples on chemical nature of their surface. An increase in equilibrium GC concentration leads to a growth of adsorption capacity of Fe_3O_4/HA NC, which becomes almost in saturation for Fe_3O_4 and Fe_3O_4/C NC. The surfaces of NC researched are characterized by rather like values of adsorption parameters (A = 25–30 mg/g), which may be caused by similar nature of adsorption centers of their surfaces and adsorption mechanisms. GC extraction extent R (%) is 25–30 %.

Magnetic properties of NC with adsorbed gemcitabine Fe_3O_4/GC, Fe_3O_4/HA/GC, Fe_3O_4/C/GC were investigated with the help of a laboratory vibration magnetometer. An idea of the investigations is based on the use of an ensemble of superparamagnetic carriers as a probe for determination of parameters and control of core-shell type nanostructures with complex composition. Hysteresis loops were measured for magnetite particles, and NC with immobilized GC. It has been determined by the magnetic granulometry methods that the thickness of GC shell in the composition of Fe_3O_4/GC NC is (2.4±0.1) nm. Considering the thickness of GC layer is equal to 2.4 nm in all the studied nanostructures, we have found the value of thickness of hydroxyapatite layer in the structure of Fe_3O_4/HA/GC NC (3.5±0.1 nm), and the thickness of C layer in Fe_3O_4/C/GC NC (3.2±0.1 nm).

The obtained data may be useful in creation of medical magnetocarried nanosystems of targeted delivery and adsorptive materials for application in oncotherapy.

Keywords: *gemcitabine, carbonization, hydroxyapatite, carbon coatings, surface, magnetite, magnetically sensitive nanocomposites, adsorption*

In works [1–10] we formulated a concept, created experimental samples, investigated and patented magnetically sensitive nanocomposites (NC) with multilevel hierarchical nano-architecture and functions of biomedical nanorobots: recognition of microbiologic objects in biological media; targeted delivery of drugs to specific cells and organs, accumulation of therapeutic doses and deposition; complex therapy by chemo-, immune-, radiation neutron capture-, hyperthermic-, photodynamic methods and diagnostics in real time regime.

As known, the targeted delivery and deposition of drug carriers in tumor area by

magnetic field give a possibility to decrease the total therapeutic dose of cytotoxic drugs considerably and, respectively, reduce to a minimum toxico-allergic reactions of an organism, and the use of local hyperthermia makes it possible, in principle, to carry out therapy of cancer diseases without application of chemical preparations [3–10].

The outlined theme investigations are goal-directly and systematically carrying out in collaboration by research workers of O.O. Chuiko Institute of Surface Chemistry, NAS of Ukraine, and R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine [1–5, 11–15]. Up to this time, with the use of magnetosensitive NC, the new native oncological drug «Feroplat» was developed for application in clinical practices in treatment of malignant neoplasms, as well as the technology of its manufacture.

«Feroplat» is a conjugate of magnetic fluid nanoparticles with cisplatin. It is a standardized remedy for increase in effectiveness of chemotherapy and overcoming of medicament resistance of malignant neoplasms, purposed for delivery of a cytostatic agent immediately into tumor tissue, which ensures its maximal coming into cells and promotes an increase in therapeutical effect. Its capability to selective accumulation in tumor improves antitumor effect of cisplatin, so increasing a biological safety level. Unlike the known chemotherapy drugs, “Feroplat” is more active with respect to tumors that are resistant to cisplatin, and proves less toxicity for normal cells. It has no analog in the world [16, 17].

This work continues our previous investigations. Its aim is the synthesis of new polyfunctional magnetosensitive nanostructures capable of the targeted delivery in the tumors of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) of drug with chemotherapeutic mechanism of action – gemcitabine, and deposition by the help of magnetic field with the additional functions of hyperthermic therapy and magnetic resonance imaging diagnostics in real time regime.

As known [18], HCC is a highly lethal kind of cancer. HCC is the second on frequency among the most expanded death reasons with cancer in the world – 745 000 patients are dead with this disease every year. HCC morbidity continues to increase, for instance in USA during the last thirty years the morbidity and mortality through HCC has tripled. The approaches of HCC treatment depend on the stage of disease to a moment of giving the diagnosis and on accessibility of complex therapy methods. However, the disease in late stages is problematic, its treatment is expensive and effective only with respect to increase in index of «qualitatively ensured life years». Prognosis with HCC is usually quite unfavourable.

The modern variants of HCC treatment, such as surgical resection of liver, transplantation of liver and locoregional therapy, including radiofrequency ablation and transarterial chemoembolization, are limited by very early stages of disease and can not prevent relapse. Moreover, most of patients (> 80 %) are at the last or non-operable stages of cancer, and the effective variants for treatment of such patients are practically absent. For such cases, the localized and systematic radiotherapy was applied simultaneously with chemotherapy, but with limited success.

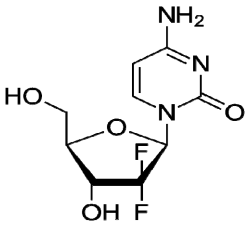
ICC is a malignant tumor of bile ducts [19]. The basic method of ICC treatment is operative. A total surgical ablation of tumor can potentially be used for ICC treatment, but prognosis keeps unfavourable because of frequent relapses and metastasis of tumors after operation. Chemotherapy and radiotherapy are used in complex with surgical method or as palliative treatment.

As cleared from the said, HCC and ICC are very heavy diseases, and perspectives of treatment are quite non-optimistic. However, in the specialized research-medical centers of the developed countries, the goal-oriented investigations are carried out with the aim of search for the ways of overcoming the problem. So, for example, in one of the approaches chosen in the Department of Gastroenterology, Hepatology and Endocrinology of Hannover Medical School (MHH), Hannover, Germany, it is planned the use of magnetosensitive nanocomposites modified with chemo- and immunotherapeutical drugs and local methods of therapy [20–22].

The said data show that the task of synthesis of new polyfunctional magnetosensitive nanostructures capable of the targeted delivery into HCC and ICC tumors of a drug with chemotherapeutic mechanism of action is actual from both scientific and practical points of view.

EXPERIMENTAL TECHNIQUES

In this work, gemcitabine (GC) was chosen as a drug of the chemotherapeutic mechanism of action. Gemcitabine is a cytotoxic drug, an antimetabolite from the group of pyrimidine antagonists. The molecular formula is $C_9H_{11}F_2N_3O_4{\cdot}HCl$, molecular weight 299.66, the structural formula of respective base is given below:



The drug exhibits cyclospecificity acting on cells in the phases S and G1/S. Gemcitabine is metabolised inside the cell under the action of nucleoside kinases with the formation of active diphosphate and triphosphate nucleosides. Diphosphate nucleosides inhibit ribonucleotide reductase, that acts as a single catalyst for reactions, leading to the formation of deoxynucleoside triphosphates, necessary for DNA synthesis. Triphosphate nucleosides compete actively with deoxycytidine triphosphate embedded in the DNA molecule and RNA. After embedding intracellular metabolites of gemcitabine into the DNA chain, another additional nucleotide is added to its growing strands. As a result, complete inhibition occur of further DNA synthesis and programmed lysis of the cell, known as apoptosis. Common side effects include bone marrow suppression, liver and kidney problems, nausea, fever, rash, shortness of breath, and hair loss. GC belongs to the list of the basic medicines of the World Health Organization, the most effective and safe medicines needed in a health system, it is commonly used off-label to treat cholangiocarcinoma and other biliary tract cancers [23, 24].

For investigation the following samples of magnetosensitive nanostructures were synthesized: ensembles of Fe_3O_4 nanoparticles, NC Fe_3O_4/HA, Fe_3O_4/C based on them. The choice of samples is explained by the necessity to obtain a protective biocompatible cover with high adsorptive properties on a surface of magnetosensitive carrier.

Synthesis of magnetite. In the work we used the spread method for obtaining of magnetite nanoparticles – liquid phase, in the base of which the process of co-precipitation of bi- and trivalent iron salts laid according to the reaction [6]:

$$Fe^{2+} + 2Fe^{3+} + 8NH_4OH \rightarrow Fe_3O_4 + 4H_2O + 8NH_4^+.$$

The size of the obtained particles was from 3 to 23 nm with the average size of 8–12 nm. Specific surface area of the synthesized magnetite was $S_{sp} \sim 110$ m^2/g. As calculated from the data of thermogravimetric analysis, the concentration of surface hydroxyl groups was 2.4 mmol/g.

The synthesized magnetite is characterized by satisfactory magnetic characteristics: coercive force $H_c = 55.0$ Oe, saturation magnetization $\sigma_s = 56.2$ Gs·cm^3/g, relative residual magnetization $M_r/M_s = 0.2$. Such characteristics are important for biomedical applications, for example in the targeted delivery of drugs through blood vessels of small diameter, in which aggregation of particles is quite undesirable.

Hydroxyapatite cover was obtained on a surface of highly dispersed magnetite by sol-gel method according to the reaction stoichiometry:

$$10Ca(NO_3)_2 + 6(NH_4)_2HPO_4 + 8NH_3 + 2H_2O \rightarrow$$
$$\rightarrow Ca_{10}(PO_4)_6(OH)_2 + 20NH_4NO_3.$$

For $Ca_{10}(PO_4)_6(OH)_2$ synthesis the necessary amount of components was calculated so that molar ratio Ca : P was within the limits of 1.67 : 1.75 with excess of ammonia (pH = 11) [6]. The obtained samples were tested by the methods of XPS and XPA. From the data of XPS for the synthesized nanocomposite samples the ratio Ca/P was 1.6–1.7. It is close to the optimal stoichiometric value for hydroxyapatite (Ca/P = 1.67). As appreciated from Fe2*p*-/Fe3*p*-line area ratio and from the increase in NC mass, thickness of hydroxyapatite layer on a surface of magnetite is ~ 4 nm. The specific surface area for Fe_3O_4/HA samples $S_{sp} = 105$ m^2/g. Concentration of the surface hydroxyl groups is ~ 2.2 mmol/g.

Carbonization of Fe_3O_4 surface and obtaining of Fe_3O_4/C NC was realized by the help of an organic substance – CS polygel (Carbomer 934).

Carbomers are the derivatives of acrylic acid, from which under certain conditions and by

use of certain methods one obtains gels used in pharmacology as the basis for soft, liquid and solid medical forms. They are ether of acrylic acid homopolymers crosslinked by allyl sucrose, allyl pentaerythritol or divinyl glycol. Molecular mass of these polymers was theoretically calculated to be within the limits from 700000 to 3–4 milliards, however methods for determination of the real molecular mass are absent. The repeated fragment (–CH_2-CH-COOH) has molecular mass from 72 to 78, containing from 56 to 68 % of carboxyl groups as calculated for onto the dry substance [25].

The nanodispersed magnetite (mass $g = 0.5$ mg) was impregnated with 3 % solution of CS polygel (Carbomer 934) ($V = 5$ mL) in the distilled water at room temperature. After drying at 115 °C, a matrix was obtained with the adsorbed organic substance and roasted at 400 °C for 2 h in argon flow. Specific surface area of Fe_3O_4/C samples was $S_{sp} = 59$ m^2/g.

The experimental results show that the process of carbonization of magnetosensitive nanocomposites is optimally carried out at 400 °C for 2 h.

Specific surface area of the samples was determined by nitrogen thermal desorption by means of a KELVIN 1042 device from «COSTECH Instruments». NP size was appreciated by formula $D_{BET} = 6/(\rho S_{BET})$, where ρ is the density of NP material, S_{BET} is the value of specific surface area calculated according the polymolecular adsorption theory of Brunauer, Emmett and Teller (BET).

Calculation of the ***concentration of hydroxyl groups*** on a surface of nanostructures was determined from the data of thermogravimetric analysis using a derivatograph Q–1500.

Adsorption of GC on a surface of magnetite and Fe_3O_4/HA, Fe_3O_4/C nanocomposites was carried out in aqueous medium in the concentration range $C_0 = 0.2$–0.8 mg/L ($g = 0.03$ g, $V = 5$ mL, pH = 7.0) for 2 h in dynamic regime at room temperature. The amount of the adsorbed substance on a surface of nanocomposites was determined by the help of a spectrophotometer at $\lambda = 268$ nm from a calibration graph. The calibration graph was obtained from UV- spectrophotometric data.

Adsorption capacity of the nanostructures A (mg/g) we calculated by formula:

$$A = (C_0 - C_{eq}) \cdot V/m,$$

where: C_0 and C_{eq} are concentration of the initial solution and the solution after adsorption (mg/L), V is volume of the solution (mL), m is mass of the sorbent (g).

Extraction extent R (%) was determined by formula: $R, \% = [(C_0 - C_{eq})/C_0] \cdot 100$.

Magnetic properties of the composites with adsorbed gemcitabine Fe_3O_4/GC, Fe_3O_4/HA/GC, Fe_3O_4/C/GC were investigated by the help of a laboratory vibration magnetometer.

RESULTS AND DISCUSSION

Adsorption characteristics were studied for surfaces of the synthesized nanocomposites with respect to gemcitabine. Results of the obtained isotherms of GC adsorption are shown in Fig. 1, *a, b, c*.

The results obtained show dependence of adsorption capacity of the investigated samples on chemical nature of their surface. An increase in equilibrium GC concentration sets off for adsorption saturation of Fe_3O_4/HA surface, with Fe_3O_4 and Fe_3O_4/C almost becoming in saturation.

On a surface of Fe_3O_4/HA and Fe_3O_4/C composites at small concentrations, a weak interaction with a surface is observed, then beginning to increase sharply with growing concentration of adsorbate.

The surfaces of NC researched are characterized by rather close values of adsorption parameters ($A = 25$–30 mg/g). It may be caused by similar nature of adsorption centers of their surfaces and adsorption mechanisms. Extraction extent R (%) is 25–30 % (Table 1).

Table 1. Characteristics of gemcitabine adsorption on a surface of nanostructures under the conditions: $C_0 = 0.8$ mg/mL, $g = 0.03$ g, $V = 5$ mL, pH = 7.0

Nanostructure	A, mg/g	R, %
Fe_3O_4	25.8	25.3
Fe_3O_4/C	30.0	29.0
Fe_3O_4/HA	30.5	24.8

Experimental results show that the synthesized nanocomposites are promising for application as adsorption materials in intracorporal (enterosorption) and extracorporal detoxification.

Magnetic properties of the synthesized nanostructures were investigated by techniques

[24, 25]. An idea of the investigations is based on the use of a superparamagnetic carrier as a probe for determination of parameters and control of complex composition nanostructures.

Hysteresis loops measured for magnetite particles and composites with immobilized gemcitabine are shown in Fig. 2 (σ is specific magnetization, H – magnetic field strength).

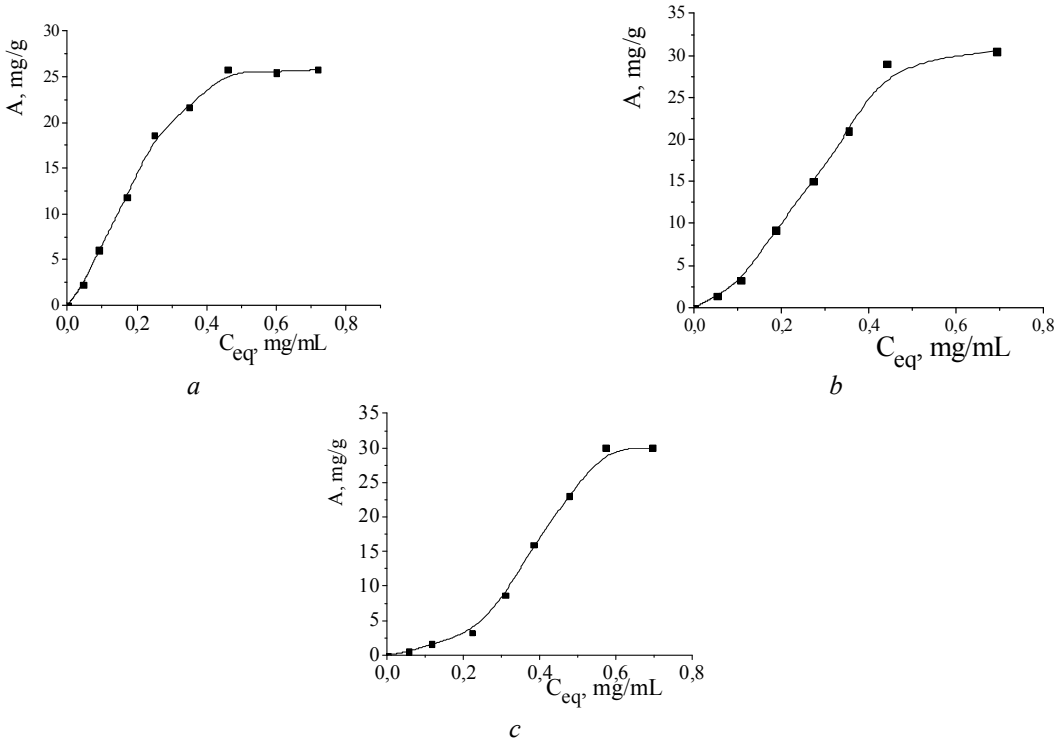


Fig. 1. Isotherms of GC adsorption on a surface of magnetite (*a*) and composites Fe_3O_4/HA (*b*), Fe_3O_4/C (*c*)

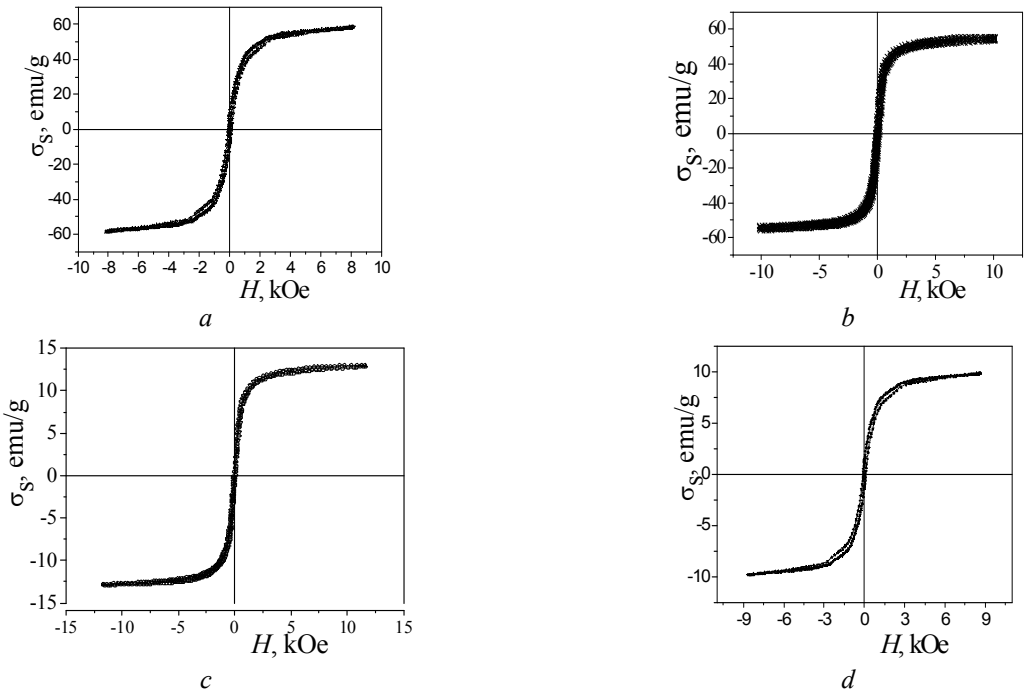


Fig. 2. Hysteresis loops for magnetite (*a*), and composites Fe_3O_4/GC (*b*), Fe_3O_4/HA/GC (*c*), Fe_3O_4/C/GC (*d*)

The saturation magnetization of composite particles is sufficient for their use as the remedies of targeted delivery of drugs and the adsorption materials for intracorporal and extracorporal detoxification of an organism.

The magnetic characteristics of magnetite and NC with adsorbed gemcitabine, obtained from the experimental hysteresis loops, are shown in Table 2.

The values of σ_s indicate the presence of shell in the composites comparing to magnetite.

Using the NC model of core – multilayer shell type and the calculation techniques [26, 27], the experimentally found values of average size of Fe_3O_4 cores (d_0), specific saturation magnetization (σ_s), mass concentration of Fe_3O_4 in NC (α_{Fe3O4}^{exp}), specific surface area of NC (S_{sp}^{exp}) we found the average value of thickness of adsorbed GC layer in the composition of Fe_3O_4/GC NC to be 2.4±0.1 nm. Considering the thickness of GC layer is equal to 2.4 nm in all the studied nanostructures, we found the value of thickness of hydroxyapatite layer in the structure of Fe_3O_4/HA/GC NC (3.5 ± 0.1 nm; in our opinion, this is satisfactorily coordinated with the value ~ 4 nm [27]) and the thickness of C layer in Fe_3O_4/C/GC NC (3.2 ± 0.1 nm).

Table 2. Magnetic characteristics of magnetite and composites with adsorbed gemcitabine

No	Sample	H_c, kOe	σ_s, emu/g	$\sigma_{H=8\ kOe}$, emu/g	σ_r, emu/g	σ_r/σ_s	α_{Fe3O4}^{calc}, %
1	Fe_3O_4	0.081(7)	60.1	58.4	7.28	0.121	100
2	Fe_3O_4/GC	0.079(9)	55.8	54.2	5.66	0.101	92.8
3	Fe_3O_4/HA/GC	0.085(9)	14.2	13.5	4.16	0.118	23.6
4	Fe_3O_4/C/GC	0.101(3)	10.2	9.7	3.85	0.114	17.1

H_c, kOe is coercive force, σ_s, emu/g is specific saturation magnetization, $\sigma_{H=8\ kOe}$, emu/g is specific magnetization in the field of 8 kOe, σ_r, emu/g is residual specific magnetization, σ_r/σ_s is relative residual magnetization, α_{Fe3O4}^{calc} is the calculated mass concentration of Fe_3O_4 in NC, %

We note that using techniques [26, 27] one can calculate: density of the shell ρ, function $h(d)$, where h, d are thickness values of the shell and diameter of Fe_3O_4 NP, respectively, specific surface area of the samples, as well as to find ρ and $h(d)$ at which NC ensembles have the maximal specific surface area. Such data may be actual for analysis of medical magnetocarried systems promising for the use in oncotherapy.

The data said show that the synthesized magnetocarried NC are promising for continuation of the goal-oriented investigations aimed at creation of a new nanotechnology for oncology, based on the use of polyfunctional nanostructures capable of the targeted delivery of chemotherapeutical drug gemcitabine and deposition. The principal capability to realize the additional functions of recognition of tumor cells, hyperthermic therapy and magnetic resonance imaging diagnostics in real time regime was substantiated in [6].

CONCLUSIONS

New polyfunctional magnetosensitive nanostructures were synthesized capable of the targeted delivery into tumors of hepatocellular carcinoma and intrahepatic cholangiocarcinoma of the drug with chemotherapeutic mechanism of action – gemcitabine. The processes of adsorption of gemcitabine from its solutions in a physiological liquid on a surface of magnetite and magnetically sensitive NC with various surface nature were investigated. Adsorption of gemcitabine is: A = 25–30 mg/g (C_0 = 0.8 mg/mL, g = 30 mg, V = 5 mL). The quantity of GC on a surface of NC was determined by spectrophotometric method at λ = 268 nm according to the calibration graph. The magnetic properties of synthesized nanostructures were studied. From the data of magnetic measurements, the size parameters of nanocomposite components were determined. The synthesized magnetocarried NC are promising for creation of a new nanotechnology

for oncology, based on the use of polyfunctional nanostructures capable of recognizing of HCC and ICC tumors, the targeted delivery of drugs of the chemotherapeutic and immunotherapeutic mechanism of action on them, and deposition with additional functions of hyperthermic therapy and magnetic resonance imaging diagnostics in real time regime.

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Синтез і властивості магніточутливих нанокомпозитів на основі магнетиту і гемцитабіну

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Метою роботи є синтез нових поліфункціональних магніточутливих нанокомпозитів (НК), здатних до цільової доставки в пухлини гепатоцелюлярної карциноми і внутрішньопечінкової холангіокарциноми лікарського препарату хіміотерапевтичного механізму дії гемцитабін (ГЦ) та депонування за допомогою магнітного поля, дослідження основних фізико-хімічних властивостей НК. Напрямок досліджень включає синтез нанорозмірного однодоменного магнетиту як магніточутливого носія, модифікування його поверхні вуглецевим покриттям задля стабілізації та хімічної функціоналізації, біофункціоналізацію НК шляхом іммобілізації ГЦ.

Для досліджень синтезовано наступні зразки НК: Fe_3O_4, Fe_3O_4/ГА, Fe_3O_4/С. Вибір зразків пояснюється необхідністю отримання на поверхні магніточутливого носія захисного біосумісного покриття з високими адсорбційними властивостями. Карбонізацію поверхні Fe_3O_4 та отримання НК Fe_3O_4/С здійснювали за допомогою органічної речовини – полігеля CS (Карбомер 934).

Адсорбцію ГЦ на поверхні магнетиту та НК Fe_3O_4/ГА, Fe_3O_4/С проводили у водному середовищі в діапазоні концентрацій C_0 = 0.2–0.8 мг/мл (g = 0.03 г , V = 5 мл, pH = 7.0) протягом 2 год у динамічному режимі при кімнатній температурі. Кількість адсорбованої речовини на поверхні НК визначали за допомогою спектрофотометра при λ = 268 нм за калібрувальним графіком.

Вивчено адсорбційні характеристики поверхонь синтезованих НК щодо ГЦ. Одержані результати свідчать про залежність адсорбційної ємності досліджених зразків від хімічної природи їх поверхні. Зростання рівноважної концентрації ГЦ призводить до збільшення адсорбційної ємності НК Fe_3O_4/ГА, яка для Fe_3O_4 та НК Fe_3O_4/С майже виходить на насичення. Поверхні досліджених НК характеризуються досить близькими значеннями адсорбційних параметрів (A = 25–30 мг/г), що може бути обумовлено подібною природою адсорбційних центрів їх поверхонь та механізмів адсорбції. Ступінь вилучення ГЦ R (%) складає 25–30 %.

Магнітні властивості НК з адсорбованим гемцитабіном Fe_3O_4/ГЦ, Fe_3O_4/ГА/ГЦ, Fe_3O_4/С/ГЦ досліджували за допомогою лабораторного вібраційного магнітометра. Ідея досліджень ґрунтується на використанні ансамбля суперпарамагнітних носіїв у якості зонда для визначення параметрів та контролю наноструктур типу ядро-оболонка складної будови. Виміряні петлі гістерезису частинок магнетиту та НК з іммобілізованим ГЦ. Методами магнітної гранулометрії встановлено, що товщина оболонки ГЦ у складі НК Fe_3O_4/ГЦ становить 2.4±0.1 нм. Вважаючи товщину шару ГЦ рівною 2.4 нм в усіх досліджених наноструктурах, знайдено значення товщини шару гідроксиапатиту в структурі НК Fe_3O_4/ГА/ГЦ (3.5±0.1 нм) та товщину шару С в НК Fe_3O_4/С/ГЦ (3.2±0.1 нм).

Отримані дані можуть бути корисними при створенні лікарських магнітокерованих наносистем адресної доставки та адсорбційних матеріалів для використання в онкотерапії.

Ключові слова: *гемцитабін, карбонізація, гідроксиапатит, вуглецеві покриття, поверхня, магнетит, магніточутливі нанокомпозити, адсорбція*

Синтез и свойства магниточувствительных нанокомпозитов на основе магнетита и гемцитабина

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Целью работы является синтез новых полифункциональных магниточувствительных нанокомпозитов (НК) для адресной доставки в опухоли гепатоцеллюлярной карциномы и внутрипеченочной холангиокарциномы лекарственного препарата химиотерапевтического механизма действия гемцитабин (ГЦ) и депонирования с помощью магнитного поля, исследование основных физико-химических свойств НК. Направление исследований включает синтез наноразмерного однодоменного магнетита в качестве магниточувствительного носителя, модифицирование его поверхности углеродным покрытием для стабилизации и химической функционализации, биофункционализацию НК путем иммобилизации ГЦ.

Для исследований синтезированы следующие образцы НК: Fe_3O_4, Fe_3O_4/ГА, Fe_3O_4/С. Выбор образцов объясняется необходимостью получения на поверхности магниточувствительного носителя защитного биосовместимого покрытия с высокими адсорбционными свойствами. Карбонизацию поверхности Fe_3O_4 и получение НК Fe_3O_4/С осуществляли с помощью органического вещества – полигеля CS (Карбомер 934).

Адсорбцию ГЦ на поверхности магнетита и НК Fe_3O_4/ГА, Fe_3O_4/С проводили в водной среде в диапазоне концентраций C_0 = 0.2–0.8 мг/мл (g = 0.03 г , V = 5мл, pH = 7.0) в течение 2 ч в динамичном режиме при комнатной температуре. Количество адсорбированного вещества на поверхности НК определяли с помощью спектрофотометра (λ = 268 нм) по калибровочному графику.

Изучены адсорбционные характеристики поверхностей синтезированных НК по отношению к ГЦ. Полученные результаты свидетельствуют о зависимости адсорбционной емкости исследованных образцов от химической природы их поверхности. Рост равновесной концентрации ГЦ приводит к увеличению адсорбционной емкости НК Fe_3O_4/ГА, а для наноструктур Fe_3O_4 и Fe_3O_4/С – близка к насыщению. Поверхности исследованных НК характеризуются достаточно близкими значениями адсорбционных параметров (А = 25–30 мг/г), что может быть обусловлено подобной природой адсорбционных центров их поверхностей и механизмов адсорбции. Степень извлечения ГЦ R (%) составляет 25–30 %.

Магнитные свойства НК с адсорбированным гемцитабином Fe_3O_4/ГЦ, Fe_3O_4/ГА/ГЦ, Fe_3O_4/С/ГЦ исследовали с помощью лабораторного вибрационного магнитометра. Идея исследований основывается на использовании ансамбля суперпарамагнитных носителей в качестве зонда для определения параметров и контроля НК типа ядро-оболочка сложного строения. Измерены петли гистерезиса частиц магнетита и НК с иммобилизованным ГЦ. Методами магнитной гранулометрии установлено, что толщина оболочки ГЦ в составе НК Fe_3O_4/ГЦ составляет 2.4±0.1 нм. Принимая толщину слоя ГЦ равной 2.4 нм во всех исследованных НК, найдено значение толщины слоя гидроксиапатита в структуре НК Fe_3O_4/ГА/ГЦ (3.5±0.1 нм) и толщину слоя С в НК Fe_3O_4/С/ГЦ (3.2±0.1 нм).

Полученные данные могут быть полезны при создании лекарственных магнитоуправляемых наносистем адресной доставки и адсорбционных материалов для использования в онкотерапии.

Ключевые слова: *гемцитабин, карбонизация, гидроксиапатит, углеродные покрытия, поверхность, магнетит, магниточувствительные нанокомпозиты, адсорбция*

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