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Adsorption immobilization of chemotherapeutic drug cisplatin on the surface of sol-gel bioglass 60S

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The features of the dissolution processes of sol-gel bioglass (BG) 60S in model physiological solutions (SBF): 0.9% NaCl (NSS) and Kokubo's was studied *in vitro*; the features of adsorption immobilization and desorbcion of cisplatin on the surface of bioglass was investigated. Samples of BG 60S (4% P_2O_5, 36% CaO, 60% SiO_2) were obtained by sol-gel synthesis. The processes of glass dissolution, change of ionic composition of NSS and Kokubo's solution were investigated by a complex of physicochemical methods. Active ion exchange processes involving SBF and BG 60S have been recorded. Identification of cisplatin adsorbed on the surface of BG 60S was performed by IR spectroscopy. The adsorption capacity, the degree of extraction of the cisplatin was determined in terms of the concentration of Pt(II) ions in the solutions before and after adsorption. The results of the mathematical processing of the experimental data indicate the possibility of using the Freundlich model to describe the processes of adsorption of cisplatin on the BG 60S surface. These experimental data indicate the slow release of cisplatin and bioactive glass components from the surface of 60S/cisplatin composites in model biological fluids and their prospects for the development of a new prolonged oncoosteotherapy drug for topical application.

Keywords: sol-gel synthesis, bioglass, cisplatin, adsorption, drug, local therapy.

Адсорбційна іммобілізація хіміотерапевтичного препарату "Цисплатин" на поверхні золь-гель біоскла 60S. *А.П.Кусяк, А.Л.Петрановська, В.А.Дубок, О.А.Бур'янов, В.С.Чорний, Н.М.Корнійчук, П.П.Горбик*

Досліджено особливості процесів біодеградації золь-гель біоскла 60S (BG 60S) у модельних фізіологічних розчинах (SBF): 0,9% NaCl (NSS) та Кокубо; вивчено особливості адсорбційної іммобілізації цисплатину на поверхні біоскла. Зразки BG 60S (4% P_2O_5, 36% CaO, 60% SiO_2) отримано методом золь-гель синтезу. Процеси розчинення BG 60S досліджено комплексом фізико-хімічних методів в статичному режимі. Зафіксовано активні процеси іонообміну за участю SBF та BG 60S. Ідентифікацію адсорбованого на поверхні BG 60S цисплатину проведено методом ІЧ-спектроскопії. Адсорбційну ємність, ступінь вилучення цисплатину визначали у перерахунку на концентрацію іонів Pt(II) в розчинах до і після адсорбції. Результати математичної обробки експериментальних даних вказують на можливість застосування моделі Фрейндліха для опису процесів адсорбції цисплатину на поверхні золь-гель скла. Експериментальні результати свідчать про повільне вивільнення адсорбованого цисплатину та компонентів біоактивного скла у середовище NSS з композитів BG 60S/ цисплатин та їх перспективність для розробки нового імплантату як системи доставки ліків з хіміотерапевтичними властивостями та пролонгованою дією для локального використання.

Исследованы особенности процессов биодеградации золь-гель биостекла 60S (BG 60S) в модельных физиологических растворах: 0,9 % NaCl (NSS) и растворе Кокубо; изучены особенности адсорбционной иммобилизации цисплатина на поверхности биостекла. Образцы BG 60S (4 % P_2O_5, 36 % CaO и 60 % SiO_2) получены методом золь-гель синтеза. Процессы растворения стекла исследованы в статическом режиме комплексом физико-химических методов. Зафиксированы активные процессы обмена ионов между физиологическими растворами и BG 60S. Идентификация адсорбированного цисплатина на поверхности биоактивного стекла проведена методом ИК-спектроскопии. Адсорбционную емкость, степень извлечения цисплатина определяли в пересчете на концентрацию ионов Pt(II) в растворах до и после адсорбции. Результаты математической обработки экспериментальных данных указывают на возможность применения модели Фрейндлиха для описания процессов адсорбции цисплатина на поверхности золь-гель стекла. Экспериментальные результаты свидетельствуют о медленном высвобождении адсорбированного цисплатина и компонентов биоактивного стекла в NSS из композитов 60S/цисплатин и их перспективность для разработки нового имплантата как системы доставки лекарств с химиотерапевтическими свойствами и пролонгированным действием для локального применения.

1. Introduction

Rapid increase and long-term maintenance of the required concentration of the drug exclusively in the center of the disease is an urgent problem in many areas of modern medicine, therapy and surgery [1–3].

The solution to the problem is to create drugs with prolonged dosed local release of drugs. The use of such drugs can reduce systemic adverse side effects of the drug on the body and optimize the local chemotherapeutic effect in the correct place [4]. This is especially important in the treatment of cancer, when the use of chemotherapeutic drugs have a significant negative impact on the weakened patients.

Another problem with the use of such drugs is the fixation and removal of the implant, which causes additional stress on the body. The use of bioactive ceramics, including various types of sol-gel glass, could solve both problems. Biocompatibility, reliable fixation as a result of direct biochemical interaction with adjacent tissues, lack of encapsulation with the formation of connective tissue, gradual biodegradation as a result of resorption and biochemical reactions are undeniable advantages of these materials [5–7].

Sol-gel bioglass (BG) is one of the most frequently used and most effective materials for implants with bone repair function, treatment of defects, recovery from injuries and local osteoporosis [6, 8]. Its resorption period is 5–36 months, depending on the implantation site, composition and structure of the glass. The largest, compared to other bioceramics, SSA sol gel glass (up to 200 $m^2 \cdot g^{-1}$) indicates its viability for use as a drug carrier. In addition, the ability to control the size and shape of micro- and mesopores is an additional way to achieve selective immobilization of organic and inorganic substances in order to increase therapeutic efficacy.

Antineoplastic drugs, in particular on the basis of *cis*-diaminodichloroplatinum, are often used in modern chemotherapy regimens. Therefore, the study of adsorption immobilization (which preserves the cytotoxicity [3]) of the drug "Cisplatin" on the surface of the BG (60S) is relevant.

The optimal medium for adsorption immobilization of cisplatin on the surface, for example, superparamagnetic carriers based on magnetite (Fe_3O_4), is NSS [3]. When adsorption immobilization of cisplatin on the surface of BG (60S), it is necessary to take into account the peculiarities of the surface structure and the ability to dissolution [5, 6]. In addition, the release of components glass can occur at different rates, so an important task in this work is to study the dissolution processes in model physiological fluids and to establish conditions for achieving optimal adsorption capacity relative to cisplatin. To compare the processes of dissolution of BG (60S) in NSS with those that can occur in the human body, we used Kokubo's SBF [9].

The aim of the work is to study the peculiarities of solubility processes of sol-gel bioglass 60S in saline and Kokubo's SBF, adsorption immobilization of cisplatin from saline on the surface of bioglass, release of adsorbed cisplatin into saline.

The results can be useful for the development of a new implant as a drug delivery system with chemotherapeutic and osteoconductive properties and prolonged action for topical use.

2. Experimental

BG (60S) has a composition (mol.%) of 60 % SiO_2, 36 % CaO, 4 % P_2O_5. The synthesis was carried out by sol-gel method using: tetraethyl orthosilicate (TEOS)

$(C_2H_5O)_4Si$, triethyl phosphate (TEF) $(C_2H_5O)_3PO$, ethanol C_2H_5OH, calcium nitrate tetrahydrate $(Ca(NO_3)_2{\cdot}4H_2O)$, 59 % solution of nitric acid (HNO_3) (all reagents of qualification "chemically pure" (Merck Schuchardtohg (Germany)). Mass ratios of precursors for the synthesis of 60S glass were: $(C_2H_5O)_4Si$, $(C_2H_5O)_3PO$:$(Ca(NO_3)_2{\cdot}4H_2O)$:H_2O:C_2H_5OH = 8.59:1:5.85:9:3.

To obtain the sol-gel glass, the TEOS, TEF and ethanol are first poured into the above proportions, stirred on a magnetic stirrer for 30 min, and sonication was applied for 5 min. For hydration and getting sol added nitric acid, mixed again on the magnetic mixer for 30 min. and again sonicated for 5 min. Separately prepare an aqueous solution of calcium nitrate, mixing the specified quantities of components on a magnetic stirrer for at least 10 min. Then a solution of calcium nitrate is added to the sol, stirred on a magnetic stirrer for at least 40 min, sonicated for 5 min and to complete the polycondensation processes withstand the sol for 24 h at room temperature and then heated in a sealed container in a dry oven for 24 h at 60°C. The resulting gel is kept eat least 48 h at 120°C and then slowly heated (at least 4 h) to 900°C and calcined at this temperature for 2 h.

The studies used the obtained fragmented nanostructured granules of 0.1–0.3 mm sol-gel glass without additional dispersion, the drug "Cisplatin-Teva" (Pharmachemi BV, the Netherlands (series 14CO4KA). Excipients: sodium chloride, hydrochloric acid, sodium hydroxide, water for injections, (pH ~ 3.5), NSS (ISO 10993-2:2004) and Kokubo's SBF [9].

Specific surface area SSA determined by the method of nitrogen thermal desorption using KELVIN 1042 Sorptometer.

The processes of the dissolution of BG (60S) were studied in static mode. Atomic absorption (for Ca^{2+}, Mg^{2+}), atomic emission (for Na^+, K^+) and photometric analysis (for SO_4^{2-}, HPO_4^{2-}) methods were used to study the change in the ionic composition of model physiological fluids (AAS C115 M1, Spectrometer Lambda 35 UV/Vis). Potentiometric measurements are made using the I-160M. The identification of the adsorbed cisplatin on the surface of the bioactive glass was performed by IR spectroscopy (Agilent Cary 630). The adsorption capacity (A), the degree of extraction (R) of cisplatin was determined in terms of the concentration of Pt(II) ions in the solutions before and after adsorption using an atomic absorption method (AAS C115 M1).

The adsorption capacity was calculated with the equation:

$$A = (C_0 - C_{eq}) \cdot V/g, \qquad (1)$$

where A ($mg{\cdot}g^{-1}$) is the amount adsorbed, C_0 and C_{eq} ($mg{\cdot}ml^{-1}$) are the initial and equilibrium concentrations of the cisplatin solution, V (ml) is the volume of the solution, g (g) is the mass of absorbent used. The removal efficiency of cisplatin (R) was obtained with the equation

$$R,\% = [(C_0 - C_{eq})/C_0] \cdot 100 \qquad (2)$$

3. Results and discussion

The study of the surface by the method of nitrogen thermal desorption showed the presence of a significant amount of SSA and pores.

BET Surface Area is 130.92 $m^2{\cdot}g^{-1}$;

Langmuir Surface Area is 171.1 $m^2{\cdot}g^{-1}$;

Total pore volume is 120.04 $mm^3{\cdot}g^{-1}$;

Micropore volume is 0.00 $mm^3{\cdot}g^{-1}$.

The processes of the dissolution of BG (60S) in aqueous solutions occur due to two main mechanisms: the exchange of ions on the surface with H^+ and H_3O^+ and the action of hydroxyl ions on the bonds in the structure of the matrix of silica. In the first mechanism, the interaction takes place in neutral and acidic solutions and leads to the dissolution of silica with the formation of a surface film on the glass (non-congruent-selective dissolution). The second mechanism is characteristic of alkaline solutions where the action of OH ions occurs simultaneously with ion exchange — dissolution occurs congruently.

In vitro studies of solubility [10, 11] and studies of biodegradation processes *in vivo* [1, 2, 5, 6, 11–15], indicate a long (5–36 months) ion exchange process resulting in the biodegradation of BG (respectively, with a decrease in glass particle size) and active bone remodeling. For bioactive ceramics ion exchange with the environment occurs without the participation of protein components of the blood during the first 7 days [6, 8]. After that, as a result of the interaction of organic components of the medium with the silica-containing layer:

$$\equiv Si{-}OH + HO{-}CH_2{-}R \rightarrow \equiv Si{-}O{-}CH_2{-}R + H_2O.$$

a strong bond is formed between the soft tissues and the surface of the bioactive glass.

This ability of bioglass to form a strong bond simultaneously with bone, cartilage

Table 1. Ion concentration in human blood plasma (pH = 7.4) and Kokubo's SBF (pH = 7.4)

Ion	C (mmol·l^{-1})		C (mg·l^{-1})
	Human blood plasma	Kokubo's SBF	Kokubo's SBF
Na^+	142.0	142.0	3266
K^+	5.0	5.0	195
Mg^{2+}	1.5	1.5	36
Ca^{2+}	2,5	2,5	100
Cl^-	103.0	147.8	5246.9
HCO^{3-}	27,0	4,2	256,2
HPO_4^{2-}	1.0	1.0	96
SO_4^{2-}	0.5	0.5	48

and soft tissues is necessary to fix the implant, as well as to restore the surface layers of bone in direct contact with muscle tissue, ligaments and tendons.

The process of the dissolution was studied for a week, measurements were performed every day, changing the "spent" fluid with "fresh" portions, which simulated the presence of the test material in the biological environment in the presence of blood flow of medium intensity. Samples of material $g_1 = g_2 = 1.0 \pm 0.001$g were poured into 50 ml of NSS (V_1) and Kokubo's SBF (V_2), respectively, and thermostated at 37°C for 24 h. Every 24 h, the material was separated from the appropriate solutions used and poured fresh. The filtrates were used to study changes in ionic composition and changes in pH over time.

The ionic composition of human plasma and Kokubo's SBF are shown in Table 1. The results of studies of changes in the pH of NSS (pH_1) and Kokubo's SBF (pH_2) over time during dissolution of BG (60S) are shown in Table 2.

Ion exchange processes and hydrolysis reactions lead to an increase in the pH of the media compared to the initial value (Table 2). For SBF Kokubo, this indicates that under selected experimental conditions, its buffer capacity is insufficient to maintain a constant pH level.

OH-ions act as a catalyst for the dissolution of the silica system, at pH > 9 the hydrolysis reaction begins to dominate, which leads to depolymerization of the siloxane systeem (–Si–O–Si–) in the glass structure and increase the concentration of surface silanol groups (≡Si–OH)) [8, 16, 17]. The formed surface structure is described as a gel-silicate layer because it is porous and contains water and silanol groups. Under such conditions, secondary reactions begin, which occur by the mechanism of coprecipitation. Silica gel provides the appropriate sorption centers Ca^{2+} and PO_4^{2-}, which either migrate from the glass or precipitate from solution, forming an amorphous film of calcium phosphate, which is gradually converted into hydroxyapatite (HA). The formed layer of HA on the silica layer, depending on its density, can act as a diffuse barrier, is biologically active and forms a medium for adsorption of growth and binding factors, proliferation and differentiation of cells.

The results of studies of changes in the concentration of ions in model environments during biodegradation of BG 60S, indicate active ion exchange processes, as a result of which the chemical composition and surface structure of 60S glass undergoes changes (Table 3).

In Kokubo's SBF medium, ion exchange processes involving Na^+, K^+, SO_4^{2-}, HPO_4^{2-} ions occur throughout the observation time (Table 3). Active adsorption of Mg^{2+} ions on the glass surface occurs in the first two days, after which these ions actively pass into the model medium. Ca^{2+} ions absent in the NSS, on the first day are actively transferred into solution from the surface of the ceramic material. At that time, the concentration of Ca^{2+} ions in Kokubo's SBF medium decreases compared to the original (100 mg·l^{-1}), which indicates their adsorption on the surface of the bioglass. In Kokubo's SBF active adsorption of HPO_4^{2-} ions is observed in the first two days, and slow adsorption of SO_4^{2-} ions beginning from the fourth day. After reaching a certain equilibrium, desorption processes become predominant.

Table 2. Changing the pH of NSS (pH_1) and Kokubo's SBF (pH_2) during biodegradation of BG 60S glass

pH	Hours							
	0	24	48	72	96	120	144	168
pH_1	6.17	8.04	9.01	8.78	8.04	8.05	8,.0	7.82
pH_2	7.55	9.44	9.17	8.53	8.41	8.53	8.43	8.47

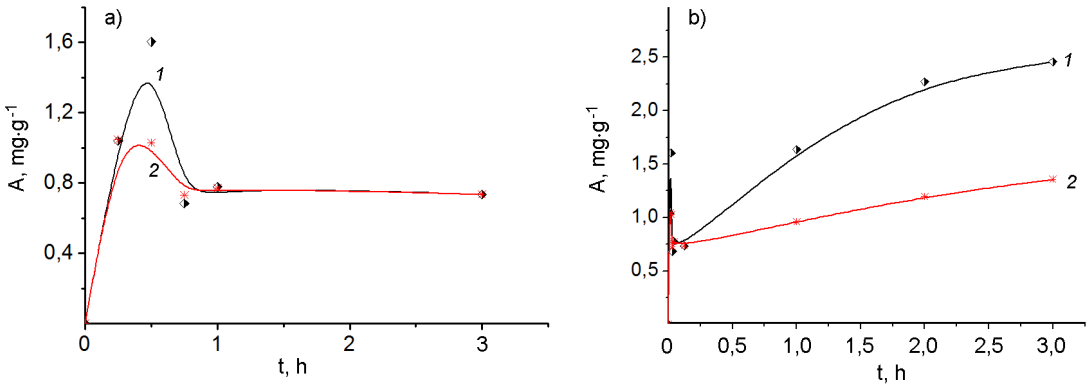

Fig. 1. Experimental kinetic curves of cisplatin sorption on the surface of BG 60S at 37.0°C (a) and 18.0°C (b).

When considering the data in Table 2 emphasized that at the stage of primary reactions that occur during the hydrolysis of glass in the environment of NSS, a near-surface layer is formed, which provides the presence of sorption centers Ca^{2+} and HPO_4^{2-}, which, in this case, mainly migrate from the glass. In addition, (Table 3) shows that Ca^{2+} ions, absent in NSS, on the first day are actively transferred into solution from the surface of the material 60S. According to the results of research in the NSS environment, the processes as a result of which the formation of the subsurface layer enriched with silicon oxide is possible, which is a characteristic feature of bioceramic materials [16–19]. Factors indicating dissolution with the formation of a silicate layer are an increase in pH (Table 2), active desorption of Ca^{2+} ions (Table 3), the absence of excess HPO_4^{2-} (use of NaCl solution).

In the mechanisms of biodegradation of glass in Kokubo's SBF, processes are distinguished that lead to the formation of a near-surface layer enriched with calcium, as a result of which a layer similar to HA can be formed. Concentrations of Na^+, Ca^{2+} ions in NSS and SBF media during dissolution of sol-gel samples BS 60S (Tables 2, 3) after 1–2 days become close, which may be a sign of establishing a certain similarity of their content in the near-surface layers due to ion exchange.

NSS, which preserves bioactivity cisplatin and has a simple ionic composition, which will simplify the interpretation of further experimental results, was chosen as the medium for studies of cisplatin adsorption on the 60S glass surface [3, 20, 21].

Given the active ion exchange processes (Table 3), their duration [1, 2, 5, 6, 10–15], and their importance in the processes of osseointegration [6, 8, 17], it was decided to study the adsorption of cisplatin on the maximum non-hydrolyzed surface of BG (60S), in nonequilibrium conditions characterized by changes in ionic composition at the interface between the glass/liquid phases. The implementation of this approach allows the optimal use of the ionic composition of the glass to provide osteoconductive properties and give its particles the function of a carrier of a

Table 3. Changes in the concentration of ions in a solution of NSS (C1) and Kokubo's SBF (C2) when dissolution BG (60S)

Ions	C, mg·l^{-1}	Hour							
		0	24	48	72	96	120	144	168
Na^+	C_1	3400	3380	3080	3280	3280	3520	3200	3400
	C_2	3320	3080	3080	3200	3160	3200	3080	3000
K^+	C_2	195	170	150	150	150	170	220	255
Mg^{2+}	C_2	36.2	0.325	19.35	50.05	47.01	57.02	40.65	50.15
Ca^{2+}	C_1	0	47	41.5	44.5	30.3	32	37.5	17.5
	C_2	100	50.5	54.5	46	37	36	26	23
SO_4^{2-}	C_2	42.86	40.60	42.10	42.10	43.60	40.60	36.09	36.09
HPO_4^{2-}	C_2	63.98	39.37	38.14	43.06	52.91	46.75	63.98	77.52

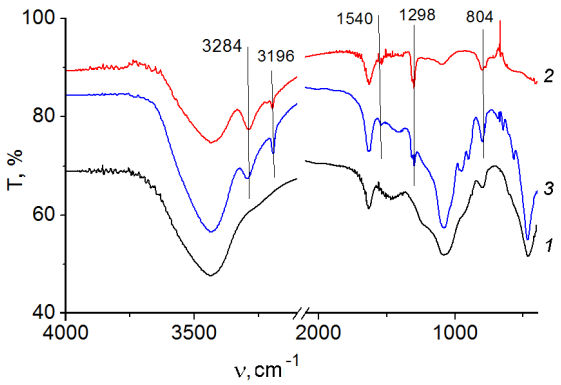

Fig. 2. IR spectra of BG 60S glass (*1*), cisplatin (*2*), composite BG 60S/cisplatin (*3*).

chemotherapeutic drug with local and prolonged action.

The adsorption processes of cisplatin on the surface of 60S glass depending on time, temperature and pH were studied. Samples of glass (g = 0.03 g), with a solution of cisplatin in NSS (V = 5 ml, $C_{Pt(II)}$ = 30 mg·l^{-1}) were thermostated at 18.0°C and 37.0°C. Changes in $C_{Pt(II)}$ were recorded for up to 72 hours (Fig. 1a, b).

Increasing the temperature to 37.0°C (Fig. 1a, b, curves *1*, *2*) contributes to the immobilization, which may indicate an improvement in the diffusion conditions of its molecules in solution.

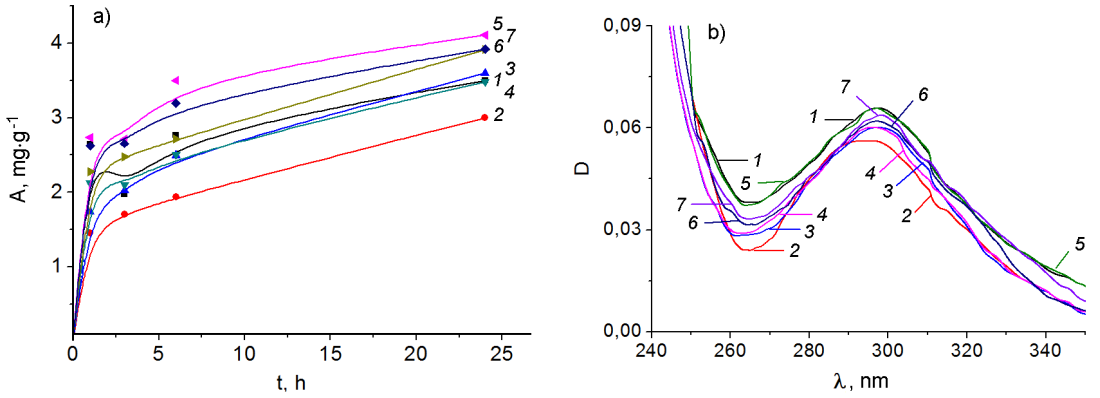

Fig. 3. Experimental kinetic curves of cisplatin adsorption on the surface of BG (60S) at different pH *1* - 3.6, $C_{0Pt(II)}$ = 37.2 mg l^{-1}; *2* - 4.6, $C_{0Pt(II)}$ = 31.2 mg l^{-1}; *3* - 5.6, $C_{0Pt(II)}$ = 34.1 mg l^{-1}; *4* - 6.6, $C_{0Pt(II)}$ = 34.1 mg l^{-1}; *5* - 7.6, $C_{0Pt(II)}$ = 37.2 mg l^{-1}; *6* - 8.6, $C_{0Pt(II)}$ = 35.1 mg l^{-1}; *7* - 9.6, $C_{0Pt(II)}$) = 35.4 mg l^{-1}.

Table 4. Kinetic parameters of cisplatin adsorption on the surface of BG (60S) depending on pH

№	pH± 0.05	Kinetic model of the pseudo-second order						
		Equation			$I/A_{eq}-A_t=1/A_{eq}+k$			
		Linear form of the eguation			$t/At=1/kA_{eq}^2(1/A_{eq})t$			
		Calculated parametres						
		C_0 ± 0.01 (mg^{-1})	A_{exp} ± 0.01 (mg·g^{-1})	R ± 0.013 (%)	k_2, g·(mg^{-1}·min^{-1})	A_{calc}, (mg·g^{-1})	V_0, mg·(g^{-1}·min^{-1})	r^2
1	3,6	37.20	3.50	49.87	0.25	3.61	3.12	0.98
2	4.6	31.20	3.01	50.90	0.18	3.14	1.67	0.97
3	5.6	34.01	3.59	56.16	0.16	3.76	2.17	0.98
4	6.6	34.01	3.48	54.42	0.21	3.60	2.66	0.98
5	7.6	37.20	4.10	58.64	0.29	4.21	4.98	0.99
6	8.6	35.12	3.91	59.27	0.19	4.05	2.92	0.98
7	9.6	35.40	3.92	58.81	0.29	4.01	4.54	0.99

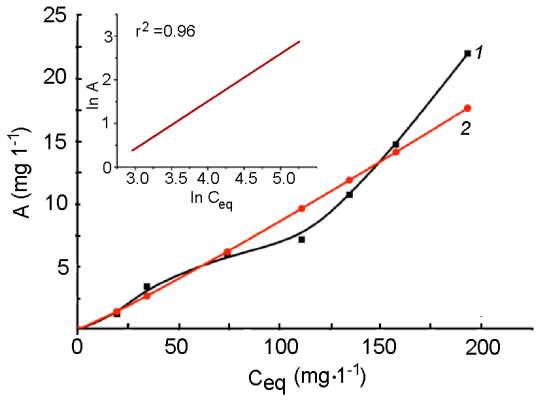

Fig.4. Isoterms of cisplatin adsorption on surface of BG (60S) $C_{Pt(II)}$ =(25 - 325) mg·l^{-1}: obtained from adsorption experiment (*1*) and calculated with Freundlich (*2*) model. The inset shows the linear plot form of the equation Freundlich.

Table 5. Parameters of cisplatin adsorption on surface of BG (60S) glass calculated using Freundlich model

Freundlich equilibrium adsorption model			
Equation	$A_{eq} = K_F C_{eq}^{1/n}$		
Linear form of the equation	$\ln A_{eq} = \ln K_F + (1/n)\ln C_{eq}$		
Calculated parameters	K_F	$1/n$	r^2
$C_{Pt(II)}$ = 25–325 mg·l^{-1}	0.056	0.91	0.96

The maximum on the kinetic curves after 30 min of contact maybe related to the adsorption processes occurring on the non-hydrolyzed surface. This characteristic can be used to work with highly dispersed material 60S glass in order to increase the adsorption capacity of the surface on the cisplatin.

The decrease in the adsorption capacity is probably due to the development of biodegradation processes of 60S glass, which are accompanied by the formation of a silicate-gel near-surface layer [8, 10, 11] and the formation of surface silanol groups.

After the formation of this layer, there is an increase in the adsorption capacity of the surface, which in time coincides with the active ion exchange processes. Within 48 h, there is an increase in the adsorption capacity without reaching saturation (A = 2.45 mg·g^{-1}, R = 49 %) (Table 3).

IR spectroscopy was used to identify cisplatin immobilized on the surface of the sol-gel glass. In terms of spectral characteristics, samples 2 and 3 are similar in maxima υ_a at 3284 cm^{-1}, υ_s at 3196 cm^{-1}; δ_a at 1540 cm^{-1}; δ_s at 1298 cm^{-1}; ρ_R — 804 cm^{-1} which are characteristic of $-NH_3$ groups, which is a confirmation of the presence of cisplatin [14] on the surface of 60S (Fig. 2).

The dependence of the sol-gel glass adsorption on pH was investigated in a static mode at a temperature of 37.0°C in the range of 1–24 h. The initial pH value in the range of 3.5–9.5 was set using 0.1 N NaOH and HCl solutions.

It turned out that the value of cisplatin adsorption is not uniquely determined by the initial pH level of the medium (Fig. 3a, Table 4). Indeed, in experiments, the monotonic increase in the initial pH level corresponds to the scatter of the values of A cispatin. For example, for samples 3 and 4 at the same C_0 and increase of pH there is a decrease in the adsorption of cispatin, and for samples 1 and 5 – an increase. This scatter exceeds the measurement errors (Table 4) and is probably due to nonequilibrium conditions of adsorption of cisplatin when dissolving of BG (60S). Studies of the spectra of optical density (Fig. 3b, Table 4) of the media from which the adsorption of cispatin, showed no significant changes in the composition of the chemotherapeutic drug cispatin, for example, due to the transition to the *trans* form or hydrolysis (due to the presence of Cl^- [24]).

Table 6. Dependences of desorption (R_D, %) of cisplatin from the surface of the composite BG (60S)/cisplatin in the model environment at different initial immobilized amounts

A, mg·g^{-1}	R_D, %				
	3 h	6 h	9 h	3 days	7 days
0.97	2.17	2.34	6.28	11.04	24.22
1.34	1.95	2.93	6.15	9.90	15.53
1.59	1.37	2.61	3.98	11.1	16.07
2.07	1.79	3.17	5.4	10.68	22.72
3.05	1.68	3.54	5.27	11.27	23.71
3.85	1.83	3.43	4.67	9.14	20.7

Experimental kinetic curves of cisplatin adsorption were analyzed using kinetic equations and models that take into account the contribution of the chemical reaction to the adsorption process [25]. Experimentally obtained values (A_{exp}) that are close to the calculated (A_{calc}), high values of the correlation coefficient $r^2 > 0.95$ for the entire pH range indicate the possibility of using a kinetic model of the pseudo-second order to

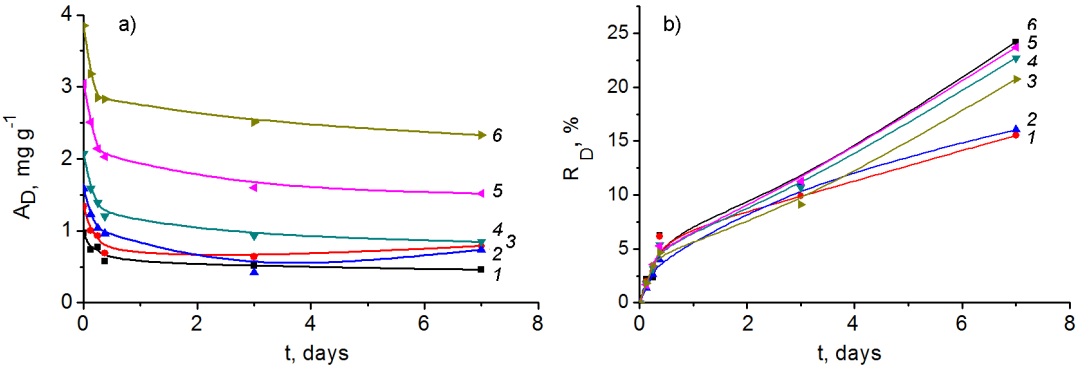

Fig. 5. Desorption (A_D) (a) and percentage of desorbed (R_D (%)) (b) cisplatin from the surface of samples with different initial drug content (A_0 (mg·g^{-1})); A_0: *1* — 0.97, *2* — 1.34, *3* — 1.59, *4* — 2.07, *5* — 3.05, *6* — 3.85. T ~ 300 K.

correctly describe the dependence of cisplatin adsorption time (Table 4).

The results of three series of measurements were processed using the methods of mathematical statistics for the values of A_{exp}, A_{calc}, R, k_2, V_0 and taking into account the accuracy of measuring instruments (for pH, C_0, C_{eq}). The measurement error of the A and R does not exceed 2.5 %.

The results of adsorption studies in the range of concentrations of 25–325 mg·l^{-1} (T = 37°C, pH_0 = 3.5) were used to construct isotherms and determine the possible mechanism of adsorption. The obtained experimental data were analyzed for compliance with the Freundlich model, which describes the sorption isotherm on a heterogeneous surface (Table 5, Fig. 4). In this model, the constants K_F, $1/n$ and r_2 characterize, respectively, the adsorption capacity, the intensity of adsorption, and the affinity of the adsorbate to the surface of the adsorbent.

The value of the correlation coefficient (r^2), close values of experimental and calculated values of A indicate the correctness of using the Freundlich model to describe the processes of cisplatin adsorption, possibly with the participation of hydroxyl groups of different chemical nature on the accessible surface of BG (60S) [8, 18, 22].

The study of desorption (A_D(mg·g^{-1})) and the percentage of desorbed cisplatin (R_D, %) from the surface of BG (60S)/cisplatin composites was performed in NSS medium, on samples obtained by constructing isotherms (Fig. 5, Table 6).

The kinetics of desorption (Fig. 5a) indicates the slow release of cisplatin from the surface of the ceramic material into the model environment (up to 15–25 % per week (Fig. 5b)). The largest amount is desorbed in the first 24 h. It is known [27] that large biomolecules, in particular antibodies, are not desorbed or little desorbed when using the same buffer in which the adsorption took place, and the nature of the adsorbent also significantly affects the ability of adsorbed biomolecules to desorption. Experimental data show that to some extent similar trends are characteristic of the studied surfaces 60S with adsorbed cisplatin.

Changes in the ionic composition of the model medium during desorption of cisplatin, close to the data shown in Table 3, which indicates the independence of the processes of dissolution and desorption. These experimental data indicate the creation of composite material BG (60S)/cis platin with slow of cisplatin release and components of bioactive glass, which is a prototype of a new integrated drug delivery system for topical use with prolonged chemotherapeutic and osteoconductive action.

4. Conclusions

The sol-gel BG (60S) was synthesized and dissolution processes in model environments of NSS and Kokubo's SBF were studied. The processes of adsorption and desorption of the chemotherapeutic drug cisplatin were studied in the environment of NSS.

The maximum on the kinetic curves (contact 30 min) may be related to the adsorption processes occurring on the non-hydrolyzed surface of the ceramic material. This feature can be used to work with highly dispersed material BG (60S) in order to increase the adsorption capacity of the surface to cisplatin. The results of mathematical processing of experimental data indicate the possibility of applying the Freundlich model to describe the studied adsorption processes. Analysis of desorption studies indicates the release of 15–25 % cisplatin

during the first seven days, regardless of its initial immobilized amount.

These experimental data indicate the possibility of adsorption immobilization of cisplatin on the surface, its slow release into the biological environment and the prospects of BG (60S)/cisplatin composites for the development of a new implant as a drug delivery system with chemotherapeutic and osteoconductive properties and prolonged action for topical use.

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