https://doi.org/10.15407/polymerj.44.02.145
UDC 678.664

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INVESTIGATION OF THE ABILITY TO BIODEGRADABILITY OF POLYURETHANE FOAM COMPOSITE MATERIALS WITH ALBUCID AND THE DYNAMICS OF ALBUCID RELEASE IN VITRO

Studies of biodegradability of polyurethane foam (PUF) composite materials with albucid under the influence of biological medium 199 (BM 199) and saline solution for 2 weeks, 1, 3 and 6 months by methods IR spectroscopy, physical-mechanical tests, DSC and TGA were conducted. It was found that the influence of BM 199 and saline solution on the structure and properties of composite materials with albucid is similar. According to the results of physical-mechanical studies under the influence of model mediums there are processes of biodegradation which are confirmed by a decrease in adhesive strength after incubation in BM 199 and saline solution. According to IR spectroscopy, biodegradation is accompanied by redistribution of hydrogen bonds of NH groups of the polymer matrix. The results of studies by the DSC method indicate a decrease of Tg and increase of ΔCP of PUF composites with albucid compared to the control, which is associated with increasing of segmental mobility of macromolecules under the influence of model mediums and due to the albucid release from polymer matrix. It was found that PUF and PUF composites with albucid in vitro remain heat-resistant materials, because after incubation in BM 199 and a saline solution there is an increase in T0 and Tmax by the TGA method. Studies of the dynamics of albucid release from the PUF matrix were carried out. It was found that the composite materials are capable to the prolonged release of the drug. The amount of released albucid is 36.0 % on the 60th day of the experiment, which does not exceed the therapeutic dose and has no toxic effects. Therefore, polyurethane foam composite materials with albucid can be proposed as promising materials for use as implants with prolonged action of albucid in ophthalmological surgery.

Ключові слова: *polyurethane foam, composite material, albucid, biological medium 199, saline solution.*

Цитування: Vislohuzova T.V., Rozhnova R.A., Galatenko N.A., Nechaeva L.Yu. Investigation of the ability to biodegradability of polyurethane foam composite materials with albucid and the dynamics of albucid release *in vitro*. *Полімерний журнал.* 2022. **44**, № 2. С. 145—154. https://doi.org/10.15407/polymerj.44.02.145

Introduction

The ability to biodegradation in the conditions imitating the environment of the organism is one of the most important characteristics of polymers for medical use as this process is accompanied by changes in the structure of the polymer which cause changes of properties and it can influence on the amount of released drug to the internal environment of an organism.

Biodegradation of polyurethanes *in vivo* occurs by two complementary mechanisms. It is hydrolytic and macrophagal. Hydrolytic biodegradation is manifested in the hydrolysis of ester, urethane and later ether bonds. Hydrolytic biodegradation *in vivo* is identical to hydrolytic biodegradation *in vitro*. Macrophage-mediated biodegradation occurs due to the phagocytic activity of macrophages and foreign body giant cells [1–3]. Experimental study of polymer biodegradation in the body using labeled preparations is a time-consuming procedure. Estimation of effective rates of polymer weight loss is also difficult due to the lack of sufficiently clear methods for separation of the implant from connective tissues and experimental errors. Therefore, predictions of the polymer biodegradability *in vivo* are based on the results of *in vitro* studies.

It is known that the biodegradation processes are influenced by such factors as the chemical composition of polymer, the hydrophilicity of polymer matrix, the presence of drug substance and the drug type etc. [4, 5]. The introduction of fillers in particular drugs into the composition of polymer materials can affect the rate of biodegradation process. For example, the presence of levamisole in the composition of epoxy-polyurethane composite accelerates the biodegradation of polymer base in the biological medium [6].

An important characteristic of polymers for medical use is the release dynamics of the drug and its quantity. It is known [7] that the drug release from polymer composites is influenced by the chemical nature of polymer and drug, their physical-chemical properties etc. Such factor as water solubility of drug determines the mechanism and kinetics of its release from a polymer matrix. Well water soluble drugs are released due to diffusion that promotes swelling of matrix and degradation of polymer, while poorly water-soluble drugs are released mainly due to degradation of polymer matrix [8, 9]. Thus, biocompatible PUF on the basis of lysine diisocyanate and glycerol developed by the authors [10] as implant materials are characterized by controlled long-term release of anticancer drug 7-tert-butyldimethylsilyl-10-hydroxy-camptothecin which occurs by diffusion and passive hydrolysis of urethane bonds.

All these parameters influencing degradation and release of drugs should be taken into account when creating prolonged-release preparations to ensure a uniform release of drugs to an organism in an acceptable quantity, which will be sufficient for the manifestation of biological activity and will not exert a toxic effect.

Polyurethane foams are widely used as polymer matrices in the creation of biologically active implant materials with prolonged release of drugs [11, 12]. Therefore, on the basis of diisocyanate prepolymer we have obtained PUF composite materials filled with albucid, which show adhesion, heat resistance and have a microporous structure [13]. Studies of cytotoxicity [14], irritant action, acute systemic toxicity and response of soft tissue of experimental animals to implantation of the obtained composites [15] were carried out. The results of studies indicate the absence of toxic and irritating action, as well as safety in accordance with international standards. This allowed recommending of PUF composite materials with albucid as implants for ophthalmological surgery.

However, there is a need to study the ability to biodegradation and the ability to drug release from the polyurethane foam matrix *in vitro*. Results of these researches will allow predicting behaviour of polymer materials *in vivo* at their further application in medical practice.

Therefore, the purpose of the work is to study the ability to biodegradation PUF composite materials with albucid by changing their structure and properties under the influence of model mediums (biological medium 199, saline solution) for 2 weeks, 1, 3 and 6 months and the dynamics of the albucid release from the polyurethane foam matrix *in vitro*.

Experimental

Materials. PUF (synthesized based on diisocyanate prepolymer using catalyst 2,4,6-tris(dimethylaminomethyl)phenol) and PUF composite materials with albucid in the amount of 5 wt. % [13] were objects of researches.

Biological medium 199 (BM 199) (BioTestLab, Ukraine, pH 7.4–7.7) and saline solution (Novo-

farm-Biosynthesis, Ukraine) were selected as a model mediums to study biodegradation. BM 199 imitates the blood plasma and is a complex mixture of proteins, amino acids, carbohydrates, fats, salts, hormones, enzymes and soluble gases. Saline solution (sodium chloride solution for infusion) contains NaCl (9 mg/ml) and water for injection.

Distilled water and drug albucid (LLC "Vitex" Pharmacy, Ukraine) (molecular weight = 214.243) were used to study the dynamics of albucid release.

The method of incubation in BM 199 and saline solution. Samples were placed in sterile tubes, poured 25 ml of model medium and kept in a thermostat at a temperature of (37 ± 1) °C for 2 weeks, 1, 3 and 6 months. Solutions of model mediums were changed daily. After defined incubation terms in the model medium, the samples were taken out, washed with distilled water and dried to a constant masse at room temperature.

Study Methods. The structure was investigated on a Tensor-37 FTIR spectrometer in the range 650–4000 cm^{-1} by the MATR method with the aid of a diamond crystal trapezoidal prism (a number of reflections of N = 1, an incidence angle of φ = 39°).

The physical-mechanical properties, in particular the adhesive strength was determined on the tension testing machine P 5 in accordance with [16]. The movement rate of the active clamp was 10 mm/min. Adhesive bonding were prepared using steel substrates.

Thermophysical properties (glass-transition temperature (T_g), changes of the heat capacity at the glass-transition temperature (ΔC_p)) have been studied by the DSC method. The study has been carried out within the interval of temperature from -90 to +200 °C (TA Instrument Q2000) at a heating rate 20 °C/min under nitrogen atmosphere. Two heating procedures have been carried out to exclude the influence of the thermal and mechanical prehistory of the material.

Thermogravimetric characteristics (onset temperature of thermal decomposition (T_0), temperature of maximum decomposition rate (T_{max}), weight loss at T_0) were studied by TGA. The study has been carried out within the interval of temperature from +20 to +700 °C (TA Instrument Q50) at a heating rate 20 °C/min under an air atmosphere.

The study of albucid release from the polymer samples was performed by spectrophotometric method. Absorption spectra of the studied solutions were obtained on the "SPECORD M-40" device in cuvettes with a layer thickness of 1 cm relative to the comparison solutions.

Preparation of solutions. Control and experimental samples (average weight 2 g) were placed in weighing bottles with the ground-in stopper, added 20 ml of distilled water. The weighing bottles were kept in a thermostat at a temperature T = (38 ± 1) °C. After defined terms the solutions were poured out and investigated their absorption spectra. The experimental solutions received from the samples containing albucid in their composition. Solutions of comparative (control solutions) obtained from control samples (from samples which do not contain albucid).

The concentration of released albucid was found on the calibration graph. For creation of the calibration graph of dependence of optical density of solutions on albucid concentration, a series of aqueous solutions of albucid with different percentage concentration: 0.00025; 0.00050; 0.00075; 0.00100 and 0.00125 were prepared. Their absorption spectra were investigated.

The amount of released albucid from polymer samples into the solution (A, %) was calculated using Equation (1) and (2):

$$A = \frac{m}{m_o} \cdot 100\%,$$

$$m = \frac{C \cdot V}{100},$$

where: A – is the amount of released albucid from the polymer samples into the solution, %; m – the amount of released albucid for certain period of time, g; m_0 – the masse of albucid introduced into the polymer, g; C – the concentration of albucid in the investigated solution, found according to the calibration graph, %; V – the volume of the solution in which performed washing-out, ml.

Results and Discussion

To study the ability to biodegradation, PUF and PUF composite materials with albucid were incubated in the model mediums (BM 199 and saline solution) for 2 weeks, 1, 3 and 6 months. The influence of model mediums was evaluated by changes in their structure, physical-mechanical, thermophysical and thermogravimetric properties before and after incubation.

The structure of PUF and PUF composite materials with albucid was investigated by IR spectroscopic

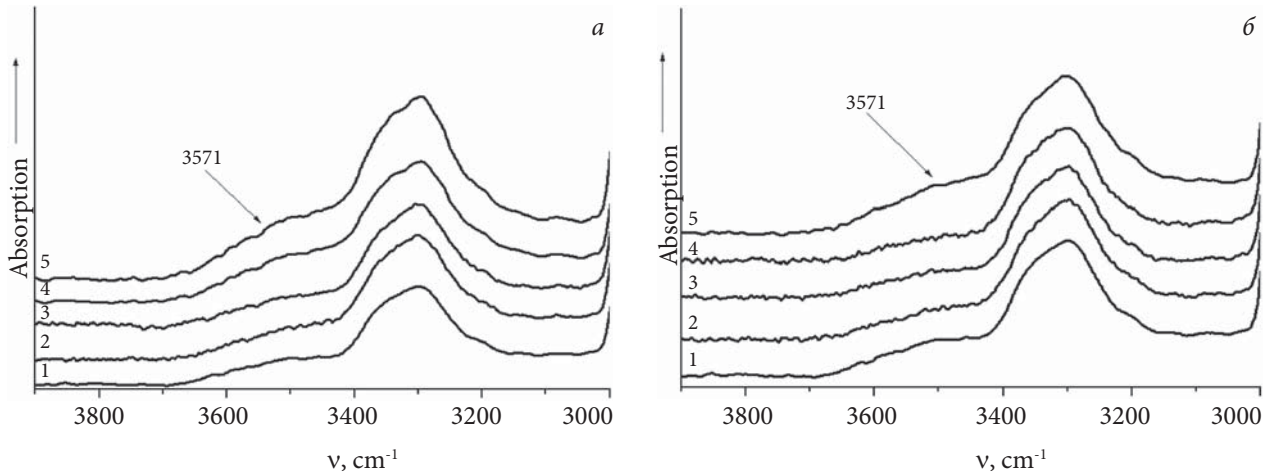

Fig. 1. Fragments of IR spectra of PUF before (*1*) and after incubation in BM 199 (*a*) and saline solution (*b*) for 2 weeks (*2*), 1 month (*3*), 3 months (*4*), 6 months (*5*) in the range of 3000–3800 cm^{-1}

tests before (control) and after incubation in BM 199 and saline solution. IR spectra were measured in the range of 4000–600 cm^{-1}. Only fragments of spectra that have changes are presented.

Changes in the valence vibrations of NH groups in the frequency interval of spectra of 3000–3800 cm^{-1} for PUF were observed. There is an increase in the intensity of the absorption band $\nu_{NH\text{-}free}$ with an approximate maximum at 3571 cm^{-1} after incubation in model mediums. It is connected with the increase in the number of hydrogen-free NH groups on the surface layer of the investigated samples (Fig. 1, curve *2–5*).

For PUF composite materials with albucid changes in the frequency interval of spectra of 3000–3800 cm^{-1} were also observed (Fig. 2). There is a decrease in the intensity of the absorption band $\nu_{NH\text{-}free}$ with an approximate maximum at 3571 cm^{-1} after incubation in model mediums. It is connected with the decrease in the number of hydrogen-free NH groups on the surface layer of the samples (Fig. 2, curve *2–5*).

Therefore, according to the results of IR spectroscopic studies under the influence of BM 199 and saline solution changes in NH groups involved in the formation of hydrogen bonds were found. These changes are due to the redistribution of hydrogen bonds and are spatial changes in the structure of the surface layer of the samples (as IR spectra are removed from the surface of polymer materials).

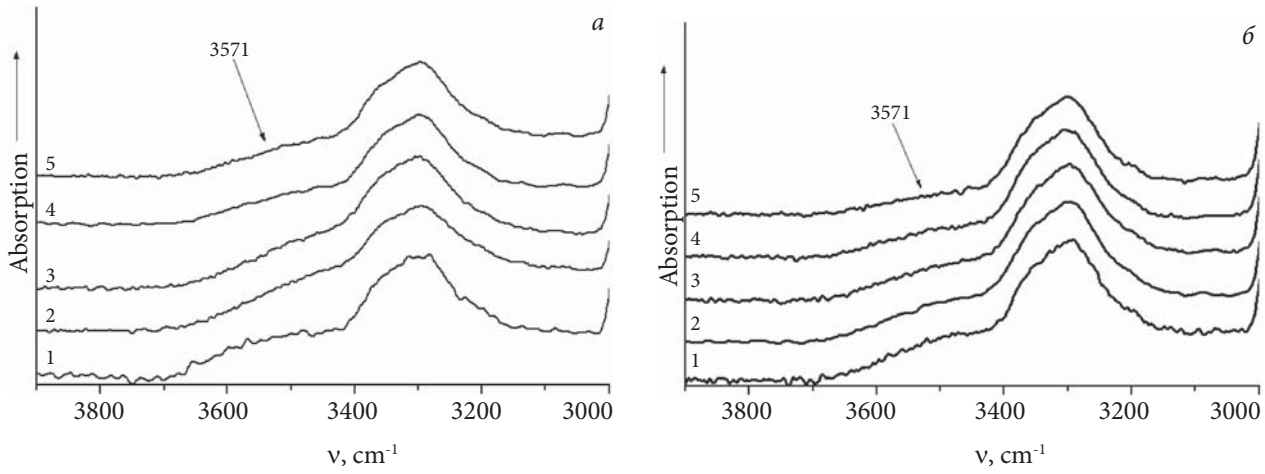

Fig. 2. Fragments of IR spectra of PUF composites with albucid before and after incubation in BM 199 (*a*) and saline solution (*b*) for 2 weeks (*2*), 1 month (*3*), 3 months (*4*), 6 months (*5*) in the range of 3000–3800 cm^{-1}

Table 1. **Adhesion strength of PUF and PUF composite materials with albucid after incubation in model mediums**

Samples	σ, MPa			
	control	2 weeks	1 month	3 months
BM 199				
PUF	1.16	0.41	0.20	0.20
PUF + albucid	1.16	0.00	0.00	0.00
Saline solution				
PUF	1.16	0.20	0.20	0.41
PUF + albucid	1.16	0.20	0.20	0.41

Physical-mechanical studies, namely changes in adhesive strength of PUF and PUF composite materials with albucid after incubation in model mediums for 2 weeks, 1 and 3 months have been conducted.

According to the results of studies of physical-mechanical properties after incubation in BM 199 there is a decrease in the adhesive strength by 5.8 times for PUF and a complete loss of adhesive strength for PUF composite materials with albucid (Table 1).

After incubation in saline solution of PUF and PUF composite materials with albucid there is a decrease in adhesive strength by 5.8 times after 2

Table 2. **Thermogravimetric characteristics of PUF and PUF composites with albucid after incubation in model mediums**

Samples	Periods of incubation	T_o, °C	T_{max}, °C	Weight loss at T_o, %
BM 199				
PUF	control	172.05	313.26	0.78
	2 weeks	205.56	331.07	0.66
	1 month	201.62	326.21	0.79
	3 months	212.64	330.75	1.07
	6 months	204.42	324.31	0.58
PUF + albucid	control	162.84	303.83	0.87
	2 weeks	185.77	303.07	1.30
	1 month	186.99	319.65	0.93
	3 months	203.10	316.14	0.85
	6 months	206.90	319.85	0.71
Saline solution				
PUF	control	172.05	313.26	0.78
	2 weeks	210.53	333.01	0.86
	1 month	209.12	328.99	0.61
	3 months	214.91	328.66	1.15
	6 months	207.24	329.30	0.50
PUF + albucid	control	162.84	303.83	0.87
	2 weeks	182.81	311.05	0.56
	1 month	200.45	308.78	0.52
	3 months	202.31	318.00	0.55
	6 months	200.56	321.73	0.47

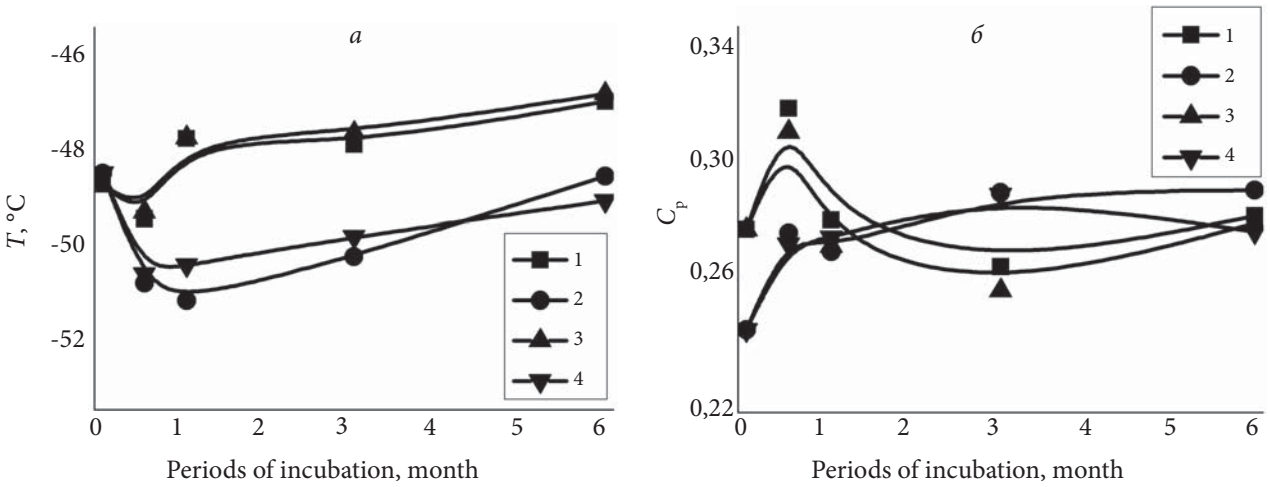

Fig. 3. Dependence of glass-transition temperature (*a*) and heat capacity (*b*) of PUF (*1*, *3*) and PUF composites with albucid (*2*, *4*) on the term of their incubation in BM 199 (*1*, *2*) and saline solution (*3*, *4*) (2nd heating procedure)

weeks and 1 month, and some increase in adhesive strength after 3 months. After 3 months of incubation in saline solution, the decrease in adhesive strength is 2.83 times compared with the control (Table 1).

The change in thermophysical and thermogravimetric properties of composite materials was evaluated after incubation for 2 weeks, 1, 3 and 6 months in BM 199 and in saline solution.

According to TGA, onset temperature of thermal decomposition (T_0) of studied PUF before incubation is 172.05 °C, while after incubation it is in the range of 201.62–212.64 °C (in BM 199) and 209.12–214.91 °C (in saline solution). T_0 of PUF with albucid before incubation is 162.84 °C, while after incubation it is in the range of 185.77–206.90 °C (in BM 199) and 182.81–202.31 °C (in saline solution) (Table 2). Consequently, after incubation in model mediums there is an increase of T_0 for both PUF and PUF composite materials with albucid.

T_0 accompanied by a slight weight loss for all samples. For PUF before incubation the weight loss is 0.78 %, after incubation in BM 199 it is 0.58–1.07 %, after incubation in saline solution it is 0.50–1.15 %. For PUF composites with albucid before incubation the weight loss is 0.87 %, after incubation in BM 199 it is 0.71–1.30 %, after incubation in saline solution it is 0.47–0.56 % (Table 2). Thus, after incubation in model mediums, the weight loss at T_0 for PUF and PUF with albucid changes nonlinearly, while after 6 months of incubation it decreases (Table 2).

The temperature of maximum decomposition rate (T_{max}) after incubation in BM 199 and saline solution for both PUF and PUF composite materials with albucid is increased. For PUF before incubation the T_{max} is 313.26 °C, after incubation it is in the range from 324.31 °C to 331.07 °C (in BM 199), from 328.66 °C to 333.01 °C (in saline solution). For PUF composites with albucid before incubation the T_{max} is 303.83 °C, after incubation in BM 199 it is in the range from 303.07 °C to 319.85 °C, after incubation in saline solution it is in the range from 308.78 °C to 321.73 °C (Table 2).

According to DSC, the T_g of the 2nd heating procedure for PUF before incubation is minus 48.64 °C, while after incubation it is in the range from minus 46.85 °C to minus 49.38 °C (in BM 199), from minus 46.68 °C to minus 49.23 °C (in saline solution). The value of T_g for PUF with albucid before incubation is minus 48.4 °C, after incubation it is in the range from minus 48.46 °C to minus 51.14 °C (in BM 199), from minus 49.00 °C to minus 50.56 °C (in saline solution). That is the presence of albucid affects the value of T_g of studied materials. After incubation in model mediums of PUF composites with albucid there is a decrease in T_g compared to control (Fig. 3*a*).

The value of ΔC_p at the glass-transition at the second heating procedure for PUF before incubation is 0.2767, while after incubation it is in the range of 0.2641–0.3175 (in BM 199), 0.2494–0.3096 (in saline solution). ΔC_p for PUF composites with albucid before incubation is 0.2429, after incubation it is in the range of 0.2692–0.2899 (in

Table 3. **Spectrophotometric study of albucid solutions**

Solution concentrations of albucid, C, %	Wavelength, λ, nm	Optical density, $D_{avg.}$
0.00025	257.0	0.1766
0.00050	255.9	0.3418
0.00075	256.0	0.5031
0.00100	257.1	0.6650
0.00125	256.5	0.8285

BM 199), 0.2717–0.2885 (in saline solution). The presence of albucid also affects the value of ΔC_p, which after incubation in model mediums of PUF composites with albucid increases compared to control (Fig. 3*b*).

The decrease in T_g and increase in ΔC_p after incubation of PUF composites with albucid in model mediums compared to the control can be explained by the increase in segmental mobility of macrochains due to redistribution of hydrogen bonds under the influence of BM 199 and saline solution and due to the albucid release from polymer matrix.

In this case, the values of T_g and ΔC_p of all samples depend on the incubation period and change nonlinearly. Thus, for PUF and PUF composites with albucid there is a decrease in T_g and an increase in ΔC_p for 2 weeks. For PUF further stay in model mediums leads to an increase in T_g and a decrease in ΔC_p, while for PUF with albucid further stay in model mediums leads to an increase in T_g and ΔC_p compared to the previous term. The

Table 4. **The results of the study of the dynamics of albucid release**

Period of study, day	Optical density of solution, $D_{cep.}$	Concentration of albucid (according to the calibration graph), *C*, %	The amount of released albucid		
			from the moment of the previous definition, *m*, g	from the beginning of the study	
				m, g	%
1	0.9791	0.00145	0.00580	0.00580	5.50
2	0.7655	0.00113	0.00678	0.01258	11.92
3	0.6441	0.00095	0.00190	0.01448	13.72
4	0.7134	0.00105	0.00063	0.01511	14.32
5	0.6563	0.00097	0.00058	0.01569	14.87
6	1.1030	0.00163	0.00033	0.01602	15.18
9	1.6350	0.00238	0.00143	0.01745	16.54
12	0.5099	0.00075	0.00150	0.01895	17.96
15	0.4563	0.00067	0.00134	0.02029	19.23
18	0.3648	0.00054	0.00108	0.02137	20.25
21	0.2428	0.00036	0.00072	0.02209	20.94
24	0.3185	0.00047	0.00094	0.02303	21.83
30	0.8079	0.00119	0.00238	0.02541	24.08
35	0.5083	0.00075	0.00150	0.02691	25.50
40	0.6438	0.00095	0.00190	0.02881	27.31
45	0.7591	0.00112	0.00224	0.03105	29.43
50	0.9624	0.00142	0.00284	0.03389	32.12
55	0.6913	0.00102	0.00204	0.03593	34.05
60	0.6980	0.00103	0.00206	0.03799	36.00

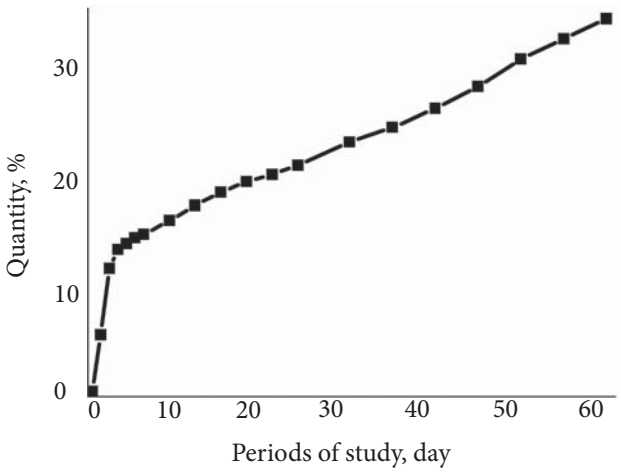

Fig. 4. The dynamics of albucid release from PUF composite materials

increase in ΔC_p after 2 weeks for PUF composites with albucid is different from unfilled PUF. This indicates an increase in segmental mobility of macrochains due to redistribution of hydrogen bonds under the influence of BM 199 and saline solution and due to the albucid release from polymer matrix.

Therefore, according to DSC, the presence of albucid affects the thermophysical properties of materials. After incubation of PUF composites with albucid in BM 199 and saline solution there is a decrease in T_g and increase in ΔC_p at the glass-transition compared with the control. This is due to an increase in the segmental mobility of macromolecules under the influence of model medium. According to the results of TGA, after incubation in model mediums there is an increase in the values of T_0 and T_{max} for both PUF and PUF composite materials with albucid. Consequently, PUF composites with albucid after incubation remain heat-resistant materials to a temperature of 185.77 °C (in BM 199) and 182.81 °C (in saline solution).

PUF composite materials with albucid (in the amount of 5 wt. %) were objects of researches of the dynamics of albucid release from polymer matrix.

The values of optical density of aqueous solutions of albucid (prepared to create a calibration graph) at the maximum of the band at wavelength λ = (256±1) nm are presented in Table 3.

The calibration graph of dependence of the optical density on concentration of albucid solutions is a straight line passing through the origin of coordinates. Thus, the possibility of quantitative analysis of albucid release by this method is confirmed.

The results of measurements and calculations of albucid release from polymer samples are presented in Table. 4.

The table shows that the incubation of samples for 60 days leads to the release of albucid in an amount of 36.00 % from the total amount of introduced drug.

Graphically the results of the dynamics of release are presented in Fig. 4.

The amount of released albucid does not exceed the therapeutic dose [17], so it will not have a toxic effect. In addition, absence of toxic effects of the drug was proved by the results of tissue culture studies, studies of irritation and acute systemic toxicity, which indicate the biocompatibility and safety of PUF composites with albucid [14].

Thus, studies of the dynamics of albucid release from the polymer matrix of PUF composites were carried out. It is established that the composite materials are capable to the prolonged release of the drug. The amount of albucid on the 60th day of the experiment is 36.0 % from the total amount of introduced drug. Therefore, the studied PUF composites with albucid can be proposed as promising implants with prolonged action of albucid for use in ophthalmological surgery.

Conclusions

The ability to biodegrade of polyurethane foam composite materials with albucid under the influence of BM 199 and saline solution for 2 weeks, 1, 3 and 6 months was investigated. It is established that the influence of BM 199 and saline solution on the structure and properties of composite materials with albucid is similar. After incubation of PUF composites with albucid in model mediums there are processes of biodegradation, which are confirmed by a decrease in adhesive strength and are accompanied by redistribution of hydrogen bonds of NH groups of the surface layer of the samples. There is also a decrease in T_g and an increase in ΔC_p under the influence of model mediums and due to the albucid release from the polymer matrix, as well as increasing the heat resistance of the studied materials. Studies of the dynamics of albucid release from the PUF matrix were carried out. It was found that the composite materials are capable to the prolonged release of the drug, the amount of which is 36.0 % on the 60th day of the

experiment. Therefore, PUF composite materials with albucid can be proposed as promising implants with prolonged action of albucid for use in ophthalmological surgery.

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Received 13.05.2022

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ДОСЛІДЖЕННЯ ЗДАТНОСТІ ДО БІОДЕГРАДАЦІЇ ПІНОПОЛІУРЕТАНОВИХ КОМПОЗИЦІЙНИХ МАТЕРІАЛІВ З АЛЬБУЦИДОМ І ДИНАМІКИ ВИВІЛЬНЕННЯ АЛЬБУЦИДУ ЗА УМОВ *IN VITRO*

Проведені дослідження здатності до біодеградації пінополіуретанових (ППУ) композиційних матеріалів з альбуцидом під впливом біологічного середовища 199 (БС 199) і фізіологічного розчину протягом 2-х тижнів, 1, 3 і 6 міс. методами ІЧ-спектроскопії, фізико-механічними випробуваннями, ДСК і ТГА. Встановлено, що вплив БС 199 і фізіологічного розчину на структуру та властивості композиційних матеріалів з альбуцидом аналогічний. За результатами фізико-механічних досліджень під впливом модельних середовищ відбуваються процеси біодеградації, про що свідчить зниження адгезійної міцності після інкубації в БС 199 і фізіологічному розчині. За даними ІЧ-спектроскопії біодеградація супроводжується перерозподілом водневих зв'язків NH-груп полімерної матриці. Результати випробувань методом ДСК свідчать про зниження T_c і підвищення ΔC_p ППУ композитів із альбуцидом порівняно з контролем, що пов'язано з підвищенням сегментальної рухливості макромолекул під впливом модельних середовищ і внаслідок вивільнення альбуциду з полімерної матриці. Методом ТГА встановлено, що ППУ та ППУ композити з альбуцидом за умов *in vitro* залишаються термостійкими матеріалами, адже після інкубації у БС 199 і фізіологічному розчині спостерігається підвищення значень $T_{\text{поч. розкл.}}$ і $T_{\text{макс. шв. розкл.}}$. Досліджено динаміку вивільнення альбуциду з ППУ матриці та встановлено, що композиційні матеріали здатні до пролонгованого вивільнення 36,0 % лікарської речовини на 60-у добу експерименту, що не перевищує терапевтичну дозу та не чинить токсичного впливу. Тому, пінополіуретанові композиційні матеріали з альбуцидом можуть бути запропоновані як перспективні матеріали для виготовлення імплантатів з пролонгованою дією альбуциду в офтальмологічній хірургії.

Ключові слова: пінополіуретан, композиційний матеріал, альбуцид, біологічне середовище 199, фізіологічний розчин.