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SYNTHESIS AND RESEARCH OF POLYURETHANE UREA WITH 2-(2-AMINOETHOXY)ETHAN-1-AMINE AND 3-{2-[2-(3-AMINOPROPOXY)ETHOXY]ETHOXY}PROPANE-1-AMINE AS MACROCHAIN EXTENDERS, AND COMPOSITIONS WITH IFOSPHAMIDE BASED ON THEM

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Polyurethane urea (PUU) was synthesized using macrochain extenders of 2-(2-aminoethoxy)ethan-1-amine (DA1) and 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine (DA3) at a molar ratio of 4,4'-diaminodiphenylmethane (DADP) to DA1 and DA3 as 30:70; 50:50; and 70:30. The tensile strength (σ) of PUU is in the range of 0.74–2.21 MPa, and the relative elongation at break (ε) is 27.4–1003%. According to the DSC method, the studied PUUs are single-phase systems. The glass transition temperature (T_g) of the PUU DA1 series is from 21.92°C to −39.48°C, and the glass transition temperature for the PUU DA3 is from −20.04°C to −33.96°C. Based on the synthesized PUUs, composite materials were prepared containing 1 wt.% of ifosfamide (IFO) (σ=0.74–2.21 MPa, and ε=31.8–276.3%). According to the results of thermophysical studies, the compositions with IFO are single-phase systems with T_g of −24.8°C to −36.22°C. Thus, the introduction of IFO into the composition leads to an increase in the packing density of the macrochain, a decrease in the size of the free volume and, consequently, a decrease in the mobility of the blocks in space and a decrease in ΔC_p. Compositions with IFO are resistant to temperatures of ~250°C, which allows thermal sterilization before use. Using the HPLC-UV method, the dynamics of IFO release from samples of PUU compositions synthesized at a molar ratio of DADP:DA1 as 0.5:0.5 and DADP:DA3 as 0.7:0.3 was investigated. It was established that IFO is released within 60 days from compositions based on PUU DA3 in the amount of 29.6%, and from compositions based on PUU DA1 in the amount of 42% with respect to the total amount of IFO introduced. The resulting composites are promising materials for medicine as means of local prolonged therapeutic action.

Keywords: polyurethane, polyurethane urea, 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine, 4,4'-diaminodiphenylmethane, 2-(2-aminoethoxy)ethan-1-amine, ifosfamide; holoxane.

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Introduction

Polyurethane ureas (PUUs) are widely used in medicine. Considering the fact that PUUs have high biocompatibility as well as exhibit tunable physicochemical and mechanical properties, they can be used as a basis for the creation of composition materials with a local prolonged therapeutic effect.

Thus, biologically active composition materials with decamethoxine [1] and lysozyme [2] based on PUUs, which contain in their structure copolymer of N-vinylpyrrolidone with vinyl alcohol, are suggested as means for the treatment of wounds and burns.

PUUs, that have silver-containing silica nanocompositions, exhibit bactericidal properties and can be used as coatings with antimicrobial properties for the production of drains and catheters in abdominal surgery [3] and implantation materials [4].

In recent years, PUUs with a wide range of physicochemical properties and biocompatibility have been developed for the purposes of tissue engineering and drug delivery [5,6]. Due to the introduction of specific block copolymers into the polymer base, PUUs demonstrate flexible physicochemical properties.

The properties of block copolyurethanes depend on the structure of the blocks that make them up, and their ability to microsegregate and formation a domain structure. By changing the ratios of components during the synthesis of initial block-copolyurethanes and by varying the ratio of flexible and rigid blocks, it is possible to regulate their final properties. As a result, polymer carriers with different operational properties and purpose can be obtained. Thus, one of the ways to govern the dynamics of drug release is to regulate the degree of swelling in water by changing the ratio between soft and rigid segments of polyurethanes [7].

Segmented PUUs are also copolymers of a type of block, which consist of alternating soft and rigid segments. The rigid segment acts as a physical cross-linking point and plays a key role in determining the mechanical properties, viscosity, elasticity and hardness of segmented polyurethane copolymers. Unlike the diol extenders used in polyurethane (PU) synthesis, where there is only one hydrogen bond N−H (H-bond) donor, the H-bonds in PUUs with a diamine as a chain extender is much more complex, as there are two N−H bonds in the urethane-urea group. It was shown that H-bond is closely related to the phase separation and properties of PUUs. However, there are fewer references to the study of PUU than PU, possibly due to the more complex structure and properties of H-bonding. Similar to isocyanates, the type of chain extender also determines the structure of the rigid segment and affects the final intrinsic PU of the bond [8−10]. Thus, via changing the ratio of introduced diamines during the synthesis of PUU, one can adjust their properties and prepare a polymer material with the desired operational characteristics.

From this point of view, attention is drawn to diamines that contain oxygen atoms in their chain, in particular 2-(2-aminoethoxy)ethan-1-amine and 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propane-1 -amine, which are additional proton acceptors and can affect the final properties of the synthesized PUUs. 2-(2-aminoethoxy)ethan-1-amine and 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine are known as water-soluble derivatives of polyethylene glycols of different molecular weight (amino−PEG−amine) and used as linkers during the creation of targeted anticancer drugs [11].

Recently, ifosfamide (IFO), a cytostatic alkylating agent of the oxazaphosphorine group, has been used for complex treatment of malignant neoplasms. IFO is used as a monodrug or in combination with other chemotherapeutic agents in the treatment of numerous tumors, including sarcomas of soft and bone tissues [12].

Up to date, there are very few works aimed at developing the polymer implantation materials with immobilized antitumor agents, in particular IFO, as means of adjuvant therapy in the treatment of pathological neoplasms.

Thus, isocyanurate-containing polyurethane compositions with the antitumor drug IFO are known for further use as implant materials, which are synthesized based on polyoxypropylene glycol, 2,4;2,6-toluene diisocyanate and 2,4,6-triisocyanate (trishexamethylene)isocyanurate (Tolonate™ HDT-LV) in N,N'-dimethylacetamide medium [13]. The developed compositions are biocompatible, but according to the results of the conducted research, after incubation in the biological environment, the synthesized samples do not undergo significant changes in structure and properties. That is, the developed compositions show biostability, which, probably, will complicate the prolonged release of ifosfamide when they are used.

Therefore, the question of synthesis of new polymer carriers and obtaining composition materials based on them with prolonged release of anticancer drugs remains relevant.

Considering the above, the aim of the work was the synthesis and analysis of the properties of a series of PUUs using 2-(2-aminoethoxy)ethan-1-amine and 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propane-1-amine as macrochain extenders and composition materials with ifosfamide based on them as perspective prolonged acting materials for medicine.

Materials and methods

Materials

Polyoxypropylene glycol (POPG) (Rokopol, MM=1000) was dried under a residual pressure of 1−3 mm Hg at the temperature of 80±5^{0}C in a flow of dry argon for 8 hours immediately before synthesis. The moisture content according to the Fisher method did not exceed 0.01−0.02%.

2,4-; 2,6-toluene diisocyanate (TDI, 80/20 wt.%) $C_9H_6N_2O_2$ (Merck, Germany) (MM=174.16; ρ=1.22 g/cm^3; T_B=133±1^{0}C; n_D^{20}=1.5678), purified by vacuum distillation at a residual pressure of

0.67 kPa, T_B=100±1°C. Used freshly distilled.

4,4'-diaminodiphenylmethane (DADPh) $C_9H_6N_2O_2$ (Merck, Germany) (MM=174.16; ρ=1.22 g/cm³; boiling point=133±1°C; n_D^{20}=1.5678), a mixture of isomers 2,4- and 2,6- in the ratio of 80:20, respectively, were purified by vacuum distillation at a residual pressure of 0.67 kPa, T_B=100±1°C. Used freshly distilled.

2-(2-aminoethoxy)ethan-1-amine (DA1), $C_4H_{12}N_2O_1$ (Merck, 95%) (Mw=104.15 g/mol; ρ=1.01 g/cm³; T_B=89°C).

3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine (DA3), $C_{10}H_{24}N_2O_3$ (Merck, 95%) (Mw=220.3 g/mol; ρ=1.005 g/cm³; T_B=186°C).

N,N'-dimethylacetamide (DMAA) (Merck, Germany) (MM=87.12; ρ=0.940–0.942 g/cm³; 99.7%) was distilled with a benzene-water mixture in a vacuum (T_B=52±1°C/14 mm Hg).

Acetonitrile (Merck, Germany) (MM=41.05; ρ=0.78 g/cm³; 99.99%).

Holoxan (Baxter, Germany), active ingredient Ifosfamide $C_7H_{15}Cl_2N_2O_2P$ (MM=261.09; melting point 39–41°C; logP (octanol–water)=0.86. White crystalline powder, well soluble in water (3780 mg/l at the temperature of 25°C); 99.99%.

Methods

Tensile strength (σ, MPa) and relative elongation at break (ε, %) of the synthesized PUUs were determined according to the ISO 527-3 on a modernized machine 2166 P-5 with a gripper expansion speed of 50±5 mm/min, and the speed of fixation of the results was 0.01 s.

Thermophysical properties (glass transition temperature (T_g), and changes in heat capacity at the glass transition temperature (ΔC_p)) were researched by the DSC method. The investigation was carried out in the temperature range of −90 to +200°C (TA Instrument Q2000) with a heating rate of 20°C/min. In order to exclude the influence of the thermal and mechanical history of the material, two heatings were performed.

Thermogravimetric characteristics (decomposition temperature (T_{decomp}), mass loss during decomposition) were studied by the TGA method. The research was carried out in the temperature range of 20 to 700°C (TA Instrument Q50 device) with a heating rate of 20°C/min in the air atmosphere.

The study of the dynamics of ifosfamide release was determined by the method of high-performance liquid chromatography (HPLC). Chromatography conditions: column: Eclipse XDB-C18, 5 μm, 4.6×150 mm; mobile phase: water:acetonitrile; flow rate of 0.5 ml/min; detector: UV 215 nm, injected volume of 20 μl.

Detection was carried out by the HPLC-UV method. The conditions of HPLC-UV determination of ifosfamide were optimized. Chromatography conditions: column: Eclipse XDB-C18, 5 μm, 4.6×150 mm; mobile phase: water:acetonitrile; flow rate of 0.5 ml/min; detector: UV 215 nm, injected volume of 20 μl. Thus, the optimal time of the release of the compound under the given chromatography conditions was determined as follows: tr=5.5 min – ifosfamide.

A series of IFO solutions with a concentration range of 0.005–0.25% were prepared for the construction of a graduation graph. Detected by HPLC-UV. A graduation graph was constructed based on the dependence of the peak area (S) on the concentration of ifosfamide. The equation of the graduation graph is as follows: $S1=(1.43\pm0.02)\cdot10^4C+(1.54\pm0.24)\cdot10^2$, where C is the concentration of ifosfamide in an aqueous solution (in %); and S is the area of the chromatographic peak of ifosfamide (R^2=0.999).

To study the dynamics of IFO release, PUU samples with immobilized IFO (m=5 g) were placed in a sealed box under argon filled with 20 ml of bidistillate with a thermostat and kept at a temperature of 37°C. To determine IFO, 1 ml of the solution was taken at regular intervals into the autosampler vial of the chromatograph, which took 20 μl for analysis, the rest of the solution was returned to the box. Quantitative assessment of the content of the drug in the solution was carried out using the appropriate calibration dependence.

Synthesis

In order to create new polymeric materials for medical purposes as promising carriers of drugs, a series of film-forming PPU based on diisocyanate prepolymer (DPP), using 4,4'-diaminodiphenylmethane (DADPh) and 2-(2-aminoethoxy)ethan-1-amine (DA1), and 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine (DA3) as extenders was synthesized. The synthesis was carried out at a different molar ratio of DADPh to DA1 or DA3 as 0.7:0.3; 0.5:0.5, and 0.3:0.7 according to the general scheme, which is similar to the one given in the article [14]. Synthesized polymers PUU DA1 and PUU DA3 are elastic, transparent films of light yellow color, 0.25–0.32 mm thick.

Synthesis of (PUU DA1)1 and (PUU DA3)1 – molar ratio of DADPh:DA1 and DADPh:DA3 as 0:1

The synthesis was carried out in two stages according to the method described earlier [14]. For the synthesis of the 2nd stage of macrochain elongation, 1.04 g (0.01 mol) DA1 or 2.2 g (0.01 mol) DA3 was added dropwise to a 20% solution of DPP in DMAA (13.48 g, 0.01 mol) at a temperature

of 20^{0}C while stirring.

Synthesis of (PUU DA1)2 and (PUU DA3)2 – molar ratio of DADPh:DA1 and DADPh:DA3 as 0.7:0.3

The synthesis was carried out in two stages. The first stage is similar to the one described above. The stage of macrochain elongation was carried out by reacting a 20% solution of DPP (0.01 mol) in DMAA with 1.38 g (0.007 mol) of DADPh at a temperature of 20^{0}C with stirring and adding 0.312 g (0.003 mol) of DA1 or 0.66 g (0.003 mol) DA3.

Synthesis of (PUU DA1)3 and (PUU DA3)3 – molar ratio of DADPh:DA1 and DADPh:DA3 as 0.5:0.5

The synthesis was carried out as previously described using a 20% solution of 13.48 g (0.01 mol) DPP in DMAA, 0.99 g (0.005 mol) DADPh, 0.52 g (0.005 mol) DA1, 1.1 g (0.005 mol) DA3.

Synthesis of (PUU DA1)4 and (PUU DA3)4 – molar ratio of DADPh:DA1 and DADPh:DA3 as 0.3:0.7

The synthesis was carried out as previously described using a 20% solution of 13.48 g (0.01 mol) DPP in DMAA, 0.6 g (0.003 mol) DADPh, 0.73 g (0.007 mol) DA1, 1.42 g (0.007 mol) of DA3.

Preparing the PUU compositions with ifosfamide

Immobilization of ifosfamide was carried out by mechanical mixing of a 20% polymer solution in DMAA with 1 wt.% ifosfamide. The solution was stirred for 10 minutes, poured into Teflon molds and dried in an oven at a temperature of 70±5^{0}C in an argon atmosphere for 94 hours until the polymer mass was constant. The obtained PUUs after immobilization of ifosfamide did not change their color and were elastic transparent films with a thickness of 0.3 mm.

Results and discussion

One of the important characteristics of polymer materials for medicine is physical-mechanical properties, therefore comparative studies of strength and relative elongation at break of rows of the synthesized PUUs were conducted depending on the ratio of the initial components.

According to the conducted investigation, the tensile strength of the synthesized PUUs is within the range of 0.74–2.21 MPa, and the relative elongation is 41.4–1003%. However, the breaking strength of the synthesized series of polymers depends both on the structure of the selected diamine as a macrochain extender and on its content.

The best physical and mechanical characteristics have the polymer synthesized in the ratio (PUU DA1)3 with a tensile strength of 1.92 MPa and a relative elongation of 75.4% and (PUU DA3)4 with a tensile strength of 1.52 MPa and a relative elongation of 1003% (Table 1).

When creating new composite materials, a scientific approach requires a thorough study of key operational parameters. For industrial compositions, this includes analysis of the phase structure of materials, determination of optimal thermal regimes of synthesis and use, as well as assessment of stability and mechanical strength [15,16]. However, special attention should also be paid to composites for medicine based on polyurethane ureas, since their structure and properties depend significantly on the ratio and characteristic of the initial components. All this is important for understanding and optimizing the properties of new materials.

Considering the fact that a change in the structure of the polymer can lead to a change in its thermophysical properties, samples of PUUs, which diverge among themselves in different content of DA, were investigated (Table 2).

The temperature dependences of the heat capacity of the synthesized PUU series using DA1 and DA2 as macrochain extenders have the same character, therefore the heat capacity curves are presented only for PUU DA1 series (Fig. 1).

According to the results of thermophysical studies one temperature transition was observed on the thermograms and, thereafter, one glass transition temperature (T_g), so the investigated systems are single-phase (Fig. 1).

Table 1

Results of physical and mechanical tests of PUU

Sample	DADPh:DA ratio, mol	Tensile strength, σ, MPa	Relative elongation at break, ε, %
(PUU DA1)1	0.0:1.0	2.21±0.03	38.8±1.5
(PUU DA1)2	0.7:0.3	1.52±0.07	27.7±1.5
(PUU DA1)3	0.5:0.5	1.92±0.12	75.4±3.6
(PUU DA1)4	0.3:0.7	0.92±0.04	41.4±1.1
(PUU DA3)1	0.0:1.0	0.88±0.06	495.7±24.4
(PUU DA3)2	0.7:0.3	0.74±0.04	153.2±13.2
(PUU DA3)3	0.5:0.5	0.74±0.02	760.6±45.9
(PUU DA3)4	0.3:0.7	1.52±0.03	1003.0±35.4
PUU	1.0:1.0:0.0	1.72±0.07	77.9±6.8

Table 2

Thermophysical properties of PUU based on DPP, DADPh and DA

Sample	DADPh:DA ratio, mol	T_g, ^{0}C		ΔC_p (J/(g.^{0}C))	
		I heating	II heating	I heating	II heating
(PUU DA1)1	0.0:1.0	–39.61	–39.48	0.3408	0.4336
(PUU DA1)2	0.7:0.3	–35.35	–34.05	0.414	0.4656
(PUU DA1)3	0.5:0.5	–34.32	–35.42	0.4334	0.4096
(PUU DA1)4	0.3:0.7	–17.77	–21.92	0.519	0.5694
(PUU DA3)1	0.0:1.0	–28.86	–33.96	0.5601	0.5480
(PUU DA3)2	0.7:0.3	–15.97	–20.04	0.5473	0.4828
(PUU DA3)3	0.5:0.5	–20.82	–20.82	0.4952	0.4435
(PUU DA3)4	0.3:0.7	–29.2	–27.32	0.5366	0.4802
PUU	1.0:0.0	–14.32	–17.63	0.5222	0.5200

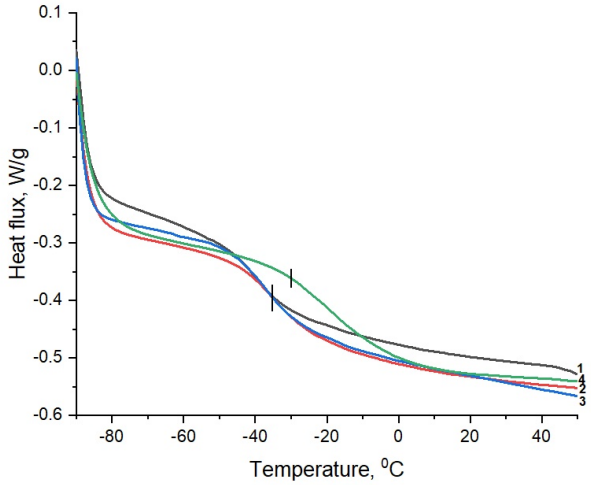

Fig. 1. Typical thermograms of PUUs based on DPP, DADPh and DA1 (2 – warm-ups): the T_g value of the 2nd heating of the studied materials of the PUU DA1 series lies in the range from –21.92^{0}C to –39.48^{0}C. 1 – (PUU DA1)1; 3 – (PUU DA1)4; 4 – (PUU DA1)3; and 5 – (PUU DA1)2

While comparing the thermophysical properties of initial PUU and PUUs synthesized by varying the ratio of DADPh to DA1 or DA3, it turns out that the original PUU has a higher T_g, which is –17.63^{0}C during the 2nd heating. That is, the introduction of DA1 and DA3 diamines into the PUU structure leads to an increase in the length of the rigid blocks and, as a consequence, to a decrease in the packing density of the macrochain, resulting in an increase in the amount of free volume, which can lead to an increase in molecular mobility and a decrease in T_g.

According to the thermophysical results for a series of PUUs, which contain DA3 as a macrochain extender, an increase in T_g and a slight decrease in ΔC_p are observed when the diamine content in the polymer structure increases during the 2nd heating. Probably, the introduction of PUU DA3 into the structure leads to an increase in the intermolecular interactions, a decrease in the molecular mobility of macrochains and an increase in the value of T_g.

With an increase in the content of DA1 in the structure of the PUUs series during the 2nd heating, an increase in the T_g and a slight increase in ΔC_p is observed, which may be associated with an increase in the packing density, which leads to a decrease in the molecular mobility and increase in T_g.

According to the TGA data, the temperature of the beginning of decomposition ($T_{decomp.start}$) of PUUs synthesized using macrochain extenders DA1 and DA3 lies in the range of 260.1^{0}C to 290.5^{0}C (Table 3) and is accompanied by a slight loss of mass (0.127–1.175%). Mass loss of samples at $T_{decomp.start}$ depends on the DA content in PUUs and has non-linear character. Maximum loss at $T_{decomp.start}$ is observed for (PUU DA1)4, synthesized at a molar ratio of 0.3:0.7 and it is 1.05%, and for (PUU DA3)3 synthesized at a molar ratio of 0.5:0.5 and it is 1.175%.

$T_{decomp.start}$ decreases when the diamine content in the PUU structure increases, and its dependence on the diamine content is nonlinear. For PUU series, there is a decrease in $T_{decomp.start}$, which is 290.5^{0}C and 276.3^{0}C for (PUU DA1)2 and (PUU DA3)1, respectively. Decomposition of the samples occurs in one stage with the temperature of the maximum decomposition rate ranging from 306.4^{0}C to 340.7^{0}C.

The next stage of the research was the immobilization of IFO on synthesized polymer carriers and preparation of composition materials with IFO, the amount of which in the composition was 1 wt.%, which does not exceed its therapeutic dose. Immobilization of IFO on a polymer carrier will allow obtaining new biologically active implant materials that can find their use as adjuncts with a prolonged therapeutic effect during antitumor therapy.

In order to investigate the effect of IFO on the properties of the obtained composition materials, physical-mechanical and thermophysical studies were

conducted using DSC and TGA methods.

According to the obtained results, the tensile strength of the compositions is within the range of 0.74–2.21 MPa, and the relative elongation is 54.1–276.3%. The best physical and mechanical characteristics of the series are achieved for the composition (PUU DA1)3+IFO with a tensile strength of 1.63 MPa and a relative elongation of 79.1% and for the composition (PUU DA3)2+IFO with a tensile strength of 2.21 MPa and a relative elongation of 70.2%. The introduction of IFO into the composition of the synthesized polymer carriers has almost no effect on the value of the tensile strength. However, a decrease in relative elongation is observed, which can be explained by the formation of a more structured system of rigid and flexible blocks and a decrease in the mobility of macrochains (Table 4).

Only one temperature transition and, accordingly, one T_g were observed on the thermograms of the studied compositions, that is, the systems are single-phase and did not change after immobilization of drug.

For PUU compositions with IFO (Table 5) in comparison with the original PUU (Table 3) during the 2nd heating, a decrease in the glass transition temperature and a slightly reduced ΔC_p values are observed. That is, the introduction of IFO into the composition leads to an increase in the packing density of the macrochain, as a result of which the amount of free volume, the mobility of blocks in space and ΔC_p decrease.

It was established that the introduction of IFO into PUUs synthesized at a DADPh:DA1 molar ratio of 0.5:0.5 has practically no effect on the T_g values of the composition, which is equal to −35.6^{0}C (Table 4) compared to −35.42^{0}C for of the initial PUU (Table 3). The introduction of IFO into (PUU DA1)3 causes an increase in ΔC_p values at the glass transition both in the 1st and in the 2nd heating, which is connected with a decrease in the packing density of macrochains and an increase in the free volume, and, consequently, an increase in molecular mobility.

According to the TGA, the temperature of the beginning of decomposition ($T_{decomp.start}$) of compositions with ifosfamide is in the range of 250.2 to 289.9^{0}C (Table 6) and is accompanied by a slight loss of mass of about 1%. Mass loss of samples at $T_{decomp.start}$ does not depend on the content of the medicinal substance in the composition of PUU and has non-linear character. Maximum loss at $T_{decomp.start}$

Table 3

Thermogravimetric characteristics of PUUs based on DPP, DADPh and DA

Sample	DADPh:DA ratio, mol	$T_{decomp.start}$, ^{0}C	$T_{decomp.vel.max}$, ^{0}C	Mass loss at $T_{decomp.start}$, %
(PUU DA1)1	0.0:1.0	289.1	340.7	0.377
(PUU DA1)2	0.7:0.3	290.5	349.2	0.127
(PUU DA1)3	0.5:0.5	286.1	330.8	0.278
(PUU DA1)4	0.3:0.7	274.8	334.3	1.05
(PUU DA3)1	0.0:1.0	276.3	306.8	0.409
(PUU DA3)2	0.7:0.3	269.2	306.4	0.117
(PUU DA3)3	0.5:0.5	260.1	309.4	1.175
(PUU DA3)4	0.3:0.7	276.9	329.1	1.013
PUU	1.0:0.0	300.3	340.1	0.023

Table 4

Results of physical and mechanical tests of PUUs based on DPP, DADPh, DA1+IFO and DADPh, DA3+IFO for different molar ratio of components

Sample	DADPh:DA ratio, mol	Tensile strength, σ, MPa	Relative elongation at break, ε, %
(PUU DA1)1+IFO	0.0:1.0	1.73±0.03	54.1±1.5
(PUU DA1)2+IFO	0.7:0.3	1.50±0.06	31.8±1.7
(PUU DA1)3+IFO	0.5:0.5	1.63±0.05	79.1±2.3
(PUU DA1)4+IFO	0.3:0.7	0.74±0.03	108.8±3.8
(PUU DA3)1+IFO	0:1.0	0.80±0.04	276.3±11.3
(PUU DA3)2+IFO	0.7:0.3	2.21±0.04	70.2±13.2
(PUU DA3)3+IFO	0.5:0.5	1.20±0.09	76.6±45.9
(PUU DA3)4+IFO	0.3:0.7	0.92±0.03	60.1±3.4
PUU+IFO	1:0	0.97±0.06	103.9±3.5

is observed for the synthesized molar ratio (PUU DA1)4+IFO as 0.3:0.7 and (PUU DA3)1+IFO as 0.0:1.0, it is equal to 0.965% and 0.451%, respectively.

Decomposition of the samples occurs in one stage with the temperature of the maximum decomposition rate ranging from 305.4^{0}C to 312.7^{0}C. The introduction of IFO into the structure of PUUs does not lead to a decrease in $T_{decomp.vel.max}$. The studied compositions of PUUs with IFO are heat-resistant up to a temperature of ~250^{0}C, which makes it possible to carry out thermal sterilization of samples without changing their characteristics.

According to the obtained results, the compositions (PUU DA1)3+IFO, with tensile strength and relative elongation at break of 1.63 MPa and 79.3%, respectively, and (PUU DA3)2+ IFO, with tensile strength and relative elongation at break of 2.21 MPa and 72%, respectively, have improved operational characteristics. Considering the above, the dynamics of the release of IFO was studied for the indicated compositions, since in view of the studied properties, they are the most perspective carriers for the delivery of drugs for using as implant materials.

It was established based on the obtained chromatography data (Fig. 4) that the amount of released IFO within 2 months for (PUU DA1)3+IFO and (PUU DA3)2+IFO is 42% and 29.6% of the mass of the injected drug substances, respectively.

The selected extenders for PUUs are hydrophobic and relatively inert, well sorb both non-polar and medium polar substances, for example, IFO due to van der Waals and dispersion interactions. However, the amount of ifosfamide during the leaching of the substance from (PUU DA1)3 is greater than from (PUU DA3)2. This is due to the fact that the DA1 extender is smaller in size, contains one hydroxyl in the structure, and, consequently, has less steric hindrance and weaker interaction with the substance. According to the results obtained in the early stages of the study for (PUU DA1)3, the drug is released quickly, and then in small amounts and evenly, and for (PUU DA3)2 it reaches a plateau on the 30th day of the study.

The obtained results are one of the important stages in the development of medical products as means of prolonged release of drugs, because it is possible to predict the dose of the drug that will be delivered to the site of injury.

Table 5

Thermophysical properties of PUU based on DPP, DADPh, DA+IFO

Sample	DADPh:DA ratio, mol	T_g, ^{0}C		ΔC_p (J/(g·^{0}C))	
		I heating	II heating	I heating	II heating
(PUU DA1)1+ IFO	0.0:1.0	–35.51	–36.16	0.396	0.467
(PUU DA1)2+ IFO	0.7:0.3	–36.02	–36.22	0.409	0.451
(PUU DA1)3+ IFO	0.5:0.5	–32.36	–35.60	0.463	0.452
(PUU DA1)4+ IFO	0.3:0.7	–27.71	–26.55	0.497	0.516
(PUU DA3)1+ IFO	0.0:1.0	–28.21	–27.03	0.467	0.421
(PUU DA3)2+ IFO	0.7:0.3	–27.57	–26.79	0.492	0.465
(PUU DA3)3+ IFO	0.5:0.5	–27.97	–24.80	0.425	0.499
(PUU DA3)4+ IFO	0.3:0.7	–34.60	–32.40	0.436	0.477
PUU+ IFO	1.0:0.0	–16.9	–15.65	0.524	0.481

Table 6

Thermogravimetric characteristics of PUU based on DPP, DADPh and DA+IFO

Sample	DADPh:DA ratio, mol	$T_{decomp.start}$, ^{0}C	$T_{decomp.vel.max}$, ^{0}C	Mass loss at $T_{decomp.start}$, %
(PUU DA1)1+ IFO	0.0:1.0	250.2	285.6	0.994
(PUU DA1)2+ IFO	0.7:0.3	264.6	310.1	0.388
(PUU DA1)3+ IFO	0.5:0.5	268.9	305.4	0.336
(PUU DA1)4+ IFO	0.3:0.7	281.8	331.8	0.965
(PUU DA3)1+ IFO	0.0:1.0	287.5	306.6	0.451
(PUU DA3)2+ IFO	0.7:0.3	283.9	307.9	0.271
(PUU DA3)3+ IFO	0.5:0.5	270.1	301.9	0.229
(PUU DA3)4+ IFO	0.3:0.7	271.2	312.7	0.032
PUU+ IFO	1.0:0.0	289.9	311.9	2.475

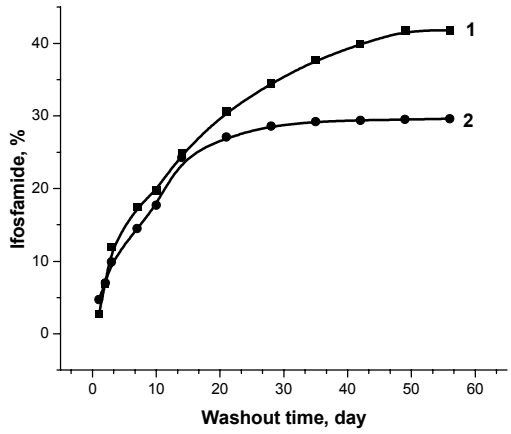

Fig. 2. Dynamics of ifosfamide release: 1 – (PUU DA1)3+IFO; and 2 – (PUU DA3)2+IFO

Conclusions

Based on the results of the research, a number of film-forming PUUs based on DPP, DADPh and macrochain extenders 2-(2-aminoethoxy)ethan-1-amine (DA1) and 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy} propan-1-amine (DA3) were synthesized at a different molar ratio of DADPh to DA as 0.3:0.7; 0.5:0.5; and 0.7:0.3. The synthesized PUUs are characterized by tensile strength in the range of 0.74 to 2.21 MPa and relative elongation at break of 27.4 to 1003%.

According to the DSC results, the investigated systems are single-phase. The T_g of the 2nd heating in the PUU DA1 series lies in the range from −21.92^{0}C to −39.48^{0}C, and in the PUU DA3 series in the range from −20.04^{0}C to −33.96^{0}C. It was established that the introduction of diamines DA1 and DA2 into the PUU structure leads to a decrease in their T_g as compared with the initial PUU (T_g=−17.63^{0}C). Thus, the introduction of DA1 and DA3 into the PUU structure leads to an increase in the length of rigid blocks and, consequently, to a decrease in the packing density of the macrochain, as a result of which the amount of free volume increases, which can lead to an increase in molecular mobility and a decrease in T_g.

According to the thermophysical results for a series of PUUs containing DA1 or DA3 as macrochain extenders, an increase in the T_g values is observed with an increase in the content of DA in the polymer structure during the 2nd heating, which can be associated with an increase in intermolecular interactions and the packing density of macrochains, and, as a result, a decrease in molecular mobility and an increase in T_g.

According to the results of TGA, the heat resistance characteristics of the synthesized PUUs depend on the diamine content. When DA1 and DA3 diamines are introduced into the PUU structure, a decrease in $T_{decomp.start}$ and $T_{decomp.vel.max}$ is observed, which has non-linear character. $T_{decomp.start}$ lies in the range of 260.1 to 290.5^{0}C and is accompanied by a slight loss of mass (0.127−1.175%).

Thus, by varying the ratios of components during the synthesis of initial PUUs and by varying the length of soft and rigid blocks, it is possible to prepare polymer carriers with adjustable final properties.

Based on PUUs synthesized from DPP, DADPh, DA1 and DA3 under different molar ratio of DADPh to DA (0.3:0.7; 0.5:0.5; and 0.7:0.3), a series of compositions with IFO was obtained. The content of IFO in the compositions was 1 wt.%. The best physical-mechanical properties show the composition based on PUU synthesized at a molar ratio of DADPh to 2-(2-aminoethoxy)ethan-1-amine of 0.5:0.5 ((PUU DA1)3+IFO) (the tensile strength and relative elongation being 1.63 MPa and 79.1%, respectively), and the composition based on PUU synthesized at a molar ratio of DADPh to 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine of 0.7:0.3 ((PUU DA3)2+IFO) (the tensile strength and relative elongation being 2.21 MPa and 70.2%, respectively).

According to the DSC results, compositions with IFO based on PUU DA1 and PUU DA3 are single-phase systems, the T_g of which lies in the range from −24.8^{0}C to −36.22^{0}C. Comparison of the heat resistance of compositions with IFO and original PUU show that the introduction of IFO in PUU leads to a decrease in the T_g and ΔC_p during the 2nd heating. That is, the introduction of IFO into the composition leads to an increase in the packing density of the macrochain, and consequently the amount of free volume decreases and the mobility of blocks in space and ΔC_p values decrease.

According to the results of TGA, the characteristics of the heat resistance of the synthesized PUUs after immobilization of IFO remaine almost unchanged. Compositions with ifosfamide are resistant to temperatures of ~250^{0}C, which allows thermal sterilization before use.

The dynamics of the release of IFO from samples of compositions based on PUUs synthesized at the molar ratio of DADPh to 2-(2-aminoethoxy)ethan-1-amine of 0.5:0.5 ((PUU DA1)3+IFO) and at the molar ratio of DADPh to 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine of 0.7:0.3 ((PUU DA3)2+IFO) was investigated by HPLC method. According to the obtained data, IFO is released in the amount of 42% for (PUU DA1)2+L and in the amount of 29.6% for (PUU DA3)2+IFO

in respect of injected drug's mass during 2 months.

The synthesized PUUs are promising polymer carriers of drugs and deserve attention for further use in medicine as composition materials of the system of prolonged release of drugs. Research in this direction can serve for the development of biologically active polymer materials as adjuncts for local prolonged therapeutic action.

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СИНТЕЗ І ДОСЛІДЖЕННЯ ПОЛІУРЕТАНОВИХ СЕЧОВИН З 2-(2-АМІНОЕТОКСИ)ЕТАН-1-АМІНУ ТА 3-{2-[2-(3-АМІНОПРОПОКСИ)ЕТОКСИ]ЕТОКСИ} ПРОПАН-1-АМІНУ ЯК ПОДОВЖУВАЧІВ МАКРОЛАНЦЮГІВ І КОМПОЗИЦІЇ З ІФОСФАМІДОМ НА ЇХ НА ОСНОВІ

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Синтезовано поліуретансечовини (ПУС) з використанням подовжувачів макроланцюга 2-(2-аміноетокси)етан-1-аміну (ДА1) та 3-{2-[2-(3-амінопропокси)етокси]етокси}-пропан-1-аміну (ДА3) за мольного співвідношення 4,4'-діамінодифенілметану (ДАДФ) до ДА1 та ДА3, рівного 30:70; 50:50; 70:30. Міцність при розриві (σ) ПУС знаходиться у діапазоні 0,74–2,21 МПа, а відносне подовження при розриві (ε) 27,4–1003%. За даними метода ДСК досліджувані ПУС є однофазними системами. Температура склування (T_c) ряду ПУС ДА1 складає від −21,92^{0}С до −39,48^{0}С, а ряду ПУС ДА3 − від −20,04^{0}С до −33,96^{0}С. На основі синтезованих ПУС одержано композиційні матеріали з іфосфамідом (ІФО) з вмістом 1 мас.% (σ=0,74–2,21 МПа, ε=31,8–276,3%). За результатами теплофізичних досліджень композиції з ІФО є однофазними системами з T_c від −24,8^{0}С до −36,22^{0}С. Встановлено, що введення ІФО в ПУС приводить до зменшення T_c та DC_p при другому прогріванні в порівнянні з вихідними ПУС. Таким чином, введення ІФО в композицію приводить до збільшення щільності пакування макроланцюга, зменшення величини вільного об'єму і, як наслідок, зменшення рухливості блоків в просторі та зниження $ДС_p$. Композиції з ІФО є стійкими до температури ~250^{0}С, що дозволяє проводити термічну стерилізацію перед використанням. Методом ВЕРХ-УФ досліджена динаміка вивільнення ІФО зі зразків композицій ПУС, синтезованих за мольного співвідношення ДАДФ:ДА1=0,5:0,5, та ДАДФ:ДА3=0,7:0,3. Встановлено, що ІФО вивільняється протягом 60 діб з композицій на основі ПУС ДА3 в кількості 29,6%, а з композицій ПУС ДА1 − 42%, від загальної кількості введеного ІФО. Одержані композити є перспективними матеріалами для медицини як засоби місцевої пролонгованої лікувальної дії.

Ключові слова: поліуретансечовини; 2-(2-аміноетокси)етан-1-аміну; 3-{2-[2-(3-амінопропокси)етокси]етокси}пропан-1-аміну; іфосфамід; холоксан.

SYNTHESIS AND RESEARCH OF POLYURETHANE UREA WITH 2-(2-AMINOETHOXY)ETHAN-1-AMINE AND 3-{2-[2-(3-AMINOPROPOXY)ETHOXY]ETHOXY} PROPANE-1-AMINE AS MACROCHAIN EXTENDERS, AND COMPOSITIONS WITH IFOSPHAMIDE BASED ON THEM

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Polyurethane urea (PUU) was synthesized using macrochain extenders of 2-(2-aminoethoxy)ethan-1-amine (DA1) and 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine (DA3) at a molar ratio of 4,4'-diaminodiphenylmethane (DADP) to DA1 and DA3 as 30:70; 50:50; and 70:30. The tensile strength (σ) of PUU is in the range of 0.74–2.21 MPa, and the relative elongation at break (ε) is 27.4–1003%. According to the DSC method, the studied PUUs are single-phase systems. The glass transition temperature (T_g) of the PUU DA1 series is from 21.92^{0}C to −39.48^{0}C, and the glass transition temperature for the PUU DA3 is from −20.04^{0}C to −33.96^{0}C. Based on the synthesized PUUs, composite materials were prepared containing 1 wt.% of ifosfamide (IFO) (σ=0.74–2.21 MPa, and ε=31.8–276.3%). According to the results of thermophysical studies, the compositions with IFO are single-phase systems with T_g of −24.8^{0}C to −36.22^{0}C. Thus, the introduction of IFO into the composition leads to an increase in the packing density of the macrochain, a decrease in the size of the free volume and, consequently, a decrease in the mobility of the blocks in space and a decrease in DC_p. Compositions with IFO are resistant to temperatures of ~250^{0}C, which allows thermal sterilization before use. Using the HPLC-UV method, the dynamics of IFO release from samples of PUU compositions synthesized at a molar ratio of DADP:DA1 as 0.5:0.5 and DADP:DA3 as 0.7:0.3 was investigated. It was established that IFO is released within 60 days from compositions based on PUU DA3 in the amount of 29.6%, and from compositions based on PUU DA1 in the amount of 42% with respect to the total amount of IFO introduced. The resulting composites are promising materials for medicine as means of local prolonged therapeutic action.

Keywords: polyurethane; polyurethane urea; 3-{2-[2-(3-aminopropoxy)ethoxy]ethoxy}propan-1-amine; 4,4'-diaminodiphenylmethane; 2-(2-aminoethoxy)ethan-1-amine; ifosfamide; holoxane.

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