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SYNTHESIS AND PROPERTIES OF PHOSPHORUS-CONTAINING PSEUDO-POLY(AMINO ACID)S OF POLYESTER TYPE BASED ON *N*-DERIVATIVES OF GLUTAMINIC ACID

Anna Stasiuk[1, ✉], Nataliia Fihurka[1], Vasyl Vlizlo[2], Sofiia Prychak[1], Dmytro Ostapiv[3], Serhii Varvarenko[1], Volodymyr Samaryk[1]

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Abstract. Poly(phosphoeter)s (PPE)s are a class of polymers possessing a high chemical functionality and biodegradability. Novel, glutamic acid based poly (phosphoeter)s were synthesized by the Steglich reaction. The developed synthetic approach allows controlling the composition and the structure of PPEs, and therefore their physical and colloidal properties. The studies on solubilization and cytotoxicity in vitro proved the potential of PPEs for drug delivery applications.

Keywords: poly(phosphoester)s, pseudo-poly(amino acid)s, glutamic acid, polyethylene glycol, Steglich reaction, drug delivery.

1. 1. Introduction

Polyesters are considered promising materials for biomedical applications[1-3] due to a number of properties – biodegradability, biocompatibility, availability of raw materials.[4-6] Their applications include various medical devices – threads, bone fixators, stents, and screws.[7-10] Researchers pay special attention to preparing polyester-based dispersed delivery systems for therapeutic agents.[11] However, polyesters based on dicarboxylic acids and diols[12] or lactones[13] do not include functional groups or active centers capable of chemisorption of biological substances and drugs, that significantly limits their use. Therefore, the synthesis of functionalized polyesters still remains an urgent problem. Solving this issue will allow preparing new forms to deliver various biologically active compounds. The introduction of phosphate groups into the polymer chain is particularly promising for this purpose as the pentavalent phosphorus atom is an excellent option for further modification or binding to low molecular weight therapeutic drugs or proteins.[14]

The first attempts to obtain phosphorus-containing polymers were made in the 1950s when scientists tried to mimic the properties of natural phosphorus-containing macromolecules.[15] To date, synthetic approaches to phosphorus-containing polyesters based on a number of monomers (PEG, lactic acid) have been developing,[16-18] which largely confirms the relevance of this task. Common methods for the synthesis of polyphosphoesters are polycondensation, transesterification, and ring-opening polymerization.[19] The obtained polymers are biodegradable, biocompatible,[20] show a low cell adhesion, low toxicity, and stealth effect.[21]. However, despite the prospects of such polymers and a large number of studies in this field, so far none of the polyphosphoesters has reached the stage of clinical trials.[22] Only a few members of this series are in preclinical studies.

In addition to all the above-mentioned properties, polymers for dispersed drug delivery systems should form stable dispersions in the aqueous medium with the nanometric size of the dispersed phase.[23] It is desirable that the dispersion stabilization takes place without additional stabilizers. Thus, the polymer should possess surface-active properties.[24] At the same time, the particles of the dispersed phase should be able to solubilize water-insoluble organic compounds. Polymer to be used for drug delivery systems should be biodegradable and non-toxic. Moreover, biodegradation products should also be non-toxic.[25,26]

This work reports on a synthetic approach to polyphosphates based on glutamic acid and polyethylene glycols. The described method is an adaptation of the developed by the authors synthetic approach to pseudo-polyamino acids (PPAA) of polyester type by the Steglich reaction.

[1] Lviv Polytechnic National University,
12 S. Bandery St., Lviv 79013, Ukraine
[2] Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies,
50 Pekarska St., Lviv 79010, Ukraine
[3] Institute of Animal Biology NAAS,
38 V. Stusa St., Lviv 79034, Ukraine
✉ *anna.v.stasiuk@lpnu.ua*

2. Experimental

2.1. Materials

Polyoxyethylene/polyoxypropylene diols (PEG/PPG) were obtained from Sigma-Aldrich and dried by refluxing in benzene with azeotropic removal of water. Phosphorus(V) oxychloride, ethanol, triethylamine, triphenylmethyl chloride, *p*-toluenesulfonic acid were obtained from Sigma-Aldrich and used as received. *N*,*N*'-Dicyclohexylcarbodiimide (DCC) and 4-dimethyl-aminopyridine (DMAP) were obtained from Alfa Aesar and used as received. The solvents (benzene, ethyl acetate, 1,4-dioxane, methanol, dichloromethane, acetone, hexane) were purified using the procedure described by several authors.[27,28]

2.2. Research Methods

2.2.1. Methods of analysis

IR spectra were taken on a ThermoScientifis iD5 ATR Nicolet iS5 IR Spectrometer by the technique of attenuated total reflection on a diamond crystal (ATR FTIR). NMR spectra of polymers were taken on JEOL's ECA Series Nuclear Magnetic Resonance (NMR) Spectrometer in automatic conditions of scanning. Analysis of NMR-spectrums was carried out using the tables of chemical shifts characteristics described by Nagornyak *et al.*[29] and Zubyk *et al.*,[30] as well as the program Shem Bio Draw Ultra 11.0.1. The number of hydroxyl groups was determined by a non-catalytic acetylation and subsequent potentiometric titration.[31,32] The particles size of the polymeric micelles was determined using Malvern Zetasizer Nano S. The surface tension was determined by the Du Nui method. Solubilization of Sudan III was performed using the procedure described by Demchuk *et al.*[33] Survival and activity of sperm oxidative enzymes were performed using the procedure described by several authors.[34,35]

2.2.2. Methods of synthesis

Ethyl dichlorophosphate (EDP) was synthesized with the following method. Phosphorus(V) oxychloride (0.20 mol) was loaded into a reactor equipped with a stirrer and was cooled on a water-ice bath to 273–278 K. Then ethanol (0.1 mol) was dripped slowly into the reactor. After complete reagent dripping the synthesis continued under stirring at 278–283 K for 2 h and at 393 K for 4 h. Ethyl dichlorophosphate was purified by vacuum distillation. The yield is 75 %.

Polyoxyethylene triphenylmethyl ether (PEG-Tr) was synthesized according to the following method. Polyoxyethylene (molecular weight 400 g/mol, 0.7 mol), triethylamine (0.13 mol) and benzene (200 mL) were loaded into a reactor equipped with a stirrer. Triphenylmethyl chloride (0.1 mol) in 100 mL benzene was dripped into the reactor. After 12 h of stirring at 298 K, the mixture was filtered. Polyoxyethylene triphenylmethyl ester was extracted with ethyl acetate (150 mL) and washed with water (3×50 mL). The organic layer was dried over anhydrous sodium sulfate (2–3 g) for 12 h. Polyoxyethylene triphenylmethyl ester was dried under vacuum to a constant weight. The yield is 95 %.

Dipolyethylene glycol ethyl phosphate (DEP) was synthesized according to the following method. Polyoxyethylene triphenylmethyl ester (molecular weight 642.28 g/mol, 0.1 mol), triethylamine (0.105 mol), and 1,4-dioxane (150 mL) were loaded into a reactor equipped with a stirrer and cooled in a water-ice bath to 273–278 K. Ethyl dichlorophosphate (0.05 mol) was dripped slowly into the reactor. After complete reagent dripping reaction mixture was stirred at 278–283 K for 2 h and 393 K for 6 h. Then the mixture was filtered and the solvent was evaporated under vacuum. Dipolyoxyethylene ethyl phosphate triphenylmethyl ether (DEP-Tr) was dissolved in 150 mL methanol. *p*-Toluenesulfonic acid was added in a catalytic amount into a reactor. The mixture was stirred at 298 K for 2 h. Then 150 mL water was added into a reactor. After 4 h of stirring at 298 K, the mixture was filtered. Dipolyethylene glycol ethyl phosphate was dried under vacuum to a constant weight. The yield of DEP-4 is 98.1 %.

N-derivatives of L-glutamic acid (GluSt, GluL) and ***pseudo-poly(amino acid)s (PPAA)*** were synthesized using the procedure described by Varvarenko *et al.*[5]

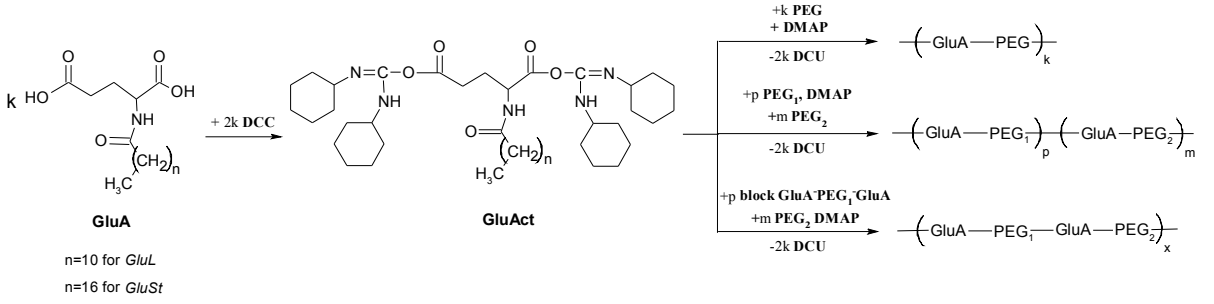
Phosphorus-containing polyesters (PPE) were synthesized with the developed method. *N*-derivatives of L-glutamic acid (GluA) (12.5 mmol), phosphorus-containing diol – dipoly(ethylene glycol) ethyl phosphate (DEP)(11.3 mmol) and dichloromethane were loaded into a reactor. A solution of DCC (25.4 mmol) and catalyst – DMAP (1.6 mmol) were dripped into the reaction mixture at the temperature of 280 K. Then the reaction mixture was maintained at 288 K for 3 h and at 398 K for 3 h. Finally, a side product of the reaction dicyclohexylurea (DCU) was filtered off and the reaction mixture was evaporated. The polymer was purified from unreacted monomers, activator, and catalyst by precipitation in acetone from hexane. The product was dried under vacuum to a constant weight.

3. Results and Discussion

The Steglich reaction is one of few effective and convenient methods for the synthesis of amino acid esters. In general, the formation of an ester bond occurs due to

the nucleophilic attack of the alcohol hydroxyl group on the activated carboxyl group of the amino acid. Carboxyl activation occurs by interaction with *N*,*N*′-dicyclohexylcarbodiimide (DCC) according to the Scheme 1. A prerequisite for a successful synthesis is the use of *N*-derivatives of amino acids, because the free amino group is a stronger nucleophile and will form a peptide bond. A convenient means of controlling the depth of polycondensation is the amount of isolated dicyclohexylurea (DCU) – a side product of the reaction, insoluble in most organic solvents.

We investigated this reaction in a system of *N*-acylated derivatives of glutamic acid (*N*-stearoyl- (GluSt) and *N*-lauryl-L-glutamic acid (GluL) and polyethylene glycols (PEG) or polypropylene glycols (PPG) of different molecular weight. Several methods for the synthesis of various pseudo-poly(amino acid)s (PPAA) based on the Steglich reaction have been developed.



Scheme 1. Polycondensation of *N*-substituted glutamic acid with PEG/PPG diols

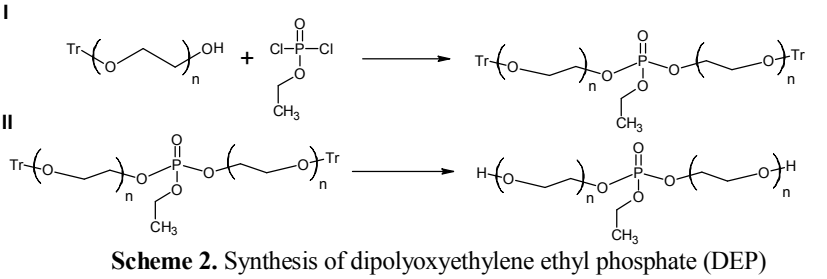
First of all, it is the synthesis of alternative PPAA based on *N*-substituted glutamic acid and diol. Modification of the basic technique involves the simultaneous loading of two different diols. This synthetic approach allows simultaneous using diols of different nature (PEG or PPG) and different molecular weights. For a number of obtained copolymers, the equivalent entry of PEG and PPG chains into the copolymer structure was confirmed.

Also, a method for the block copolymers synthesis by the Steglich reaction has been developed. Reactive blocks with terminal carboxyl groups of general structure GluA-PEG-GluA[36] were used for further polycondensation with a diol differing from that present in the block structure.

Thus, synthetic approaches for a number of PPAA based on *N*-derivatives of glutamic acid and PEG/PPG diols have been developed. These techniques allow regulating the structure and composition of the final copolyester by introducing blocks and monomers of different nature and molecular weight. This, in turn, is an effective way to regulate the hydrophilic-lipophilic balance, and hence the colloidal properties of the obtained polyesters. Thereby, the developed method allows obtaining polyesters capable of forming self-stabilized nanosized dispersions in aqueous and physiological solutions. This fact is crucial for the synthesis of promising polymer drug delivery systems.

As was shown above, a developed synthetic approach to pseudo-poly(amino acid)s of polyester type allows using diols of different nature. Therefore, it seems appropriate to functionalize this class of molecules by introducing a phosphate group into the structure of the diol. For this purpose, polyoxyethylene glycols with ethyl phosphate group were previously synthesized.

The synthesis of dipolyoxyethylene ethyl phosphate (DEP) was carried out in two stages. At the first stage, the dipolyoxyethylene ethyl phosphate triphenylmethyl ether (DEP-Tr) was obtained via a reaction between ethyldichlorophosphate (EDP) and polyoxyethylene triphenylmethyl ether (PEG-Tr) according to Scheme 2. Protection of one of the hydroxyl groups in the polyoxyethylene is necessary to prevent the reaction of both hydroxyl groups, which could lead to polycondensation. IR spectrum of the obtained DEP-Tr is shown in Fig. 1. Table 1 shows the DEP-Tr yield in syntheses with different molecular weights of polyoxyethylene triphenyl ester.



Scheme 2. Synthesis of dipolyoxyethylene ethyl phosphate (DEP)

Triphenylmethyl protection of hydroxyl groups was removed in an acidic environment. The completeness of deprotection was controlled by the amount of isolated triphenylmethanol that precipitates. Also, it was confirmed by IR spectroscopy due to the disappearance of absorption bands from 590 and 680 cm^{-1} in the spectrum. The structure of the obtained product was confirmed by ^{1}H and ^{35}P NMR spectroscopy, and the isolated product was characterized by the number of hydroxyl groups (Table 1).

As Table 1 shows, the experimentally determined number of hydroxyl groups satisfactorily corresponds to the calculated one. The yields of DEP-Tr are expectedly high and do not depend on the PEG molecular mass. In contrast, high yields of the DEP product are observed only for polyoxyethylenes with a molecular mass of 600 Da and above. When using PEG with a lower molecular mass, a part of the obtained product is lost during the purification procedure.

The obtained DEP is used in the synthesis of phosphorus-containing polyesters (PPE) by the Steglich reaction according to Scheme 3. In this study, *N*-stearoyl-glutamic acid was used as it gave high yields of PPAA of the polyester type described above. The ratio between the number of hydroxyl and carboxyl groups 9:10 provides an excess of hydroxyl groups. DCC was used in 10% excess to carboxyl groups.

Table 1. Comparative characteristics of DEP synthesis

Synthesis name	Molecular mass of PEG-Tr, Da	DEP-Tr yield, %	DEP yield, %	The number of hydroxyl groups, g eq(OH groups)/g(DEP) exp.	The number of hydroxyl groups, g eq(OH groups)/g(DEP) calc.
DEP-2	442.28	98.1	61.7	0.00396	0.00417
DEP-4	642.28	95.9	98.1	0.002111	0.00226
DEP-6	842.28	95.0	97.0	0.00156	0.00148
DEP-10	1242.28	97.2	94.0	0.000861	0.00096

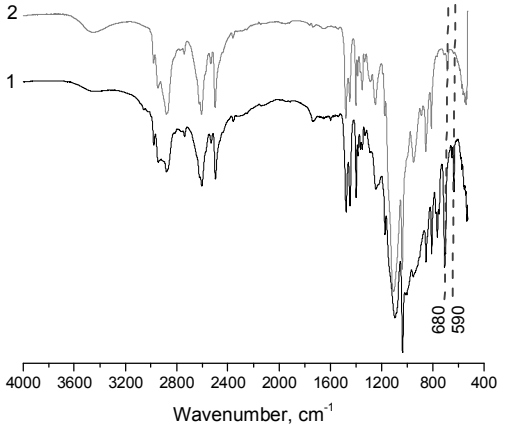
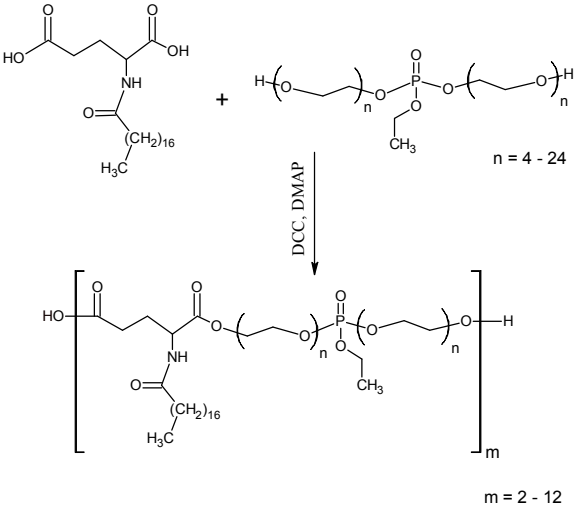


Fig. 1. IR spectra of dipolyoxyethylene ethyl phosphate triphenyl ester (DEP-4-Tr) (1) and dipolyoxyethylene ethyl phosphate (DEP-4) (2)



Scheme 3. Synthesis of PPE with an ethylphosphate group

Table 2. The characteristics of obtained PPE

Sample no	Diol	Reagents ratio			DCU yield, %	Polyester yield, %	CMC, %	Maximum reduction of surface tension, Mn/m
		GluSt	Diol	DCC				
1	DEP-4	10	9	22	97–99.6	95–97	0.033	39
2	DEP-6	10	9	22	97–99.7	96–98	0.028	41
3	PEG-400	9	10	21	98–99.5	97–99	0.0021	45

Table 2 shows the DCU yields, these values allow controlling the completeness of the reaction and the yield of the resulting polyester after its separation from the reaction mixture. In Table 2 samples 1 and 2 are polyphosphoesters obtained using the corresponding modified macromolecules of polyethylene glycol (DEP). Sample 3 is PPAA obtained under similar conditions using unmodified polyethylene glycol. It can be concluded that the introduction of the ethyl phosphate group in the structure of polyethylene glycol does not significantly affect the yield of DCU and polyester. One can assume that this modification does not significantly affect the peculiarities of the Steglich reaction. This assumption is confirmed by the NMR spectra. Fig. 2 shows the NMR spectrum of PPE with the scheme of its signals (Fig. 2a) in comparison with the corresponding spectrum of PPAA obtained with unmodified PEG (Fig. 2b). The assignment of signals and the ratio of their intensities fully confirm the expected structure of polyesters. Fig 2a in comparison with Fig. 2b shows the expected signal complication in the range of 3.8–4.8 ppm due to methylidene groups in the *α*-position to the phosphorus group (G protons) with a corresponding change in the ratio of their intensity and the relative increase in signal intensity. Also, the signal intensity of the ethyl group in the ethyl phosphate group (L) changes, in the range of 3.4–3.8 ppm, and a corresponding change in signal intensity in the range of 1.2–1.4 ppm takes place – methyl protons of the above-mentioned ethyl group (M) are observed on the background of methylidene group protons of the alkyl fragment.

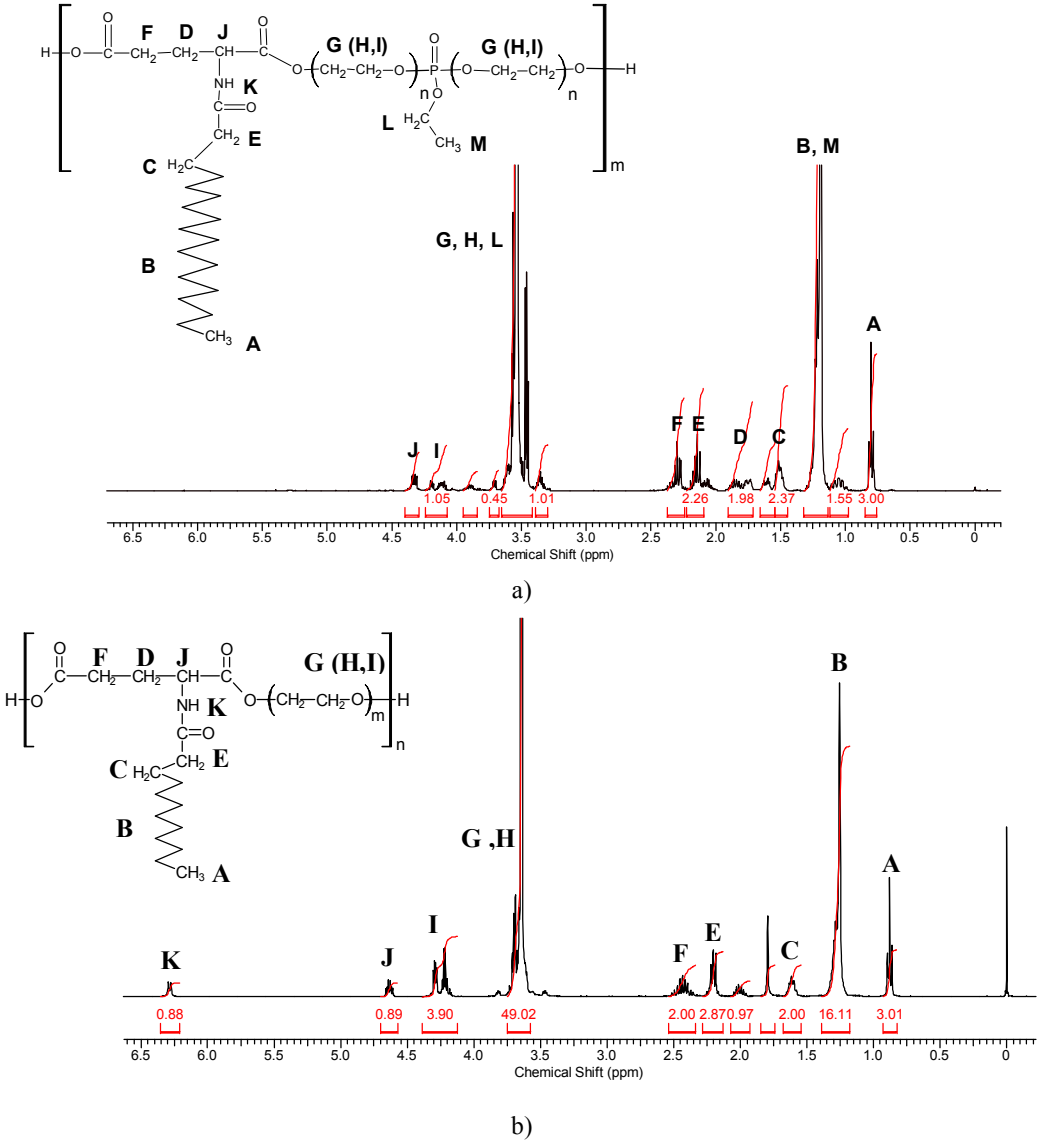


Fig. 2. ^{1}H NMR spectra of PPE based on GluSt and DEP-4 with ethyl phosphate group (a); PPAA based on GluL and PEG-600 (b)

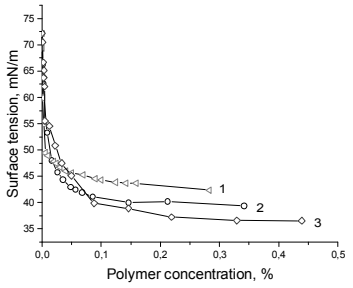


Fig. 3. Surface tension isotherms of PPAA (GluSt/PEG400) (1); PPE (GluSt/DEP-4) with ethyl phosphate group (2) and PPE (GluSt/DEP-4) with phosphate group (after hydrolysis) (3)

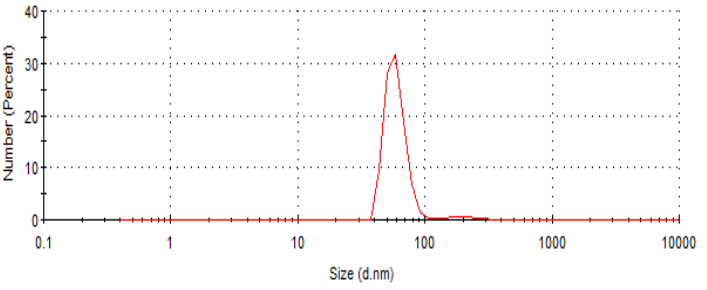


Fig. 4. Size distribution curve of the PPE (GluSt/DEP-4) with a phosphate group (after hydrolysis)

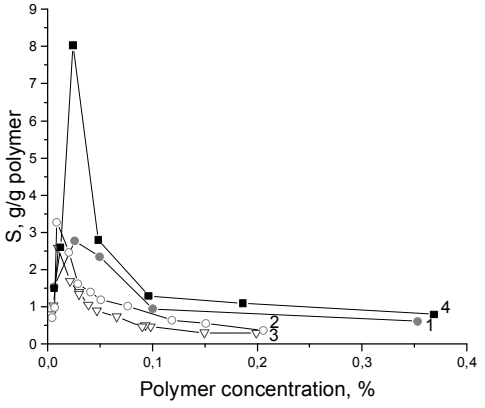


Fig. 5. Solubilization capacity of PPE (GluSt/DEP-4) with ethyl phosphate group (1); PPAA (GluSt/PEG400) (2); PPAA (GluSt/PEG600) (3) and PPE (GluSt/DEP-4) with phosphate group (after hydrolysis) (4)

As was mentioned in the introduction, to be suitable for drug delivery systems, polymers should possess surface-active properties. It is shown, pseudo-poly(amino acid)s of polyester type obtained based on N-stearoyl glutamic acid and polyethylene glycols have these properties. Moreover, studies of the obtained PPE revealed that the introduction of ethylphosphate group into the polyoxyethylene fragment to some extent affects surface-active properties, but PPEs are still surface-active. Fig. 3 shows the surface tension curves of PPE obtained using DEP of different molecular weights in comparison with PPAA of the similar structure obtained using unmodified PEG.

These curves confirm that the synthesized PPE have similar surfactant properties; the values of this activity given in Table 2 show that PPEs are even more surface-active compared to PPAA with a similar structure. Accordingly, PPEs have the ability to form self-stabilized dispersions with a nanometric dispersed phase in aqueous media. This confirms the particle size distribution of the dispersed phase obtained by the dynamic light scattering method (Fig. 4).

Fig. 5 shows the dependence of the solubilization capacity of the obtained PPE in comparison with the corresponding analogs of PPAA. It should be noted that with approximately the same solubilization capacity of phosphorus-containing polyesters PPEs (curve 1) in comparison with non-phosphorus-containing analogs PPAAs, PPEs have a wider range of concentrations where high solubilization capacity is maintained (*curves* 2 and 3). There is a rapid increase in solubilization capacity (curve 4) after hydrolysis of the ethyl phosphate group to the phosphate group under mild conditions. Thus, one can argue that the introduction of the phosphate group into the structure of the polyoxyethylene fragment leads to an increase in the absorption and solubilization properties of aqueous dispersions.

The cytotoxicity of the obtained PPE was studied using their effect on the survival of bull sperm and the activity of oxidative enzymes (Table 3). The introduction of polyesters into the nutrient medium in doses of 100 μg/ml does not reduce cell survival. It indicates the absence of cytotoxic effect of the resulting polyester. This conclusion is confirmed by additional studies – these doses of polyester also do not reduce the activity of oxidative processes.

Table 3. Sperm survival and the activity of their oxidative enzymes under the action of PPE (GluSt/DEP-4) with phosphate group (after hydrolysis) (n = 8, M±m)

Dosage, μg / ml	Survival, h	Enzymes activity, units	
		Succinate dehydrogenase (SDH)	Cytochrome oxidase (CHO)
100	54.0±7.04	11.8±2.69	18.3±2.55
50	51.0±5.09	14.2±2.48	17.5±1.95
10	60.0±8.49	15.8±3.98	14.2±2.74
Correlation, η	0.148	0.256	0.301
Control	54.0±9.25	17.5±3.49	14.2±2.48

4. Conclusions

This report presents the experimental material on a convenient synthetic approach to a new class of polyester by irreversible polycondensation of N-alkyl derivatives of dicarboxylic α-amino acids with polyoxyethylene glycols containing phosphates in their structures. Synthetically convenient polycondensation techniques can be constructed by the Steglich reaction mechanism. Obtained poly(phosphoester)s form self-stabilized aqueous dispersions with nanometric dispersed phase. Studies show that aqueous dispersions of the obtained polymers are able to solubilize significant amounts of water-insoluble organic compounds and are non-toxic. Based on the described experimental data, it can be concluded that the developed method of polyphosphoesters and a set of properties make them promising for use as polymer disperse delivery systems for therapeutic agents.

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СИНТЕЗ ТА ВЛАСТИВОСТІ ФОСФОРОВМІСНИХ ПСЕВДОПОЛІАМІНОКИСЛОТ ПОЛІЕСТЕРНОГО ТИПУ НА ОСНОВІ N-ПОХІДНИХ ГЛУТАМІНОВОЇ КИСЛОТИ

Анотація. *Поліфосфоестери (ПФЕ) – це клас полімерів, що володіють високою хімічною функціональністю та здатністю до біологічного розкладання. Синтезовані нові поліфосфоестери на основі глутамінової кислоти за реакцією Стегліха. Розроблений синтетичний підхід дозволяє контролювати склад і структуру ПФЕ, а отже, їх фізичні та колоїдні властивості. Дослідження солюбілізації та цитотоксичності in vitro довели потенціал застосування ПФЕ для доставки лікарських препаратів.*

Ключові слова: *поліфосфоестери, псевдополіамінокислоти, глутамінова кислота, поліетиленгліколь, реакція Стегліха, доставка ліків.*