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Polymeric Chemistry

A Novel Biodegradable Surfactant with Dual Function on the Basis of Amino Acid Based Epoxy-Poly(ester amide)

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Biodegradable surfactants represent a groundbreaking innovation in the field of medicine. They offer significant advantages over non-degradable ones including enhancing a drug solubility, stability and bioavailability. Furthermore, they can be used for constructing biodegradable drug delivery carriers such as micro- and nanoparticles (NPs). The main goal of this research is the synthesis and study of a novel biodegradable water soluble polymer having the dual function – the function of a surfactant, on the one hand and the function of a PEGylating agent, on the other hand. The new biodegradable surfactant/PEGylating agent PEG-PEA was synthesized using a two-step procedure: the solution active polycondensation of bis-nucleophilic monomer (L6) with a mixture of bis-electrophilic monomers (8-NS/NtES) at the first step, leading to the formation of the precursor – epoxy-copoly(ester amide) $[8L6]_{0.5}$-$[t$ES-L6$]_{0.5}$, followed by a further polymer-analogous reaction of $[8L6]_{0.5}$-$[t$ES-L6$]_{0.5}$ with the methoxy-PEG-amine. Contrary to the initial precursor – epoxy-copoly(ester amide) $[8L6]_{0.5}$-$[t$ES-L6$]_{0.5}$, the obtained PEG-PEA is water-soluble and can form micelles similar to other traditional surfactants. Moreover, PEG-PEA has the ability to stabilize the pseudo-protein NPs prepared from the poly(esteramide) 8L6 using the nanoprecipitation method. The fabricated NPs had the average diameter and polydispersity index of 143.5 nm and 0.177 nm, respectively, which are suitable for practical/biomedical application of NPs as drug delivery vehicles. The novel biodegradable surfactant/PEGylating agent PEG-PEA was successfully synthesized and characterized. Biodegradable stable NPs on the basis of pseudoprotein 8L6 were prepared by nanoprecipitation method using the synthesized PEG-PEA. At this the obtained PEG-PEA served as both a new biodegradable surfactant and a PEGylating agent, making it promising for biomedical application.

biodegradable surfactant, PEGylating agent, micelles, pseudo-protein, nanoparticles

Biodegradable surfactants have emerged as a transformative innovation in the field of medicine [1]. These surfactants, designed to naturally degrade over time, address two crucial concerns in healthcare: patient safety and environmental impact. Traditional surfactants, which are often non-biodegradable, can pose risks to patients and contribute to ecological harm [2, 3]. In the realm of

pharmaceuticals, biodegradable surfactants offer significant advantages. They enhance drug solubility, stability, and bioavailability while minimizing the potential for long-term toxicity [3]. Furthermore, biodegradable surfactants are highly promising for constructing biodegradable drug delivery carriers such as micro- and nanoparticles (NPs). The latter are becoming more and more popular nowadays since the biodegradable nanocarriers can enzymatically degrade in the physiological environment and safely to be cleared from the body.

When biodegradable NPs are designed for the use as drug delivery vehicles, one important issue to consider is the protection of NPs from the attack of the organism's immune system. When nanocarriers are in the physiological environment, they rapidly adsorb biomolecules such as proteins and lipids on their surface forming a protein "corona" [4, 5]. The formation of protein corona around NPs changes their size, surface chemistry, solubility, aggregation and surface charge and, hence the protein corona can influence the biodistribution, cellular uptake, and macrophage capture of NPs [4, 5]. In other words, the therapeutic potentialities of polymeric NPs may be compromised by particle recognition by the macrophages. It is known that NPs functionalized with hydrophilic polymers show more long-lasting circulation and decreased macrophage recognition of many types of NPs. One of the efficient ways to render the NPs surface hydrophilic is their "PEGylation" which represents the process of treating the NPs' surface with polyethylene glycol (PEG). Long chains of PEG form a random cloud around the NP, thereby preventing plasma proteins (opsonins, which enhances phagocytosis) absorption. Therefore, PEGylation of NPs is essentially important for their practical application in medicine.

The main goal of this research was the synthesis and study of novel biodegradable surfactant having dual function – the function of a surfactant, on the one hand and the function of a PEGylating agent, on the other hand. The new biodegradable surfactant/PEGylating agent was synthesized on the basis of the obtained amino acid based epoxy-copoly(ester amide) **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** and mPEG-amine-2000. The micelle formation by the PEG-PEA and its influence on the NPs' fabrication and stability were studied.

Experimental

Materials. Fumaric acid, phosphorus pentachloride, *p*-nitrophenol, L-leucine, p-toluene-sulfonic acid monohydrate (TosOH.H2O), and 1,6-hexanediol were purchased from Sigma-Aldrich. Methoxy-PEG-amine with average molecular weight 2,000 Da (mPEG-amine-2000) was purchased from Laysan Bio. N,N-dimethylacetamide (DMA) and Dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich. All the chemicals were used as received. The dialysis bag (MWCO 25 kDa) was purchased from Spectrum Laboratories, Inc. (Rancho Dominguez, CA, USA). The pseudo-protein 8L6 selected as a basic polymer for constructing NPs, was originally synthesized *via* the interfacial polycondensation as reported previously [6, 7].

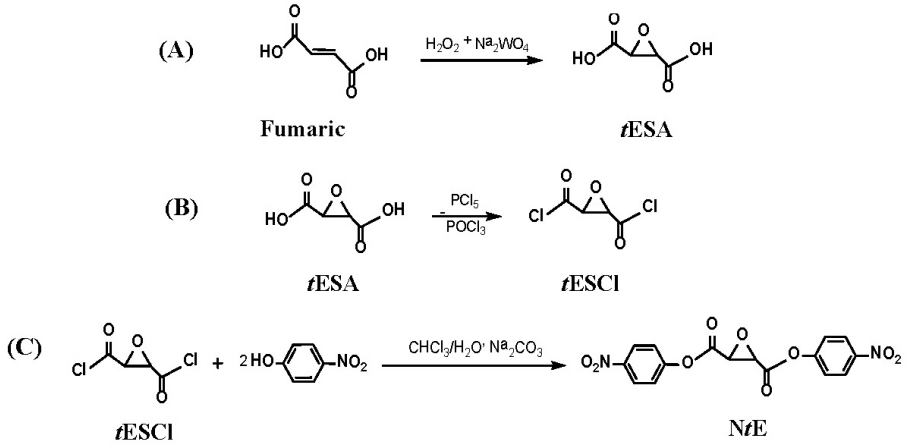
Synthesis of monomers. The synthesis of a key bis-electrophilic monomer – di-*p*-nitrophenyl ester of trans-epoxy succinic acid (labelled as **N*t*ES**) was performed using the three-step procedure (Scheme 1) as it was reported previously [8]; all the obtained data listed below coincided well with the reported ones.

Step 1. The synthesis of trans-epoxy-succinic acid. At the first step, the *trans*-epoxy succinic acids (***t*ESA**) were synthesized by the epoxidation of fumaric acid according to Scheme 1 (A). Epoxidation of fumaric acid was done using hydrogen peroxide and sodium tungstate as a catalyst. The obtained ***t*ESA** was recrystallized from diethyl ether/petroleum ether (50/50) mixture. Yield: 47.0%. m.p. 211-212.

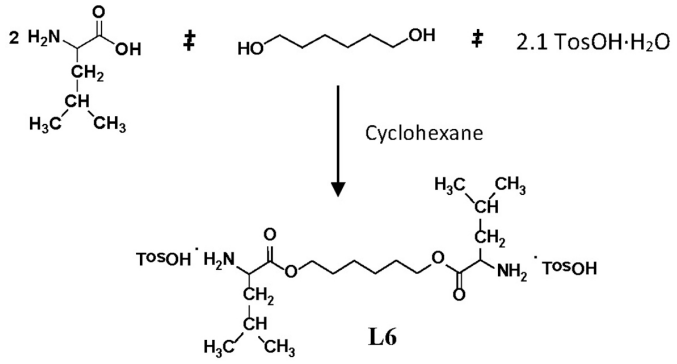
Step 2. The synthesis of trans-epoxy-succinyl dichloride. The synthesis of dichloroanhydride - trans-epoxy-succinyl dichloride (***t*ESCl**) was carried out by interaction of the obtained ***t*ESA** with phosphorus pentachloride (Scheme 1 "B"). The obtained ***t*ESCl** was recrystallized from petroleum ether. Yield: 78%. m. p. 51-53 °C.

Step 3. The synthesis of activated diester - di-p-nitrophenyl-trans-epoxy succinate. The activated diester - di-*p*-nitrophenyl-*trans*-epoxy succinate (**N*t*ES**) was synthesized according to Scheme 1 (C). **N*t*ES** was synthesized *via* Schotten-Baumann procedure: to a chilled (5° C) and vigorously stirred solution of *p*-nitrophenol (27.8 g, 0.2 mol) and sodium carbonate (21.2 g, 0.2 mol) in 500 mL of water, a solution of dichloride ***t*ESCl** (16.9 g 0.1 mol) in chloroform (130 mL) was added at once and stirred for 0.5 h, during which solid precipitate was formed. The solid product was then filtered off, washed thoroughly with ice water, dried in a vacuum at 60°C and recrystallized from acetone. Yield: 76%, m. p. 183-184°C.

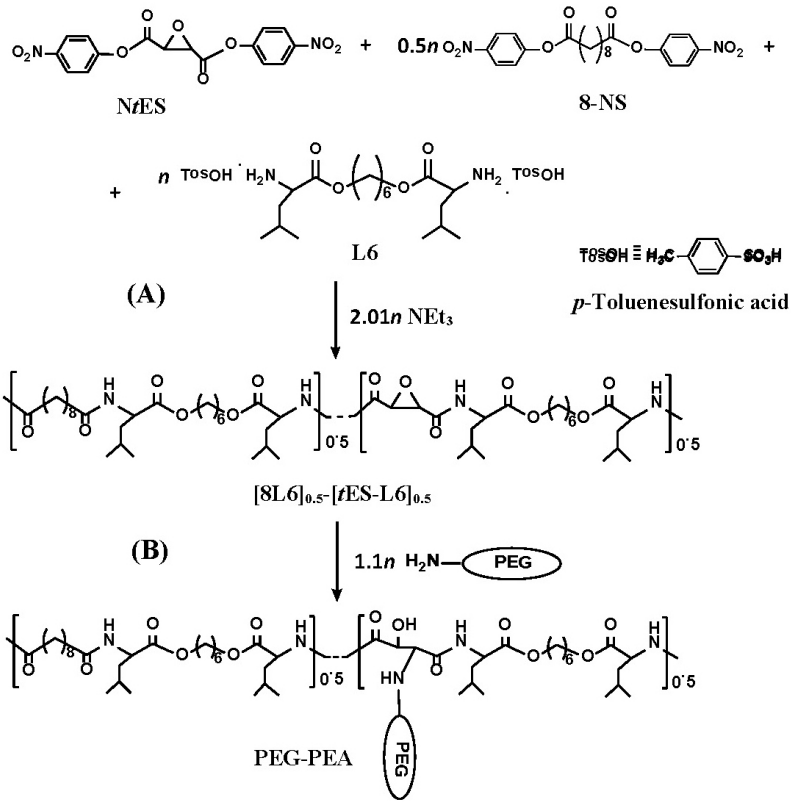
Synthesis of a key bis-nucleophilic monomer, L6. The synthesis of a key bis-nucleophilic monomer – di-*p*-toluenesulfonic acid salts of bis-(L-leucine)-1,6-hexylene diester (labeled as **L6**) was performed following the Scheme 2 by previously reported procedure [7, 9]. Briefly, **L6** monomer was obtained by direct condensation of L-lysine (2 moles) with 1,6-hexanediol (1 mole) in refluxed cyclohexane in the presence of *p*-tuluenesulfonic acid monohydrate (**TosOH·H$_2$O**, 2.1 mole) which serves as both α-amino groups protector and condensation reaction catalyst (that is why it is used in a small excess – 2.1 moles instead of 2.0 mole). Yield of **L6**: 90%, m. p. 190-192°C.



Scheme 1. Three-step synthesis of key activated diester **N*t*ES**: (**A**) - synthesis of epoxy-diacid ***t*ESA**, (**B**) - synthesis of epoxy-dichloride ***t*ESCl**, and (**C**) - synthesis of activated epoxy-diester **N*t*ES**.



Scheme 2. Synthesis of **L6** monomer by direct condensation of leucine (**L**) with 1,6-hexanediol.



Scheme 3. Two step synthesis of the goal biodegradable surfactant/PEGylating agent **PEG-PEA**.

Synthesis of a biodegradable surfactant/ PEGylating agent. The goal biodegradable surfactant/PEGylating agent (labelled ad **PEG-PEA)** was synthesized according to two-step procedure depicted in Scheme 3. At the first step the intermediate epoxy-copoly(erster amide) **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** was synthesized by solution active polycondensation in DMA of bis-nucleophilic monomer **L6** with a mixture of bis-electrophilic monomers **8-NS** / **N*t*ES** at a mole ratio 1.0/0.5/0.5, accordingly, at r.t. for 18 h (Scheme 3 **A**). The resulting copolymer **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** was precipitated in water, filtered off, washed with distilled water for several times and dried under reduced pressure at 40°C for 96 h over water absorbent (P_2O_5).

At the second stage (Scheme 3, **B**) the intermediate epoxy-copoly(ester amide) **8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** was interacted with mPEG-amine-2,000 resulting in the goal hydrophilic copolymer **PEG-PEA**. For this, 200 mg (0.42 mmol) of **[8L6]$_{0,5}$-[*t*ES-L6]$_{0,5}$** and 840 mg (0.42 mmol) of mPEG-amine-2000 was dissolved in 2 mL DMA and stirred for 24 h at 60°C. After completing the reaction, the solution was poured in 50 mL hexane and the precipitated product was separated and dried under reduced pressure at 50°C for 48 h. The structures of initial co-polymer **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** and the obtained bifunctional **PEG-PEA** were confirmed by FTIR and NMR spectroscopy.

[8L6]$_{0.5}$-[tES-L6]$_{0.5}$. ^{1}H NMR (400 MHz, DMSO-d6, δ): 0.9 (24H, s, CH(C<u>H</u>$_3$)$_2$), 1.1-1.84 (40H, O-CH$_2$-(C<u>H</u>$_2$)$_n$-, C<u>H</u>(CH$_3$)$_2$ and –CH-C<u>H</u>$_2$-CH-), 2.05 (4H, t, -CO-C<u>H</u>$_2$), 3.60 (2H, s, C<u>H</u>-O epoxy), 4.04 (8H, -O-C<u>H</u>$_2$-), 4.27 (4H, -NH-C<u>H</u>-CO), 8.1 (2H, d, CH$_2$-CO-N<u>H</u>-CH-), 8.82 (2H, d, O-CO-N<u>H</u>-CH- and O-CH-CO-N<u>H</u>-CH-). ^{13}C NMR (100 MHz, DMSO-d6, δ): 23.0, 24.6, 25.2, 28.3, 29.03, 46.1, 50.8, 52.7, 64.7, 166.1, 172.0, 172.5, 172.8.

PEG-PEA. ^{1}H NMR (400 MHz, DMSO-d6, δ): 0.88 (24H, s, CH(C<u>H</u>$_3$)$_2$), 1.12-1.84 (40H, O-CH$_2$-(C<u>H</u>$_2$)$_n$-, C<u>H</u>(CH$_3$)$_2$ and –CH-C<u>H</u>$_2$-CH-), 2.09 (4H,

t, -CO-C<u>H</u>$_2$), 3.51 (PEG -O-CH$_2$-CH$_2$-O-), 3.60 (1H, C(OH)-C<u>H</u>), 4.04 (8H, -O-C<u>H</u>$_2$-), 4.24 (4H, -NH-C<u>H</u>-CO), 4.62 (1H, C(OH)-C<u>H</u>), 7.90-8.35 (5H, N<u>H</u>). The obtained **PEG-PEA** has the following molecular weight characteristics: Mw = 36,800, Mn = 28,400, Đ = 2.58.

Micelle formation. The micelle formation ability of the obtained **PEG-PEA** was studied by dissolving it in water and examining micelle parameters by DLS technique. Briefly, 10 mg of **PEG-PEA** was dissolved in 2 mL of deionized water and analyzed by DLS using the Zetasizer machine. For comparison, the standard surfactants were also analyzed at the same conditions. The results of micelle study are shown in Table 1.

Preparation of pseudo-protein NPs using PEG-PEA as a surfactant/PEGylating agent. The synthesized surfactant of dual function **PEG-PEA** was checked for its ability to stabilize NPs. For this reason, we prepared the pseudo-protein NPs using the **PEG-PEA** as a surfactant. NPs were prepared by nanoprecipitation method on the basis of L-leucine based pseudo-protein **8L6** under the optimal conditions previously established for pseudo-proteins [10, 11]. In brief, 30 mg of **8L6** was dissolved in 1.0 mL of DMSO and the obtained solution (organic phase) was added dropwise (dropping rate 12 drops/min) to 10 mL of water containing 50 mg of **PEG-PEA** at the stirring rate of 700 rpm. The suspension of NPs, obtained after the complete addition of the organic phase, were additionally stirred for 15 min and then dialyzed against distilled water for 48 h using the dialysis bag with MWCO 25 kDa. The obtained PEGylated **8L6** NPs (labelled as **PEG-PEA-8L6 NPs**) were kept at low temperature (4°C) for stability study. Separately, for comparison, **8L6** NPs were also prepared without using any surfactants under the same conditions used for fabricating **PEG-PEA-8L6 NPs**.

Measurements and Techniques. The synthesized monomers and polymers were characterized by Fourier-transform infrared spectroscopy (FT-IR), 1H & 13C nuclear magnetic resonance (NMR) spectroscopy and gel permeation chromatography (GPC). The 1H & 13C NMR spectra were recorded at 300 K on a JEOL ECP 500 NMR spectrometer operating at 500 MHz. The CDCl3 (for monomers) and DMSO-d6 (for polymer) were used as solvents and internal standards. The weight-average (Mw), number-average (Mn) molecular weights, and molecular weight distribution (Dispersity, Đ) of the polymers were determined on a GPC machine (Waters Associates, Inc., Milford, United States). Columns were calibrated with poly(methyl methacrylate) standards. **PEG-PEA** micelles and the obtained NPs were characterized by size (average diameter, AD), particle size distribution (polydispersity index, PDI), and zeta-potential (ZP), which were determined by dynamic light scattering (DLS) technique using the analyzer machine Zetasizer Nano ZS (Malvern Instruments, Malvern, UK).

Results and Discussion

Monomer synthesis. The synthesis of a key bis-electrophilic monomer – N***t***ES** was performed using the three-step procedure: (i) The synthesis of trans-epoxy-succinic acid – ***t*ESA**, (ii) The synthesis of trans-epoxy-succinyl dichloride – ***t*ESCl**, and (iii) The synthesis of activated diester – trans-epoxy-succinyl dichloride – N***t*ES** (Scheme 1). The goal monomer N***t*ES** was obtained in good yield (71%). The FT-IR and NMR studies proved the presence of all key functional moieties of the synthesized monomer. A key bis-nucleophilic monomer – di-*p*-toluenesulfonic acid salts of bis-(L-leucine)-1,6-hexylene diester – **L6** was synthesized by direct condensation of L-lysine with 1,6-hexanediol in refluxed cyclohexane in the presence of p-tuluenesulfonic acid monohydrate (TosOH·H$_2$O). The goal monomer **L6** was obtained in good yield (90%) and the structure was proved by FT-IR and NMR studies.

Synthesis and characterization of PEG-PEA. The novel biodegradable surfactant/ PEGylating agent **PEG-PEA** was synthesized according to two-step procedure (Scheme 3). At the first step the intermediate epoxy-copoly(ester amide) **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** was synthesized by solution active poly-condensation in DMA of bis-nucleophilic monomer **L6** with a mixture of bis-electrophilic monomers **8-NS** / **N*t*ES** at a mole ratio 1.0/0.5/0.5, accordingly. At the second stage, **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** was interacted with mPEG-amine-2,000 resulting in the goal hydrophilic copolymer **PEG-PEA**. Structures of the initial co-polymer **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** and the goal **PEG-PEA** were confirmed by FTIR and NMR spectroscopy. Together with ^{1}H NMR spectroscopy, successful modification of epoxy group with PEG-amine was proved by complete disappearance of the epoxide band at 895 and 3062 cm^{-1} combined with appearance of the broad band at ≈ 3500 cm^{-1} characteristic for OH group. Furthermore, it should be underlined that the initial precursor of **PEG-PEA** – co-polymer **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** is water insoluble whereas the goal **PEG-PEA** dissolves in water. Bifuctional **PEG-PEA** revealed micelle forming parameters very similar to those for traditional surfactants (Table 1). As it is shown in Table 1, AD and ZP of **PEG-PEA** micelles were 18.3 nm and -15.6 mV, respectively which are similar to those for standard surfactants.

Table 1. Characteristics of micelles of standard surfactants and new biodegradable surfactant PEG-PEA

Surfactant	AD (nm)±SD	PDI ±SD	ZP (mV)±SD
Tween 20	11.3 ± 0.3	0.244 ± 0.021	-9.5 ± 0.8
Brij010	19.2 ± 0.3	0.174 ± 0.016	-11.1 ± 0.5
Kolliphor P188	9.2 ± 0.4	0.273 ± 0.025	-13.9 ± 1.5
Triton X-100	10.4 ± 0.7	0.254 ± 0.021	-6.5 ± 0.5
Mowiol 4-88	20.0 ± 1.3	0.263 ± 0.023	-13.0 ± 1.9
PEG-PEA	18.3 ± 1.1	0.185 ± 0.020	-15.6 ± 1.5

Note: SD – standard deviation of three parallel measurements.

Preparation and characterization of NPs using the PEG-PEA. The synthesized bifunctional surfactant **PEG-PEA** was checked for its ability to stabilize polymeric NPs. For this reason, NPs based on the pseudo-protein 8L6 were prepared using the **PEG-PEA** as both a surfactant and a PEGylating agent. The obtained NPs were labelled as **PEG-PEA-8L6 NPs**. For generating **PEG-PEA-8L6 NPs**, we used the nanoprecipitation method [10, 11]. It should be noted that the synthesized bifuctional **PEG-PEA** has very similar polymeric backbone with the backbones of the polymers 8L6 used as a matrix for NPs. These structural similarities between the **8L6** and **PEG-PEA** provide a high affinity of macro-chains that, in turn, provide a firm anchoring of the PEGylating agent (**PEG-PEA**) to the NPs surface. It is also important to note that the **PEG-PEA** plays a dual role when preparing NPs – it acts as a surfactant indispensable for generating NPs by nano-precipitation method, and their simultaneous PEGylation, i.e. coating the NPs with PEG-cloud. As it is known, PEG-cloud prevents the NPs from opsonins' adsorption, thus protecting them from the inactivation by immune system.

PEG-PEA-8L6 NPs were successfully prepared using the novel biodegradable surfactant **PEG-PEA**. The DLS analysis showed that AD and ZP of the obtained **PEG-PEA-8L6 NPs** were 143.5 nm and -21.4 mV, respectively (Table 2). As regards PDI, the **PEG-PEA-8L6 NPs** were characterized by a narrow particle size distribution (PDI ≤ 0.5). It should be underlined that PDI values of 0.2 and below are desired and acceptable for polymer-based NPs [12, 13]. Hence, in respect of a size distribution, the obtained **PEG-PEA-8L6 NPs** are suitable for practical (medicinal) application [14]. Moreover, the stability study of **PEG-PEA-8L6 NPs** revealed their high sustainability upon storage refrigerated (Table 3) – no substantial change of AD and PDI or aggregation was observed during six months of storage. Compared to **PEG-PEA-8L6 NPs**, those prepared without surfactants were

less stable and partially aggregated during preparation (Table 2). It has to be noted that the developed synthetic strategy can be applied to hetero-bifunctional amino-PEGs for constructing NPs having functionalized PEG-clouds suitable for farther modifications of drugs' nanovehicles.

Table 2. Comparison of the freshly prepared PEG-PEA-8L6 NPs with the 8L6 NPs prepared without any surfactants

Sample	AD (nm) ± SD	PDI ± SD	ZP (mV) ± SD
PEG-PEA-8L6 NPs	143.5 ± 1.4	0.177 ± 0.015	-21.4 ± 1.8
8L6 NPs without any surfactant §	156.8 ± 2.4§	0.282 ± 0.031§	- 16.3 ± 1.3§

Note: § - partially aggregated sample; SD – standard deviation of three parallel measurements.

Table 3. Stability of the prepared PEG-PEA-8L6 NPs upon storage at 4°C

Measurement time			
Freshly prepared	**After 1 month**	**After 3 months**	**After 6 months**
AD (nm) ± SD [PDI ± SD]			
143.5 ± 1.4 [0.177 ± 0.015]	**144.2 ± 1.1** [0.173 ± 0.016]	**143.2 ± 1.8** [0.181 ± 0.012]	**146.3 ± 1.5** [0.184 ± 0.017]

Note: SD – standard deviation of three parallel measurements. The average diameters of the NPs are given in bold.

Conclusion

The novel biodegradable bifunctional surfactant **PEG-PEA** was successfully synthesized using a two-step procedure. This process comprises the solution active polycondensation of the bis-nucleophilic monomer **L6** with a mixture of bis-electrophilic monomers **8-NS/NtES**, leading to the formation of the initial epoxy-copolymer **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$**, followed by a further polymer-analogous reaction of **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$** with mPEG-amine-2000. Compared to the initial precursor **[8L6]$_{0.5}$-[*t*ES-L6]$_{0.5}$**, the obtained **PEG-PEA** is water-soluble and can form micelles similar to other traditional surfactants. Moreover, the synthesized **PEG-PEA** has the ability to stabilize pseudo-protein NPs. Thus, **PEG-PEA-8L6 NPs** were successfully prepared by nanoprecipitation method using **PEG-PEA** as a biodegradable surfactant. The fabricated **PEG-PEA-8L6 NPs** had an AD and PDI of 143.5 nm and 0.177, respectively, which are suitable for practical application of NPs as an effective drugs' delivery vehicles. The synthesized **PEG-PEA** serves as both a new biodegradable surfactant and a PEGylating agent providing the protective PEG-cloud around NPs.

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პოლიმერული ქიმია

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ბიოდეგრადირებადი ზედაპირულად აქტიური ნაერთები (ზან) წარმოადგენს სიახლეს მედიცინის სფეროში. მათ გააჩნიათ მნიშვნელოვანი უპირატესობები არადეგრადირებად ზან-ებთან შედარებით. ამ უპირატესობებს შორის აღსანიშნავია წამლის ხსნადობის, სტაბილურობისა და ბიოშეღწევადობის გაუმჯობესების უნარიანობა. გარდა ამისა, ბიოდეგრადირებადი ზან-ები შეიძლება გამოყენებულ იქნეს ბიოდეგრადირებადი წამლის მიმწოდებელი სისტემების შესაქმნელად, როგორიცაა მიკრო- და ნანონაწილაკები (ნნ). წინამდებარე ნაშრომის მთავარ მიზანს წარმოადგენს ახალი ბიოდეგრადირებადი ბიფუნქციური ზან-ის სინთეზი და კვლევა. აღნიშნულ ნაერთს გააჩნია ორმაგი ფუნქცია, ერთი მხრივ, ის ასრულებს ზან-ის ფუნქციას და, მეორე მხრივ, ის მოქმედებს როგორც მაპეგილირებელი აგენტი. ახალი ბიოდეგრადირებადი ზან-ის/მაპეგილირებელი აგენტი PEG-PEA სინთეზირდა ორსაფეხურიანი პროცედურის თანახმად. პირველ საფეხურზე მოვახდინეთ ბის-ნუკლეოფილური მონომერის (L6) აქტიური პოლიკონდენსაცია ბის-ელექტროფილური მონომერების ნარევთან (8-NS/NtES), რის შედეგადაც მივიღეთ საწყისი ეპოქსი-თანაპოლიმერი [8L6]0.5-[tES-L6]0.5. სინთეზის მეორე ეტაპზე განვახორციელეთ მიღებული ეპოქსი-თანაპოლიმერის [8L6]0.5-[tES-L6]0.5 ურთიერთქმედება მეთოქსი-PEG-ამინთან და მივიღეთ საბოლოო პროდუქტი PEG-PEA. საწყის წინამორბედთან (თანაპოლიმერი [8L6]0.5-[tES-L6]0.5) შედარებით, მიღებული ბიოდეგრადირებადი PEG-PEA წყალში ხსნადია და სხვა ტრადიციული ზან-ების მსგავსად წყლის არეში წარმოქმნის მიცელებს. უფრო მეტიც, PEG-PEA-ს გააჩნია ნანოპრეციპიტაციის მეთოდით მიღებული პოლიმერული ნნ-ების სტაბილიზაციის უნარი. მიღებული ნნ-ების საშუალო დიამეტრი და პოლიდისპერსიის ინდექსი შეადგენდა 143,5 ნმ და 0,177 ნმ, შესაბამისად, რაც მისაღებია ნნ-ების ბიოსამედიცინო გამოყენებისთვის. სინთეზირებულია ახალი ბიოდეგრადირებადი ზან/მაპეგილირებელი აგენტი PEG-PEA და შესწავლილია მისი თვისებები. PEG-PEA-ს, როგორც ზან-ის გამოყენებით, მიღებულია ფსევდოპროტეინული ნნ-ები ე.წ. ნანოპრეციპიტაციის მეთოდით. სინთეზირებული ახალი PEG-PEA ბიფუნქციურია და ასრულებს როგორც ზან-ის, ასევე მაპეგილირებელი აგენტის ფუნქციას, რაც მას პერსპექტიულს ხდის ბიოსამედიცინო გამოყენებისათვის.

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