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PECULIARITIES OF THE MOLECULAR MASS DISTRIBUTION OF FLUORESCEIN-CONTAINING COPOLYESTERS SYNTHESIZED BY THE STEGLICH REACTION

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Abstract

The properties of polymers are substantially determined by their molecular mass and molecular mass distribution. At the same time, the average molecular mass of the polymers does not characterize them complete enough, particularly it does not describe the properties of the polymers of special purpose, which are produced for drug delivery and drug release. In this case the accurate assessment of the properties of polymers is especially needed. The article deals with the research of the composition of fractions and functional homogeneity of new amphiphilic copolyesters. Fluorescein-containing amphiphilic copolyesters of N-acyl derivatives of glutamic acid and polyether diols, which form self-stabilized dispersions in aqueous media can be considered as promising multifunctional polymers and may be used in biomedicine.

The molecular mass fractionation of copolyesters was carried out with the use of dialysis. The obtained polymers and their fractions were analyzed by exclusion chromatography and functional analysis, the surface tension was determined.

A detailed molecular mass distribution of copolyesters was obtained byusing the efficient exclusion chromatography, as well as due to the rather high mass of the monomers. The content of individual fractions, their functionality and colloid-chemical properties were quantitatively compared. It was shown that despite the different molecular mass the individual fractions of a copolyester were homogeneous with identical properties. This allowed us to describe such copolyesters as the good base for the creation of drug delivery systems and nanodiagnostics.

Keywords: molecular mass distribution; copolyesters; fluorescein; Steglich reaction; drug delivery systems.

ОСОБЛИВОСТІ МОЛЕКУЛЯРНО-МАСОВОГО РОЗПОДІЛУ ФЛУОРЕСЦЕЇНВМІСНИХ КОПОЛІЕСТЕРІВ СИНТЕЗОВАНИХ ЗА РЕАКЦІЄЮ СТЕГЛІХА

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Анотація

Властивості полімерів значною мірою визначаються їх молекуляною масою та молекулярно-масовим розподілом. При цьому середня молекулярна маса полімеру, зазвичай характеризує його недостатньо повно, особливо для полімерів спеціального призначення створених для застосування у якості систем доставки та вивільнення лікарських засобів в організмі для яких точна оцінка властивостей є необхідною.

В статті розглядається дослідження фракційного складу та функціональної однорідності нових амфіфільних кополіестерів. Флуоресцеїнвмісні амфіфільні кополіестери N-ацилпохідних глутамінової кислоти та поліетердіолів, утворюючи самостабілізовані дисперсії у водних середовищах, можуть розглядатися як перспективні багатофункційні полімери для використання в біомедицині.

Методом діалізу проведено фракціонування кополіестерів за молекулярною масою. Отримані полімери та їх фракції охарактеризовано методами ексклюзійної хроматографії та функціонального аналізу та визначенням поверхневого натягу. Завдяки використанню ефективної ексклюзійної хроматографії, а також доволі високих молекулярних мас мономерів було отримано детальні молекулярно-масові розподіли кополіестерів і проведена кількісна порівняльна оцінка вмісту окремих фракцій їх функціональності та колоїдно-хімічних властивостей. Показано, що незважаючи на різні значення молекулярної маси окремі фракції у складі кополіестерів є однорідними за складом і тотожними за властивостями. Це дозволяє вважати такі кополіестери придатними як основи для створення систем транспорту ліків та нанодіагностики.

Ключові слова: молекулярно-масовий розподіл; кополіестери; флуоресцеїн; реакція Стегліха; системи доставки ліків.

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ОСОБЕННОСТИ МОЛЕКУЛЯРНО-МАССОВОГО РАСПРЕДЕЛЕНИЯ ФЛУОРЕСЦЕИНСОДЕРЖАЩИХ СОПОЛИЭФИРОВСИНТЕЗИРОВАННЫХ ПО РЕАКЦИИ СТЕГЛИХА

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Аннотация

Свойства полимеров в значительной степени определяются их молекуляной массой и молекулярно-массовым распределением. При этом средняя молекулярная масса полимера, обычно характеризует его недостаточно полно, особенно для полимеров специального назначения использование которых предвидится в системах доставки и высвобождения лекарственных средств в организме для которых точная оценка свойств является необходимым условием. В статье рассматривается исследования фракционного состава и функциональной однородности новых амфифильных сополиэфиров. Флуоресцеинсодержащие амфифильные сополиэфиры N-ацилпроизводных глутаминовой кислоты и полиэтердиолов, образуя самостабилизованные дисперсии в водных средах, могут рассматриваться как перспективные многофункциональные полимеры для использования в биомедицине.

Для фракционирования сополиэфиров по молекулярной массе использовали метод диализа. Полученные полимеры и их фракции охарактеризованы методами эксклюзионной хроматографии, а также определение поверхностного натяжения и функционального анализа.

Благодаря использованию эффективной эксклюзионной хроматографии, а также довольно высоких молекулярных масс комономеров для синтеза были получены молекулярно-массовые распределения сополиэфиров и проведена количественная сравнительная оценка содержания макромолекул отдельных фракций, их функциональности и коллоидно-химических свойств. Показано, что несмотря на разные значения молекулярной массы, отдельные фракции в составе сополиэфиров являются однородными по составу и тождественными по свойствам. Это позволяет использовать такие сополиэфиры в качестве основы для создания систем транспорта лекарств и нанодиагностики.

Ключевые слова: молекулярно-массовое распределение; сополиэфиры; флуоресцеин; реакция Стеглиха; системы доставки лекарств.

Introduction

Creating drug delivery systems based on nanoscale particles is an urgent task at the current stage of the development of chemistry [1–5]. In addition to biocompatibility and non-toxicity the polymers for the production of modern nanocontainers must have certain properties, the main of which are: i) the presence of surface activity and ability to self-assemble into nanoscale particles; ii) the ability to form stable dispersed systems and operation of the ones as nanocontainers; iii) the presence of fragments in the macromolecules that provide address targeting in the pathological zone (target) and their traceability in the body [6–9]. Analysis of the studies in the field of drug delivery systems has shown that the main focus is on amphiphilic copolymers, which make it possible to create aggregate-resistant nano- and micro-sized colloidal systems with specific properties [10–12]. The inject of lipophilic and hydrophilic fragments in a certain ratio into their macrochains enable them to form hierarchies of self-assembled micellar structures. By changing the nature of the constitutional units of the original monomers it is possible to create a specific chemical structure of macromolecules, to distribute the functional groups and to form micellar structures of various morphologies [13; 14]. In the creation of polymeric drug delivery systems, the molecular mass of the polymer is important because it greatly affects the formation of nanoparticles, their stability over time and their steadiness in different biomedical environments [15; 16]. One of the most important properties ofa polymer is the molecular mass distribution of macromolecules. In some natural polymers, such as in most globular proteins, the molecules have the same molecular mass. However, in the case of modification of natural polymers (e.g., 2-hydroxyethyl starch, dextran) or synthetic polymers, the macromolecules with different molecular mass are present in the final product.It may have different properties depending on the method of production. In this case, it may be difficult to predict the behavior of the polymer-based drug accurately in the body [17]. We have obtained a series of amphiphilic copolyesters via the activated Steglich esterification reaction. These products are good for the creation of multifunctional dispersed drug delivery systems. The purpose of this work is to study the molecular mass distribution of copolyesters obtained via copolycondensation of N-derivatives of glutamic acid, polyoxyetherglycols and fluorescein and its effect on colloid-chemical characteristics in aqueous medium.

Experimental

Average molecular mass, molecular mass distribution and polydispersity coefficient of copolyesters were determined by Size-Exclusion Chromatography (SEC) with the use of a Waters Corporation chromatograph (USA) with a Waters 2998 refractometer detector and Waters 1515 Isocratic HPLC pump. Tetrahydrofuran was used as an eluent with a flow rate of 0.1 ml/min. The standards (polyether diol) with narrow molecular mass distribution were used for calibration. The average MM, MM distribution, content of a fraction and polydispersity coefficient were obtained using the appropriate software.Separation of copolyesters by dialysis was performed using a Spectra/Por 6 Dialysis Membrane with a capacity of 2.5 kDa (Cole-Parmer, USA). A container formed from the membrane was loaded with 20 ml of copolyester dispersion and placed in a container with 500 ml of water. The mixture was kept under slight stirring for 5 days; water was changed twice a day. The aqueous solution was evaporated with a rotary evaporator to obtain a low molecular mass copolyester fraction. The content of the dialysis bag was evaporated and the main fraction of copolyester was obtained.

The surface tension was determined by the Du Nui method. The values of the surface tension and the critical micelle concentration of copolyesters were calculated according to the method represented in [18].

The content of fluorescein in polymers was determined after their hydrolysis in an alkaline medium by spectrophotometry (UNICO 1201 spectrophotometer, "United Products & Instruments, Inc.", USA) [24].

Preparation of fluorescein-containing copolyesters by Steglich reaction were conducted according to the procedure described in [23].

Results and Discussion

Investigations of the production of a copolyester by the irreversible copolycondensation method using the Steglich esterification reaction showed that this method has ample opportunity to construct copolyester macromolecules of a definite structure and functionality [19–21]. According to the mentioned reaction, we obtained and characterized a number of polymer products, which differ by the substituent R- in N-substituted glutamic acid, mass of polyoxyethylene diol (PEG 600, 1000) and the content of fluorescein. A generalized structure of fluorescein-containing copolyesters is shown in Fig. 1.

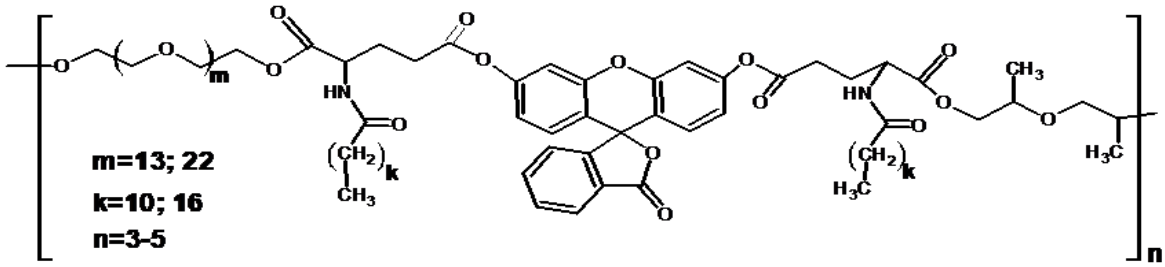

Fig. 1. Generalized structure of fluorescein-containing copolyester

Lipophilic (N-stearoyl or N-lauroyl glutamic acids) and hydrophilic polyoxyethylene glycols, which are combined in a one macromolecule provide amphiphilic properties of the resulting copolyesters and are able to reduce surface tension on the water/air boundary to 35–45 mN/m and form self-stabilized dispersed media in the water. Since visualization is one of the key problems in the study of the efficiency of drug delivery systems, we injected the fragments of a compound with chromophore groups (fluorescein) into the structure of copolyester macromolecules. Investigations of critical micelle concentration (CMC), equilibrium distribution of synthesized macromolecules of copolyesters between aqueous and lipophilic phases ($P_{o/w}$), ability to form self-stabilized dispersions with particles of the size of 150-300 nm (D) and solubilize water-insoluble compounds (Table 1), allow to consider them as perspective foundation for the future drug delivery system. Due to the fluorescein fragments they can be tracked in the body, enabling to develope the new diagnostic nanoinstruments based on them [22; 23]. Synthesis via the Steglich reaction allows to obtain oligomeric products with a polycondensation degree of 3-10. The results of NMR spectroscopy, photometry and determination of functional groups indicate the presence of all monomeric units in the composition of oligomeric macromolecules [24].

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At the same time, it is evident from the data of exclusion chromatography that the molecular mass distribution (which is a characteristic for all investigated polymers of this type) is represented by several discrete fractions with different molecular mass (Fig. 2). In this case, the issue of the homogeneity of their composition and their functionality is of particular interest. The high priority should be given to the fractions with low molecular mass (MW= 500 ÷ 2150 Da), the share of which in the copolyester is low (14 %), but the extent of the reproduction of polymer properties is not determined. It is known from the previousstudies that fractions with molecular mass of 514 and 810.

Table 1

Colloid-chemical characteristics of aqueous dispersions of synthesized copolyesters

Sample number	Copolyster structure	Fluorescein content, %	CMC, %	D, nm (at C=0.013%)	Solubilization$_{max}$, g Sudan/ g copolyester	$P_{o/w}$
PomF-1	GluLa-PEG600-DPG-F	5.2	0.0069	210	2.4	2.85
PomF-2	GluLa-PEG1000-DPG-F	1.87	0.0094	163	5.87	0.31
PomF-3	GluSt-PEG600-DPG-F	9.69	0.0102	315	1.6	1.52
PomF-4	GluSt-PEG1000-DPG-F	2.87	0.0128	232	6.0	2.36

Da are the fragments of a side rearrangement reaction of the carboxyl group of N-substituted glutamic acid activated with dicyclohexylcarbodiimide [19]. However, it should be noted that for the considered copolyesters the total content of the rearrangement fragments is not more than 1% and has no significant effect on colloid-chemical properties [25]. To separate the low molecular mass fractions and to study their properties, it was carried out the fractionation of copolyesters by dialysis using a membrane with a capacity of 2.5 kDa. Due to the relatively high mass of the monomer units and the use of efficient exclusion chromatography, the content of each fraction of the copolyesters was quantified (Fig. 2, Table 2).

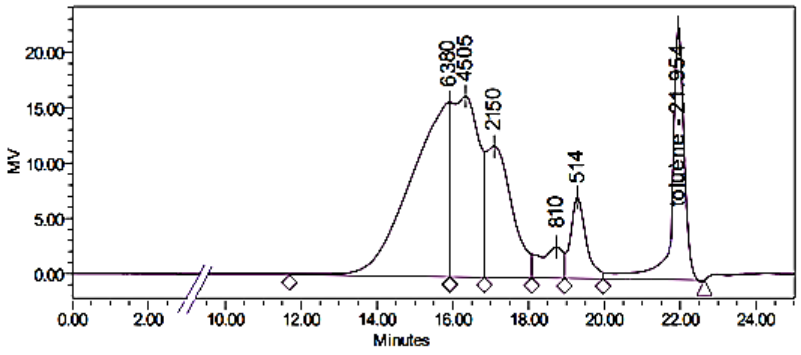

Fig. 2. Gel permeation chromatogram of copolyester PomF-2.

Table 2

MM distribution of copolyester PomF-2 before and after dialysis

Fraction MM	Fractions content of copolyester, %	
	before dialysis	after dialysis
514*	1.3	1.3
810*	0.9	0.3
2150	11.8	1.2
4505	0.4	0.4
6380	85.6	96.8

Note. * - no separation of the lipophilic low molecular mass fractions with MW 514 and 810 occurred through the membrane; they are the result of GluLa carboxyl groups rearrangement and apparently continue to be solubilized in the copolyester dispersion particles [22].

The change in the copolyester fractions content before and after dialysis is shown in Table 2. The fraction with MW = 6380 Da was almost 97% of the resulting copolyester due to the appropriate reduction of the fraction with MW = 2150 Da.

The values of surface tension of copolyesters solutions and separated fractions determined by the DuNui method showed exactly the same

character of surface tension isotherms for the PomF-2 copolyester fraction with MW = 2150 Da

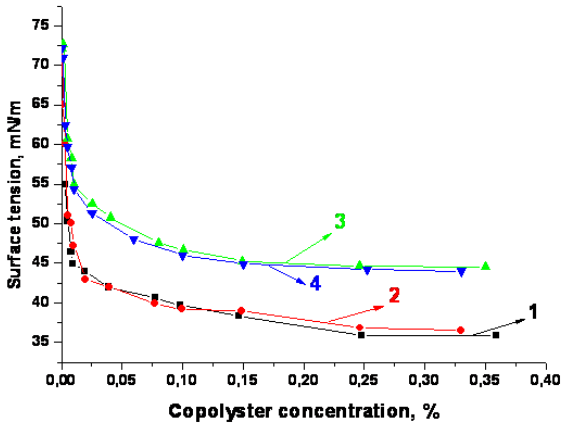

Fig. 3. Surface tension isotherms: 1) PomF-2 copolyester fraction with MW = 6380 Da, 2) PomF-2 copolyester fraction with MW = 2150 Da, 3) PomF-3 copolyester fraction with MW = 1795 Da, 4) PomF-3 copolyester fractions with MW = 4150 ÷ 8540 Da.

Previously, it was found that the colloid-chemical properties of copolyesters of this type are determined by the molecular mass ratio of hydrophilic and lipophilic fragments, which is reflected by the GLB value [26]. The values are calculated using quantitative composition characteristics of the PomF-2copolyester obtained by the ^{1}H NMR spectroscopy. For the fraction as a whole and the fraction separated by dialysis the values of GLB are 7.7 and 7.9 respectively. It is obvious that no significant change is observed, which is also confirmed by the similarity of their surface tension isotherms. So, the surface-active properties of such copolyesters slightly depend on their molecular mass.

Table 3

MM distribution of copolyester PomF-3 before and after dialysis

Fraction MM	Fraction content of copolymer, %	
	Before dialysis	After dialysis
598*	3.8	4.1
840*	10.5	10.1
1235	0.3	0.3
1795	28.7	7.7
4150	29.8	39.0
7135	9.4	12.4
8540	17.5	26.4

Similar studies were performed for copolyester based on GluSt and PEG600 (Table 3), which had significantly higher content of fluorescein. Fluorescein is less reactive in esterification reactions. So, when using fluorescein in large quantities (0.16 mol% in the synthesis of polymer PomF-3 against 0.05 mol% in the case of polymer PomF-2) a significant increase in the polydispersity of the obtained copolyester is observed. This contributes to the increase in the share of the fractions with smaller MW. In this case, it was established gravimetrically that 21% of the loaded copolyester has passed through the membrane during dialysis. The SEC method confirmed that after dialysis the content of the fraction with MW = 1795 Da in the copolyester has decreased by four times. The content of fluorescein has also decreased from 9.69% to 7.88%. It was calculated that the fraction separated during dialysis contained 17.4% of fluorescein. The obtained data suggest that the molecular mass of 1795 Da with the specified fluorescein content and logical sequence of copolyester units may correspond with acceptable accuracy (± 10%) to the fraction, the structure of which is represented by the following sequence of monomer units F-GluSt-PEG600-GluSt-DPG. It should be noted that the resulting fraction contains all monomers that were used in the initial reaction mixture for the synthesis of copolyester. However, for the copolyester parts which were separated by dialysis, there is no difference in their colloid-chemical properties. Surface tension isotherms for the fractions with MW of 1795 Da and 4150 ÷ 8540 Da are overlapped within the determination accuracy (Fig. 3, curves 3,4). Thus we may assert that the individual fractions in the copolyester composition are quite homogeneous and have the similar properties.

Conclusion

It is shown that the obtained statistical copolyesters are characterized by unconventional for copolyesters molecular mass distribution. Quantitative assessment of each fraction of the obtained copolyesters, which was carried out using the effective exclusion chromatography indicated that despite the number of the comonomers was used and their possible unequal reactivity, only a limited number of fractions with different molecular mass were formed. The separation of copolyesters by dialysis made it possible to isolate some of the fractions, carry out gravimetric analysis and study their composition and properties. The analysis showed that the fractions of different molecular mass of fluorescein-containing copolyesters were homogeneous. It was also established that the molecular mass is not the factor that determines the colloid-chemical characteristics of copolyesters in general and their individual fractions.

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