ORIGINAL ARTICLES

SOLUBILIZATION OF HYDROPHOBIC BACTERIOCHLORIN–BASED PHOTOSENSITIZER IN MICELLES OF SURFACTANTS

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Abstract

The aim of the paper was to obtain a stable micellar emulsion of potent photosensitizer (PS) – *O*-propyloxime-*N*-propoxybacteriopurpurinimide methyl ester absorbing light in long-wave region of the spectrum (λ_{max} = 800±2 нм). Solubilizates of the dye based on different surfactants (Kolliphor ELP, Poloxamer 407, Emuxol 268) were obtained. Taking into account the physical and chemical parameters, the most potent micellar emulsion for injection was selected and characterized. The emulsion based on Kolliphor ELP remains stable for 4 months, with no changes in the fluorescence spectrum and absorption, as well as the particle diameter.

Keywords: photosensitizer, photodynamic therapy, bacteriochlorin, solubilizer, emulsion.

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СОЛЮБИЛИЗАЦИЯ ГИДРОФОБНОГО ФОТОСЕНСИБИЛИЗАТОРА БАКТЕРИОХЛОРИНОВОГО РЯДА В МИЦЕЛЛАХ ПОВЕРХНОСТНО-АКТИВНЫХ ВЕЩЕСТВ

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Резюме

Целью настоящей работы являлось получение стабильной мицеллярной эмульсии перспективного фотосенсибилизатора (ФС) – метилового эфира *О*-пропилоксим-*N*-пропоксибактериопурпуринимида, поглощающего в длинноволновой области спектра (λ_{max} = 800±2 нм). В процессе работы были получены солюбилизаты красителя на основе поверхностно-активных веществ (ПАВ): Kolliphor ELP, Poloxamer 407, Эмуксол 268. По физико-химическим параметрам отобрана и охарактеризована наиболее перспективная мицеллярная эмульсия ФС для парентерального введения. Выбранная эмульсия на основе Kolliphor ELP остается стабильной в течение 4 мес, в течение которых остаются неизменными спектр флуоресценции и поглощения и диаметр мицелл.

Ключевые слова: фотосенсибилизатор, фотодинамическая терапия, бактериохлорин, солюбилизатор, эмульсия.

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Introduction

Photodynamic therapy (PDT) is a dynamically developing method of treating pathologies of various nature, including malignant neoplasms. With its high efficiency of treatment, PDT has been widely used in clinical practice [1-3]. The advantages of PDT are its minimal invasiveness, selectivity of exposure, possibility of repeated use if necessary, a favorable cosmetic effect, as well as the ability to use the technique both as an independent treatment method and in combination with other antitumor therapy methods [4–6].

To date, the main drugs used in PDT are photosensitizers (PS) based on porphyrins, chlorins, and phthalocyanines [7, 8], which are intensively absorbed in the region of 630–685 nm, where the permeability of biological tissues is low. This PS group is characterized by high activity against tumors of small volume. It should be noted that phthalocyanine-type PSs circulate continuously in the body, which leads to prolonged skin toxicity [9]. In connection with the above reasons, the researchers are conducting a directed search for new highly effective dyes, including among compounds of the bacteriochlorin series, which absorb in the region of 700–900 nm [10–13]. PSs of this type are predominantly hydrophobic compounds; therefore, in order to make their intravenous administration possible, the dosage form of the dye has to be a stable emulsion [14].

The most common surfactants used to produce injectable forms of hydrophobic substances are the following: polyethylene glycol, cremophore, pluronics and their aqueous solutions. Co-solvents of this series are pharmaceutical excipients that increase the solubility and stability of drugs, increase the bioavailability and, therefore, the effectiveness of the treatment with the use of photodynamic therapy [14-17].

The aim of this work was to obtain a stable micellar emulsion of methyl ester O-propyloxime-N-propoxybacteriopurpurinimide.

Materials and methods

Photosensitizer

The photosensitizer substance is O-propyloxime-N propoxybacteriopurpurinimide methyl ester absorbing in the region of 800±2 nm [18].

Producing colloidal solutions of surfactants

To obtain colloidal surfactant solutions with a concentration of 4% (mass/volume), weighed portions of solubilizers Kolliphor ELP (BASF, Germany), Poloxamer 407 (Sigma-Aldrich, USA), Emuksol 268 (FSUE "SSC" NIOPIK", Russia) were dissolved in injection-grade water (LLC "Groteks", Solopharm, Russia) and stirred for 10 minutes until complete dissolution. Stirring was done with a magnetic stirrer (ThermoScientific, UK) at a temperature of 25, 40, 50, 60, 70, and 80°C. Next, the colloidal solution was subjected to sonication for 10 or 20 minutes. The efficiency of the formation of colloidal solutions was evaluated by the nature of micelles formation by dynamic light scattering which determined the diameter of the particles in the solution. The analysis was performed on a Delsa™Nano C particle size, ξ potential, and flat surface analyzer (BeckmanCoulter, USA). The light source was a diode laser operating at a fixed wavelength of 658 nm. Each measurement was carried out at least 3 times, then the average value of the diameter of the micelles was calculated.

Preparation of solubilizers based on surfactants

To obtain a PS emulsion based on various surfactants (Kolliphor ELP, Poloxamer 407, Emuxol 268), a dye sample was dissolved in methylene chloride (dichloromethane, CP, OOO "Khimmed", Russia) and added in small portions to a 4% surfactant solution heated on magnetic stirrer to 42°C, which is the boiling point of methylene chloride, with constant stirring and barbotage with argon. The process was continued until the solvent completely evaporated, then the emulsion was cooled to room temperature and sterilized through a Millipore membrane filter (Corning, Germany) with a pore size of 0.22 μm.

The assessment of the stability of solubilizers based on surfactants

The stability assessment included an analysis of the absorption and fluorescence spectra over time and the particle size distribution of surfactant-based photosensitizer emulsions.

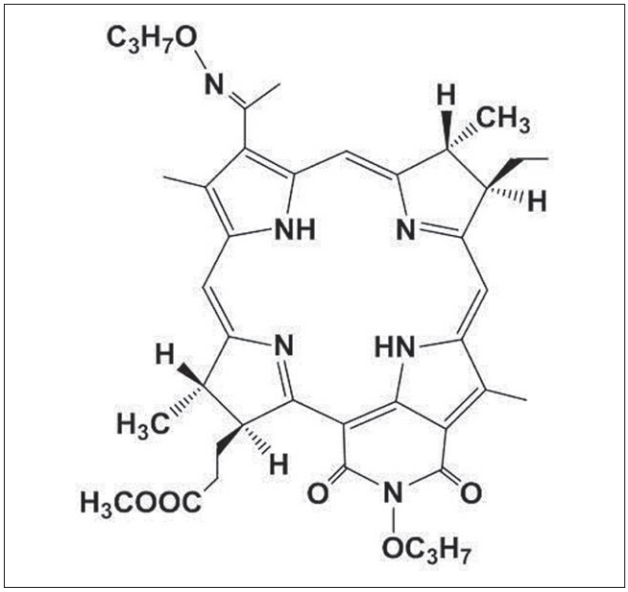

Рис. 1. Химическая формула фотосенсибилизатора
Fig. 1. Chemical formula of the photosensitizer

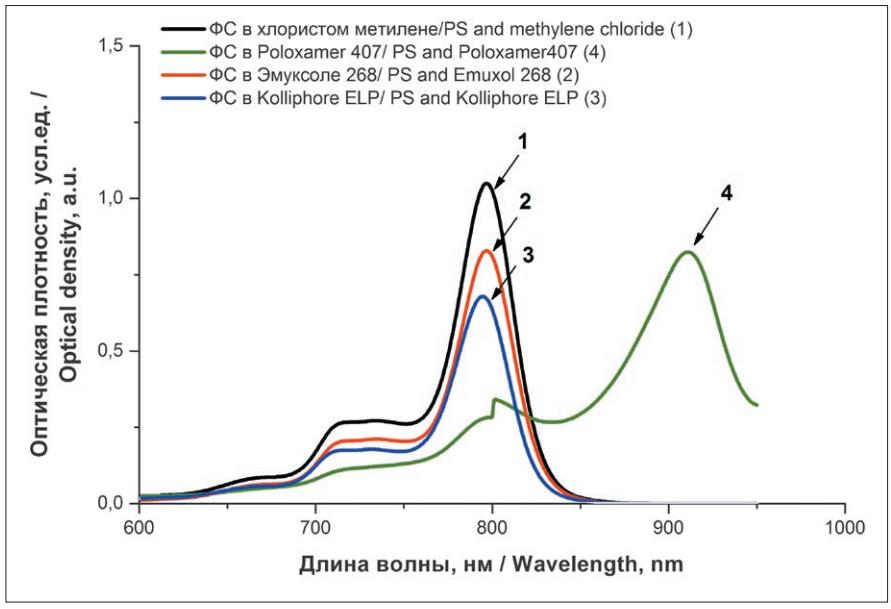

Рис. 2. Абсорбционные спектры ФС в хлористом метилене (1), в составе эмульсии на основе Kolliphor ELP (2), Poloxamer 407 (3) и Эмуксол 268 (4)
Fig. 2. Absorption spectra of the PS in dichloromethane (1), in the emulsion based on Kolliphor ELP (2), Poloxamer 407 (3) and Emuxol 268 (4)

PS solutions were prepared *ex tempore* by serial dilution of the starting emulsions with known concentrations. Absorption and fluorescence spectra were recorded on a Genesys 2 spectrophotometer (ThermoSpectronic, USA) and on a laser analyzer for fluorescence diagnosis of LESA tumors (OOO "BIOSPEC", Russia), respectively. The measurements were carried out *ex tempore*, as well as after 2, 4, 24 hours, 7 days, 1 and 4 months of storage in a dark place. Fluorescence was excited by a He-Ne laser at a generation wavelength of 632.8 nm with an optical resolution of 2 nm in the wavelength range from 400 to 1000 nm. During mathematical processing, the spectrum of the background fluorescence of the solvent was subtracted from the recorded spectra and integrated within the range from 300 to 900 nm. The concentration of the active substance in the solution was 20 μg/ml. In the course of the studies, the position of the maxima on the absorption and fluorescence spectra, the optical density, the fluorescence intensity, and also the nature of the change in the profile of the PS spectra were evaluated.

To determine the particle size in solution, the dynamic laser light scattering (DLS) method was used. The analysis was performed on a Delsa™Nano C particle size, ξ potential, and flat surface analyzer. Before the experiment, the emulsions were sterilized through a 0.22 μm Millipore membrane filter. The solutions for the research were prepared *ex tempore* by successive dilutions of the starting emulsions to a final concentration of the active substance of 40 μg/ml. Each measurement was carried out at least 3 times, after which the average diameter of empty micelles and micelles with the introducted photosensitizer was calculated.

Photosensitizer photo stability assessment

The solutions were prepared *ex tempore* by successive dilutions of the initial emulsion in the Igla MEM culture medium (NPE "PanEco", Russia) containing 10% fetal calf serum to a final concentration of the active substance of 25 μg/ml. 150 μl of PS solution was introduced to the wells of a flat-bottomed 96-well microplate (Corning, USA). A 500 W halogen lamp with a KS-19 broadband filter (λ ≥ 720 nm) and a 5 cm thick water filter were used as an optical radiation source. The power density was 18 ± 1.0 mW/cm^2, and the light dose was 5, 10, 20, 50, and 100 J/cm^2. The radiation power was monitored with an IMPO meter (RPA "Polyus", Moscow). The fluorescence intensity was evaluated before and after irradiation. During mathematical processing, the spectrum of the background fluorescence of the solvent was subtracted from the recorded spectra and integrated within the range from 300 to 900 nm.

Results and discussion

Producing colloidal solutions of surfactants

To solubilize PS, the following surfactants were used as cosolvents: Kolliphor ELP, Emuxol 268 and Poloxamer 407. Kolliphor ELP is a non-ionic solubilizer obtained by mixing castor oil with ethylene oxide in a ratio of 1:35; Emuxol 268 is a block copolymer of ethylene oxide with

Таблица
Физико-химические свойства солюбилизатов на основе различных ПАВ
Table
Physicochemical properties of solubilizates based on various surfactants

Название ПАВ Name of surfactant	$\omega_{ПАВ}$, % $\omega_{surfactants}$, %	λ_{max}, нм λ_{max}, nm	ε, $M^{-1}cm^{-1}$ ε, $M^{-1}cm^{-1}$	Диаметр частиц, нм Diameter of particles, nm		Стабильность Stability
				Без субстанции Without substance	С субстанцией With substance	
Kolliphor ELP	4	800±2	29285	10,7±0,3	10,5±0,40	4 мес 4 months
Emuxol 268	4	910±2	–	12,0±1,1	362±15 535 ±201	не стабилен not stable
Poloxamer 407	4	800±2	23492	28,5±2,0	27,5±2,5	2 ч 2 hours

propylene oxide and propylene glycol; Poloxamer 407 is a triple block copolymer of ethylene oxide and propylene oxide [19]. During the preparation of colloidal solutions, it was found that Kolliphor ELP effectively forms micelles at room temperature without the use of ultrasound. The size of the resulting particles in this case is 10.7 ± 0.3 nm.

The smallest particle size in a colloidal solution based on Emuxol 268 was observed after heating to 40°C and sonicated for 10 min (12.0±1.1 nm). Samples based on Poloxamer 407, prepared at 40 and 50°C and sonicated for 10 min, had a particle diameter of not more than 30.0 nm. Thus, a heating temperature of 40°C and the ultrasonication time of 10 minutes were chosen as the most optimal emulsion preparation parameters.

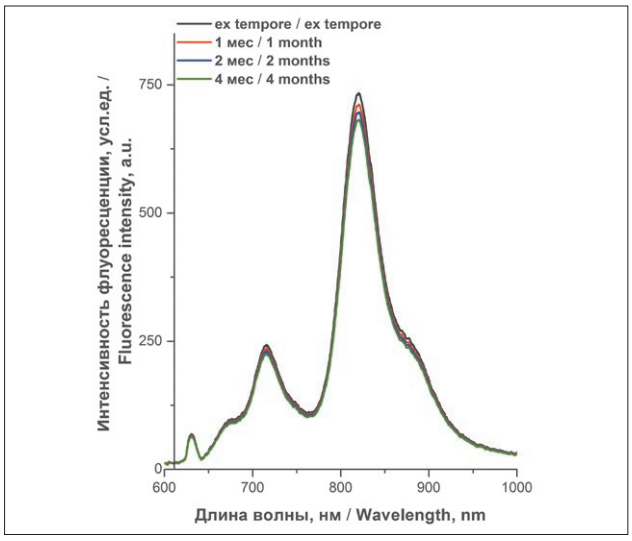

Рис. 3. Спектры флуоресценции ФС в составе эмульсии на основе 4% Kolliphor ELP во времени
Fig. 3. Fluorescence spectra of the PS in the 4% Kolliphor ELP-based emulsion in time

Assessment of physicochemical properties of surfactant-based solubilizates

An analysis of the obtained data showed that the intensity of the main absorption band of solubilizates based on Kolliphor ELP (OD = 0.810) and Poloxamer 407 (OD = 0.635) was the highest (Fig. 2). Perhaps this is due to the fact that these surfactants have the longest hydrophobic regions, while Poloxamer 407 has a larger hydrophobic core volume [20, 21]. It was shown that the choice of a particular solubilizer does not affect the form of the electronic absorption spectrum of the substance (Fig. 3). The maximum fluorescence of PS under these conditions is recorded at 822 ± 2 nm.

The solubilization of the substance in Emuxol 268 led to its instant aggregation, with the expansion of the main absorption band and the formation of a new band with a maximum in the region of 910±2 nm, which corresponds to the formation of an aggregated form of the dye (Fig. 2). The data on the determination of particle diameter confirm the aggregation of the dye, with the diameter of the solubilizate micelles exceeding 5000 nm (see table).

Solubilizers based on Kolliphor ELP and Poloxamer 407 were monodisperse with an average particle diameter of 10.5±0.40 and 27.5±2.5 nm, respectively.

The photosensitizer in the composition of the Poloxamer 407-based emulsion is stable for 2 hours, after which the shape of the electronic spectrum changes with the appearance of a high-intensity long-wave peak in the region of 895±2 nm, as well as the disappearance of the main absorption band in the region of 800±2 nm, which indicates aggregation of the substance in the solution resulting in a 100% decay of fluorescence. Perhaps this effect is due to the fact that a large hydrophilic part of the Poloxamer 407 polyethylene oxide blocks is capable of hydration, the result of which is the penetration of

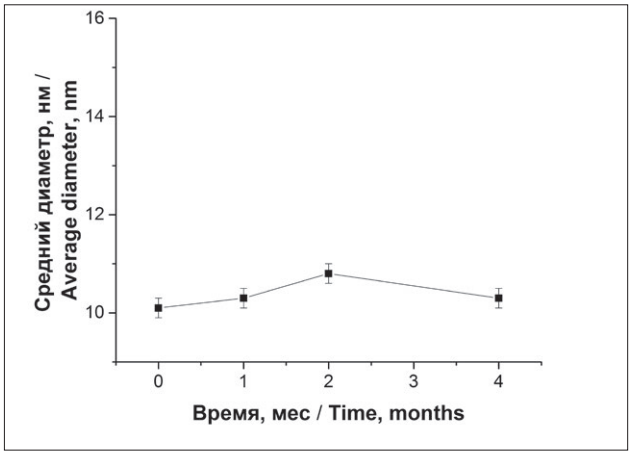

Рис. 4. Изменение диаметра частиц ФС в составе эмульсии на основе 4% Kolliphor ELP во времени
Fig. 4. Change in the diameter of the PS particles in the on 4% Kolliphor ELP-based emulsion in time

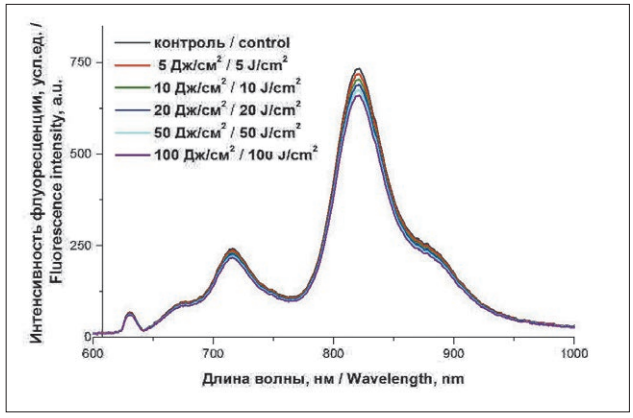

Рис. 5. Спектры флуоресценции ФС в составе эмульсии на основе 4% Kolliphor ELP до воздействия света и после облучения дозой света в 5, 10, 20, 50 и 100 Дж/см²
Fig. 5. Fluorescence spectra of the PS in the 4% Kolliphor ELP-based emulsion: before and after irradiation at a dose of 5, 10, 20, 50 and 100 J/cm²

water into the micelle nuclei and their further aggregation.

Based on the obtained data, it was found that the Kolliphor ELP-based solubilizate remains stable for 4 months, and throughout the entire observation period there are no changes in the fluorescence and absorption spectra and particle diameter (table, Fig. 3-4).

Assessment of the photostability of a photosensitizer in an emulsion based on Kolliphor ELP

It is shown that when the studied PS is irradiated in the composition of an emulsion based on Kolliphor ELP up to 100 J/cm² the dye is not prone to fading: no changes in the spectrum profile and fluorescence intensity were observed (Fig. 5).

Conclusion

Based on the data on solubility and stability, a micellar emulsion of PS based on Kolliphor ELP was selected, characterized by stability both during storage (4 months) and irradiation (up to 100 J/cm²). The micellar emulsion of methyl ester of O-propyloxy N-propoxybacteriopurpurinimide based on Kolliphor ELP is a promising substance and is of great interest for further studies in the field of photodynamic therapy of malignant neoplasms, since the use of this dye will make it possible to treat patients with large volume and deep-laying tumor formations.

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