EFFECT OF THE COMPOSITION OF COMBINED SOLID LIPID PARTICLES WITH GEFITINIB AND A PHOTOSENSITIZER ON THEIR SIZE, STABILITY AND CYTOTOXIC ACTIVITY

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Abstract

The creation of combined nanomedicines and their controlled release under the influence of photoinduction is an actively developing branch of scientific research. This work is devoted to the development of models of solid lipid nanoparticles for a well-known antitumor drug – gefitinib in combination with a photoindicating agent – a photosensitizer from the phthalocyanine group. Nanoparticles were obtained by several methods: hot homogenization with stearic acid, sesame oil and Tween 80 and by one-step dispersion with copolymers of lactic and glycolic acids and polyvinyl alcohol. In vitro experiments when irradiating particles with a laser in the near-infrared range (about 730 nm) proved the advantage of using combined nanoparticles with gefitinib and a photosensitizer compared to monotherapy, while the activity in terms of IC_{50} was 5.1-8.7 times higher for gefitinib and 1.5-1.8 times for the photosensitizer.

Key words: solid lipid nanoparticles, aluminum phthalocyanine, gefitinib, in vitro, photoinduced activity

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ВЛИЯНИЕ СОСТАВА КОМБИНИРОВАННЫХ ТВЕРДЫХ ЛИПИДНЫХ ЧАСТИЦ С ГЕФИТИНИБОМ И ФОТОСЕНСИБИЛИЗАТОРОМ НА ИХ РАЗМЕР, СТАБИЛЬНОСТЬ И ЦИТОТОКСИЧЕСКУЮ АКТИВНОСТЬ

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Резюме

Создание комбинированных нанопрепаратов и их контролируемое высвобождение под воздействием фотоиндукции активно развивающаяся отрасль научных исследований. Данная работа посвящена разработке моделей твердых липидных наночастиц для известного противоопухолевого препарата – гефитиниба в комбинации с фотоиндицирующим агентом – фотосенсибилизатор из группы фталоцианинов. Наночастицы получали несколькими методами: горячей гомогенизацией со стеариновой кислотой, кунжутным маслом и твином 80 и путем одностадийного диспергирования с сополимерами молочной и гликолевой кислот и поливиниловым спиртом. В опытах *in vitro* при облучении частиц лазером в ближнем инфракрасном диапазоне (около 730 нм) было доказано преимущество применения комбинированных наночастиц с гефитинибоми фотосенсибилизатором по сравнению с монотерапией, при этом активность по показателю $ИК_{50}$ была выше в 5,1-8,7 раз для гефитиниба и в 1,5-1,8 раз для фотосенсибилизатора.

Ключевые слова: твердые липидные наночастицы, алюминия фталоцианин, гефитиниб, *in vitro*, фотоиндуцированная активность

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Introduction

After the discovery of the first tyrosine kinase inhibitor (TKI), imatinib, studies on the synthesis of various substances with a similar mechanism of action followed. Most TKIs are antitumor agents, and some are used as anti-inflammatory agents. However, in the process of studying TKIs, it was found that despite their efficacy, these compounds are hepatotoxic, extensively metabolized and have limited bioavailability, and resistance develops rapidly when administered. These negative aspects can be mitigated by developing new generations of TKIs or by creating the most effective and safe dosage forms (DF), including selective action [1]. In addition, the activity of TKIs can be increased by using in combination with other antitumor drugs.

Various nano- and microstructures, including hybrid ones [2], have shown great potential for the development of biomarkers and chemotherapeutic agents due to their multifunctional adjustability and biocompatibility [3, 4]. One of the promising areas of development of antitumor therapy is the creation of nanosystems with controlled discharge. For example, photoinduced discharge, due to the inclusion of a photosensitizer (PS) in the nanocarrier, which is activated when exposed to light with a wavelength absorbed by this PS, can lead to the release of a chemotherapeutic agent, exerting a combined effect on the tumor. The most preferable approach to the development of such nanostructures is to use a PS with radiation in the near IR range of 700–850 nm as a photoinducer, which has the greatest ability to penetrate into biological tissues and needs low intensity below 30 mW/cm^2 [5].

The aim of this study was to develop a nanosystem based on solid lipid nanoparticles (SLN) with the chemotherapeutic agent gefitinib (GFT) and aluminum phthalocyanine (APhC) PS. GFT is a TKI and is widely used in the treatment of lung cancer both as monotherapy and in combination with other agents. GFT is poorly soluble in water, and therefore is used in clinical practice in the form of tablets, due to which it has insufficiently high bioavailability. This problem can be solved by developing a DF with GFT in the form of nanoparticles, ensuring the delivery of the drug to the tumor due to its nanosize, the effect of increased permeability and retention (EPR) based on tumor neovascularization [6], and controlled release of GFT from nanoparticles under photoexposure.

Materials and Methods

Materials

GFT (MSN Laboratories Private Limited), APhC (Merck Life Science LLC), stearic acid (SA, Himedia), sesame oil (SO, Merck Life Science LLC), Tween 80 (Montanox 80, Seppic), phosphatidylcholine S 100, SPC (PhC, Lipoid), copolymer of lactic and glycolic acids Purasorb PDLG 5010 (CPLG, Corbion), chitosan extra pure (Ch, Sisco Research Laboratories), polyvinyl alcohol hydrolyzed 88% (PVA, Acros Organics), sucrose, pure for analysis, trehalose dihydrate, extra pure, mannitol, pure for analysis (Himmed), chloroform, chemically pure (Vekton).

Equipment

Laboratory scale DL-120 (AND), analytical scale OHAUS Analytical Plus AP 100S (OHAUS Corporation), magnetic stirrer IKA® C-MAG HS 4 (IKA Werke GmbH & Co KG), vacuum pump Büchi V-700 (BÜCHI Labortechnik AG), immersion homogenizer Polytron PT 1200 E (Kinematica), ultrasonic homogenizer Bandelin Sonopuls HD 2070 (Bandelin), freeze-dryer Edwards Minifast DO.2 (Ero Electronic SpA), pH meter HANNA pH 2211 (Hanna Instruments), spectrophotometer Cary 100 (Agilent Technologies).

Methods for obtaining model combinations

1) By hot homogenization [7] using SA and SO as the lipid phase and Tween 80 as the aqueous phase in various ratios (SLN-1). The preparation of the compositions began with melting SA at 70-100°C on a magnetic stirrer, then SO was added by weight and GFT and APhC were dissolved in the resulting mixture with stirring (300 rpm) and constant heating. A glass with the resulting composite was dispersed on an immersion homogenizer with the gradual addition of an aqueous solution of Tween 80 for 1 hour. The resulting particles were ground on an ultrasonic disperser and filtered under pressure. The scheme for producing is shown in Fig. 1.
2) By the method of one-stage dispersion [8, 9] with CPLG and PhC under vacuum, where chloroform was used as the organic phase, and a 1-2% solution of PVA with or without chitosan (SLN-2) as the aqueous phase. The method for obtaining particles involved prolonged mixing (for 24-32 h) of a chloroform solution of GFT and APhC and an aqueous solution of PVA and chitosan under vacuum. After evaporation of chloroform, the resulting dispersion was crushed and filtered under pressure. The scheme of obtaining SLN-2 models is shown in Fig. 2.

The particles were ground using a combination of homogenization (5,000 rpm, 60 min) and ultrasonic dispersion (5 min, 60%). To increase the shelf life of the nanoparticles, lyophilization was performed using the method [10].

Quality control of all obtained SLNs was carried out by measuring the quantitative content, pH, particle size, ζ-potential [10, 11] and studying the stability during storage. Analysis of the quantitative content of GFT and APhC in SLNs was carried out spectrophotometrically at

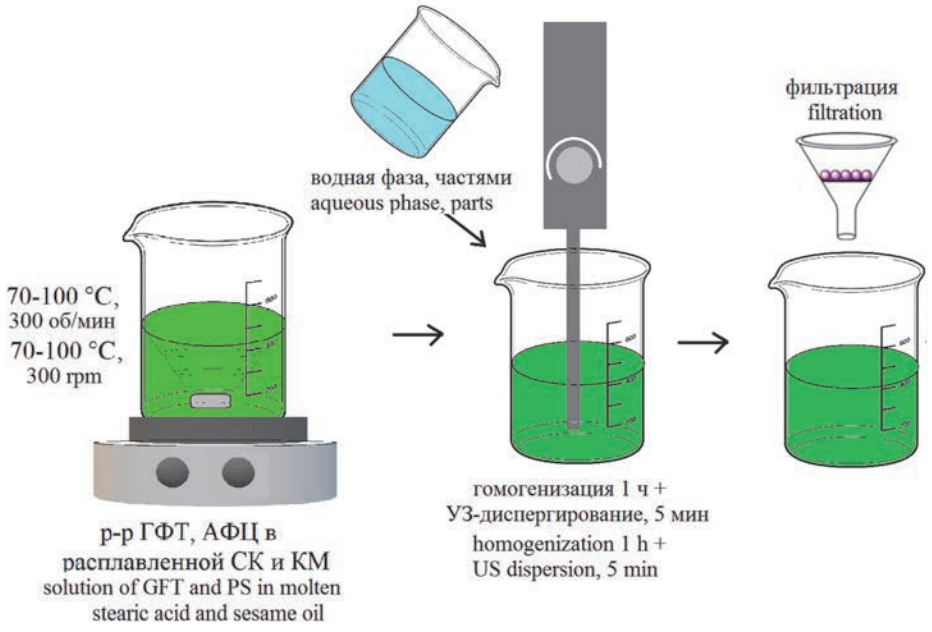

Рис. 1. Схема получения моделей ТЛН-1 методом горячей гомогенизации.
Fig. 1. Scheme for producing SLN-1 models by hot homogenization.

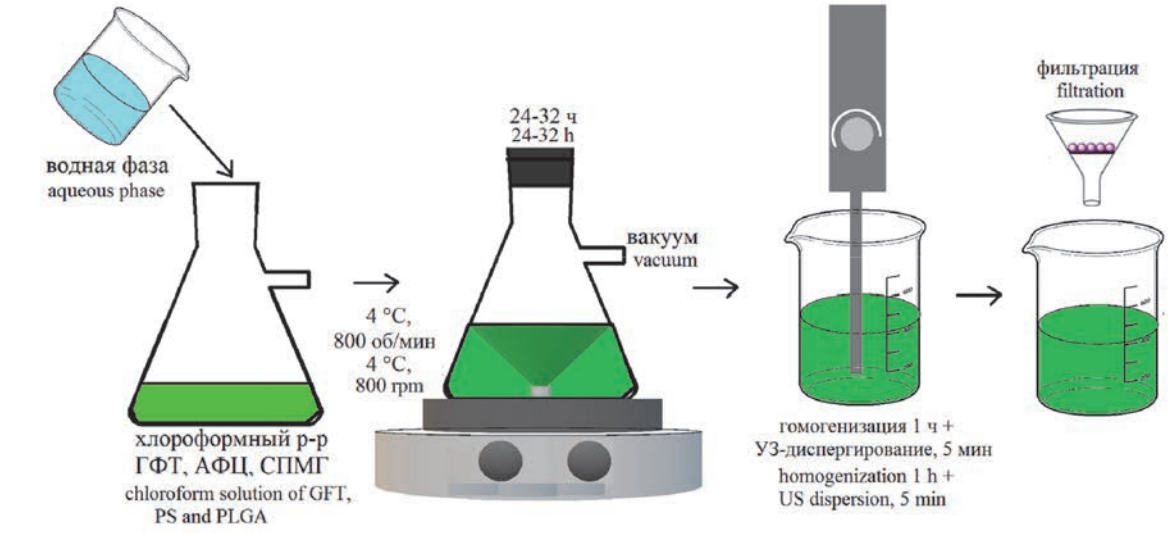

Рис. 2. Схема получения моделей ТЛН-1 методом горячей гомогенизации.
Fig. 2. Scheme for producing SLN-1 models by hot homogenization.

wavelengths of 338±3 nm and 717±3 nm, for GFT and APhC, respectively.

Cytotoxic activity

The study of the cytotoxic activity of SLN included the study of dark and photoinduced cytotoxicity on the lung carcinoma cell line A549 obtained from the Cell Line Bank of the N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation. The cell lines were cultured using the standard technique [12]. The MTT test was carried out using the routine method [13], irradiation was carried out 24 hours after the drug administration for 20 minutes with a LED source with a wavelength of 730 nm, then the cells were incubated for 24 hours.

Statistical processing was performed using standard Microsoft Excel 2007 packages and GraphPad Prism software (GraphPad Software Inc.). Each experiment was repeated at least three times, the results were presented as the mean ± standard deviation (SD). IC_{50} concentrations were calculated by nonlinear regression. Statistical significance was determined at $p<0.05$.

Results and discussion

The composition of SLN-1 is based on SA and SO, since the inclusion of liquid lipid in a solid lipid allows compounds to be embedded both between fatty acid chains and between lipid layers [7], which increases the loading capacity of active substances and reduces the explosive release of compounds. To select the optimal

composition of nanoparticles, model mixtures with different ratios of excipients were prepared (Table 1).

According to Table 1, it is evident that the content of surfactants and SA has a significant effect on the formation of a stable colloidal system, so an increase in the content of Tween 80 from 0.4% (No. 1) to 2.0% (No. 4) allows obtaining dispersion samples without sediment, and a decrease in SA from 2.0% (No. 1) to 0.7% (No. 4) prevents thickening, i.e. composition 4 with an average particle size of 236±4 nm, ζ-potential of -20±2.0 mV and pH = 6.1 turned out to be the most optimal. To stabilize the selected composition, lyophilization was carried out using cryoprotectors – mannitol, trehalose, and then the obtained samples were studied for the main quality indicators. The most optimal for forming a lyophilisate "tablet" was the use of 5% cryoprotector solutions (Table 2).

In the samples without cryoprotectant, the formation of a lyophilic structure did not occur, the samples with mannitol and trehalose at a concentration of 5% not only formed a homogeneous dry porous mass during lyophilization, but also retained the SLN-1 indicators after rehydration of the lyophilisate (rehydration time is 1 min). However, the composition of SLN-1 with trehalose after rehydration remained stable for a longer time (about 30 days) in appearance (homogeneous suspension without signs of stratification and sedimentation).

SLN-2 was obtained using CPLG, which are currently widely studied due to their biocompatibility and biodegradability in the body. Based on the experience of preparing SLN-1 models, SLN-2 compositions were prepared in a ratio of GFT to APhC as 4:1 (Table 3, Fig. 3).

The data in Table 3 and Fig. 3 show that the stability of the resulting suspension directly depends on the amount of CPLG and PhC. Attempts to reduce the amount of CPLG and PhC led to a decrease in the inclusion of GFT and APhC by 6-30% and the precipitation of substances.

Таблица 1
Составы ТЛН-1
Table 1
Compositions of SLN-1

№	Массовое соотношение Ratio			Внешний вид Appearance of samples	
	ГФТ:АФЦ GFT: APhC	ГФТ:СК GFT:SA	СК:КМ:твин-80 SA:S.oil:twin- 80	после получения after receipt	через 24 ч after 24 h
1	4,5:1	1:11	2,2:1:0,4	неоднородная дисперсия с осадком, быстро загустевает heterogeneous dispersion with sediment, thickens quickly	неоднородная густая дисперсия сосадком heterogeneous thick dispersion with sediment
2	3,3:1	1:17	2,2:1:4,3	однородная дисперсия, быстро загустевает homogeneous dispersion, thickens quickly	густая дисперсия thick dispersion
3	3,7:1	1:10	2,2:1:4,3		
4	4:1	1:7	1,3:1:3,7	однородная дисперсия homogeneous dispersion	однородная дисперсия homogeneous dispersion

Таблица 2
Влияние криопротекторов на показатели качества ТЛН-1
Table 2
The influence of cryoprotectors on the quality indicators of SLN-1

Криопротектор Cryoprotector	Внешний вид лиофилизата Appearance of the lyophilisate	pH	Размер частиц, нм Nanoparticle size, nm	ζ-потенциал, мВ ζ-potential, mV	Эффективность включения ГФТ/АФЦ, % Entrapment efficiency GFT/AphC, %
маннит 5% mannitol 5%	однородная сухая пористая масса светло-зеленого цвета homogeneous dry porous mass of light green color	6,4-6,8	220±13	-16±1,1	100/40
трегалоза 5% trehalose 5%		7,3-7,4	245±15	-15±1,2	92/44
-	прозрачная пленка transparent film	6,8-7,0	235±11	-14±0,9	90/48

Таблица 3
Составы ТЛН-2
Table 3
Compositions of SLN-2

№	Массовое соотношение Ratio		Внешний вид Appearance of samples	
	ГФТ:СМПГ GFT:CPLG	СПМГ:ФХ:ПВС:Х CPLG:PhC:PA:Ch	после получения after receipt	через 24 ч after 24 h
1	1:30	60:40:40:1 ФХ — SPC PhC – SPC	однородная суспензия homogeneous suspension	однородная суспензия homogeneous suspension
2	1:30	60:16:40:1 ФХ – S100 PhC – S100		осадок sediment
3	1:20	40:15:40:1 ФХ — SPC PhC – SPC		однородная суспензия, осадок через 5 сут homogeneous suspension, sediment after 5 days
4	1:15	30:15:40:1 ФХ — SPC PhC – SPC		однородная суспензия, осадок через 3 сут homogeneous suspension, sediment after 3 days
5	1:15	30:15:20 ФХ – SPC, безХ PhC – SPC, without Ch		осадок sediment

The SLN-2 model of composition No. 1 turned out to be the most optimal with the inclusion of GFT at 87%, APhC at 99%, an average particle size of 243±11 nm, a neutral ζ-potential and a pH of 5.5. Monitoring this model over time using the above indicators showed its stability for 14 days at a storage temperature of 2-8°C. Lyophilization of this composition is planned for the future.

The cytotoxic activity of the selected models of SLN-1 (composition 4 with 5% trehalose) and SLN-2 (composition 1) was studied *in vitro* experiments on the A549 lung cancer cell model (Fig. 4, 5, Table 4).

In the study of dark and photoinduced cytotoxicity, combined SLN-1 and 2, as well as monodrugs (GFT substance and SLN-1 and SLN-2 models with only APhC) were introduced into cells in concentrations of GFT at doses of 1.56-100 μg/ml. The GFT substance is not phototoxic, the difference between the IC_{50} of the substance with and without irradiation is ~3%. According to IC_{50}, photoinduced cytotoxicity when exposed to a laser with a energy dose density of 33 J/cm^2 in both models was 3.5-4.6 times higher than dark toxicity, which indicates a synergistic effect of the drug and PDT. Compared with monotherapy, the combinations were 5.1-8.7 times more effective for GFT and 1.5-1.8 times more effective for APhC. Close IC_{50} values between SLN-2 without irradiation and the GFT substance indicate photoinduced release of GFT from DF and low toxicity of excipients in this composition, while SLN-1 is sufficiently cytotoxic

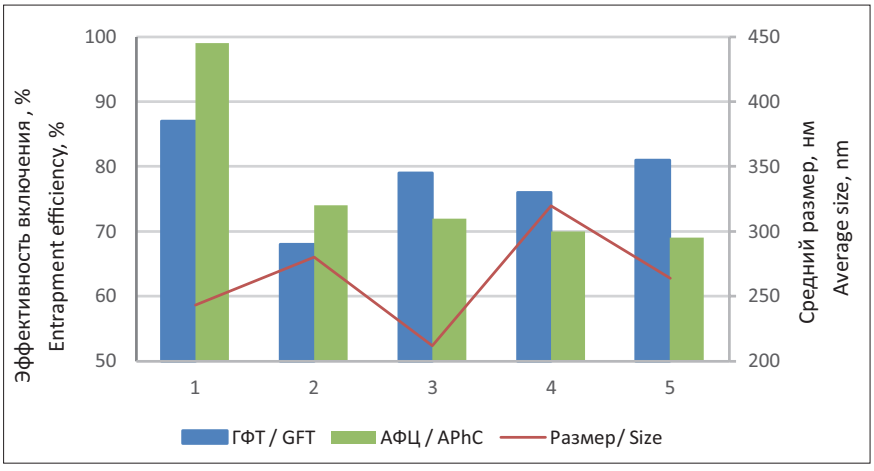

Рис. 3. Влияние состава вспомогательных веществ на эффективность включение ГФТ, АФЦ и на средний размер частиц в ТЛН-2.
Fig. 3. The influence of the composition of excipients on the efficiency of the inclusion of GFT, APhC and on the average particle size in SLN-2.

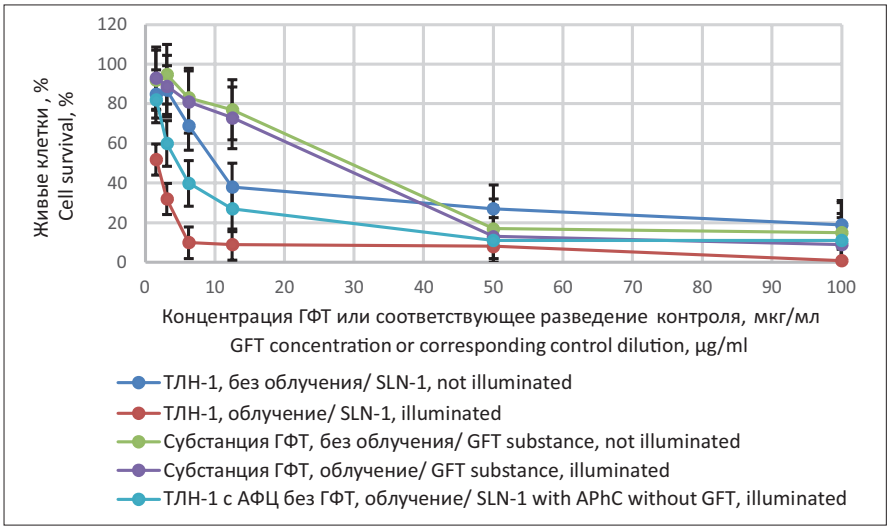

Рис. 4. Цитотоксическая активность ТЛН-1 на клетках А549, время инкубации 24 ч, для значений $ИК_{50}$ $p \leq 0,05$.
Fig. 4. Cytotoxic activity of SLN-1 on A549 cells, incubation time 24 h, for IC_{50} values $p \leq 0,05$.

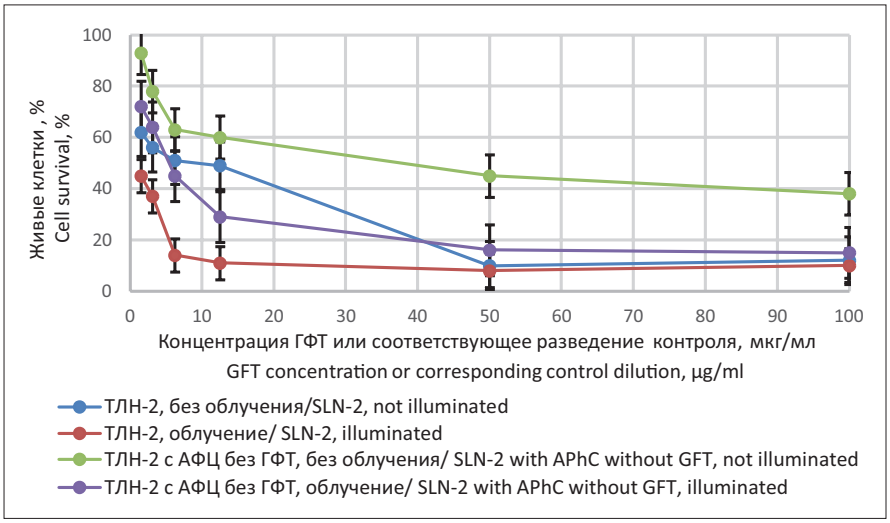

Рис. 5. Цитотоксическая активность ТЛН-2 на клетках А549, время инкубации 24 ч
Для значений ТЛН-2$ИК_{50}$и ТЛН-2с АФЦ без ГФТ (без облучения и с облучением) $p \leq 0,05$.
Fig. 5. Cytotoxic activity of SLN-2 on A549 cells, incubation time 24 h, for IC_{50} values $p \leq 0,05$.

Таблица 4
$ИК_{50}$ исследуемых образцов на модели А549
Table 4
IC_{50} of tested samples on model A549

Образец препарата Drug sample	ТЛН-1*, мкг/мл SLN-1, μg/ml	ТЛН-2*, мкг/мл SLN-1, μg/ml
ТЛН без облучения SLN not illuminated	8,5	19,0
ТЛН с облучением SLN illuminated	2,4	4,1
Субстанция ГФТ без облучения GFT substance, not illuminated	21,6	
Субстанция ГФТ с облучением GFT substance, illuminated	20,9	
ТЛН с АФЦ без ГФТ без облучения SLN with APhC without GFT, not illuminated	-	22,5
ТЛН с АФЦ без ГФТ с облучением SLN with APhC without GFT, illuminated	4,3	6,2

* $p \leq 0,05$

even without irradiation. The presented data indicate the prospects for further study of the SLN-2 nanoparticle model on other cell lines.

Conclusion

As a result of complex studies on the creation of combined photoinduced nanosystems of GFT and PS with high cytotoxic activity, two models of SLN-1 and SLN-2 were obtained and studied with the IC_{50} indices of 2.4 and 4.1 μg/ml, respectively. In further studies, it is planned to improve the composition based on CPLG and PhC and study its phototoxicity on other cell lines, as well as select the optimal irradiation mode.

Data on the producing and study of SLN with photo-induced release can serve as a methodological approach for the development of various chemotherapeutic agents with stimulus-sensitive release.

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