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Research Article

Properties and antitumor activity of combined polymeric nanoparticles based on gefitinib and a photosensitizer

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Abstract

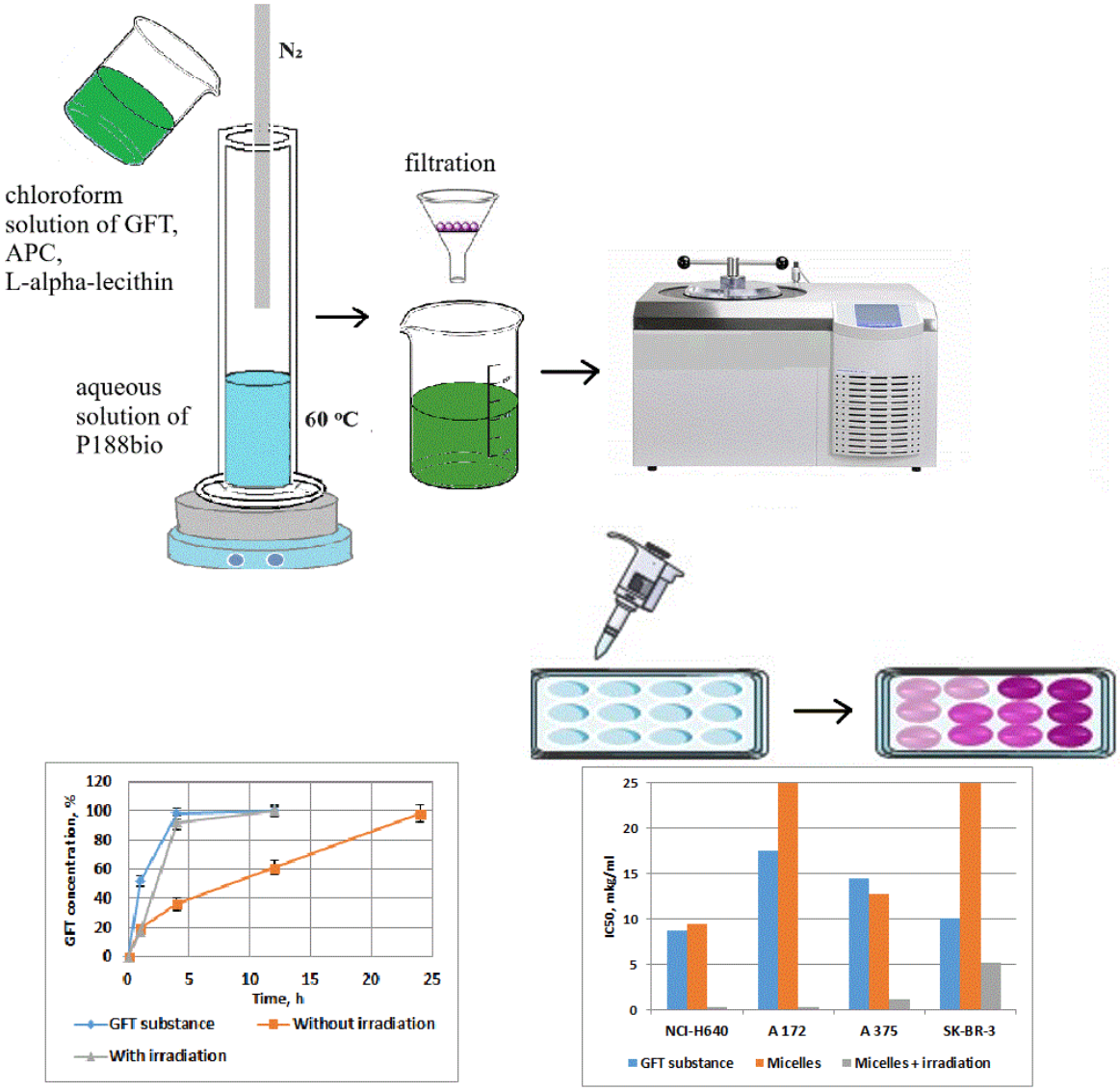
Introduction: Gefitinib (GFT) is a moderately lipophilic small quinazoline molecule with proven efficacy in treating locally advanced or metastatic non-small cell lung cancer. Due to the broad activity of GFT and other tyrosine kinase inhibitors, researchers worldwide strive to create various nanoparticles based on these substances, including their combinations with other active molecules. This study investigated morphology, release, and cytotoxic activity of micellar form of combination particles with GFT and a phthalocyanine photosensitizer in various tumor models.

Materials and Methods: The micellar model was obtained by mixing/emulsifying the aqueous and organic phases using a continuous flow of nitrogen gas, an aqueous solution of poloxamer 188 as the aqueous phase, and a chloroform solution of the active substances as the organic phase. Conventional analytical and biological methods were used to characterize the obtained micelles. The average particle size and polydispersity index of the samples were determined by dynamic light scattering and microscopy. Release from particles was determined in vitro by quantifying free GFT released through the dialysis insert. Cytotoxic activity was studied on the cell lines of lung cancer NCI-H640, glioblastoma A 172, melanoma A 375, and breast cancer SK-BR-3.

Results and Discussion: The micelles with GFT, a photosensitizer, poloxamer 188, and polyvinylpyrrolidone were spherical and nanosized. 50% of the encapsulated GFT was released from the micellar model in a phosphate buffer medium within about 10.0 h. Testing of micelles on a panel of four tumor cell lines in the dose range of 0.1-20 μg/mL showed high cytotoxic activity of the studied model, especially for lung cancer and glioblastoma.

Conclusion: The obtained data suggest a promising in-depth study of micellar nanoparticles of GFT with a photosensitizer, especially concerning lung cancer and glioblastoma.

Graphical abstract



Keywords

gefitinib polymeric nanoparticles; photosensitizer; release in vitro; study of cytotoxic activity; lung cancer NCI-H640; glioblastoma A 172; melanoma A 375; breast cancer SK-BR-3

Introduction

Nitrogen-containing heterocycles are a valuable source of pharmacophores for the development of new active molecules, and more than 75% of FDA-approved molecules contain N-heterocyclic moieties. Small molecules with nitrogen-containing heterocycles are valuable scaffolds for developing new inhibitors of various cellular signaling biomolecules.

Epidermal growth factor receptor (EGFR) mutations, a common oncogenic driver in non-small-cell lung cancer (NSCLC), can be targeted by EGFR tyrosine kinase inhibitors to improve patient prognosis. EGFR mutations have been identified in various domains of the protein, including the extracellular, transmembrane, and juxta membrane regions, each contributing to tumorigenesis in distinct ways (Van den Bent et al. 2009). The EGFR exon 19 deletion and exon 21 L858R mutations are the most common activating and sensitizing EGFR mutations, accounting for 85–90% of EGFR mutation-positive cases (He et al. 2023).

Gefitinib (GFT) is a moderately lipophilic small quinazoline molecule and an established treatment for locally advanced or metastatic NSCLC (Șandor et al. 2023). In clinical studies, GFT exhibited high and sustained blood levels over a 24 h period, with a bioavailability of 60% (Rawluk et al. 2018). The efficacy of GFT stems from its 4-anilinoquinazoline core, which serves as a potent EGFR-TK inhibitor by mimicking ATP and preventing the phosphorylation of EGFR. Specifically, GFT binds to the T790 residue of the EGFR through a hydrogen bond formed between the nitrogen on the 4-anilinoquinazoline core and Met793. Additionally, it interacts with the L858 residue via multiple carbon–hydrogen bonds with Leu718, Gln791, Pro794, and Gly796 (Dickerson et al. 2024).

In addition to lung cancer, GFT has also been studied for the treatment of breast, cervical, colon, head and neck, ovarian, and hepatocellular cancers (Ibrahim et al. 2021; Rahman et al. 2014). In glioblastoma multiforme murine xenograft models, GFT combined with others cytotoxic agents produced both cancer regression and tumor growth inhibition, improving the rate of survival. GFT in combination with temozolomide in U87MG cell line induced cytotoxic effects with IC50 values of 11 μM (Karami et al. 2022). *In silico* modeling has shown the interaction of GFT with key breast cancer proteins, namely dihydrofolate reductase (PDBID: 4KD7), HER2 kinase (PDBID: 3RCD), epidermal growth factor receptor (PDBID: 1M17), and NUDT5 (PDBID: 5NWH) (Almasoudi et al. 2024).

GFT in combination with bevacizumab was effective in treating NSCLC with rare EGFR mutations and overcoming acquired C797S resistance that arose after the use of second- and third-generation drugs. After two months of treatment, the patient exhibited a significant reduction in the size of lung, brain, and liver metastases compared with their previous dimensions. Overall survival exceeded 60 months (Lu W et al. 2025).

Due to the broad activity of GFT and other tyrosine kinase inhibitors, researchers worldwide strive to create various nanoparticles with them, including combination treatments. A study of the GFT substance and solid lipid GFT nanoparticles produced by the emulsification-evaporation method using glyceryl tristearate, lipoid 90H, and Kolliphore 188 showed the activity of GFT on MCF-7 breast cancer cells. The IC50 was 4.0822 μM for the substance and 2.7814 μM for the nanoparticles (Aljuffali et al. 2023).

Dasatinib and crizotinib encapsulated in poly(styrene-co-maleic acid) micelles showed highly potent antiproliferative effects in four glioblastoma cell lines and *in vitro* models of angiogenesis and vascular mimicry (Greish et al. 2017).

The complex biology of NSCLC, characterized by crosstalk between multiple signaling pathways, requires a multifaceted treatment approach. Combinations of tyrosine kinase inhibitors with chemotherapeutic agents, as recently demonstrated in the FLAURA-2 trial with osimertinib in combination with a platinum doublet, have shown promising enhancement of the antitumor response and delay of the resistance (Attili et al. 2023).

In previous studies, we obtained several models of combined nanoparticles with GFT and an aluminum phthalocyanine (APC) photosensitizer, including polylactide particles, liposomes, and micelles. *In vitro* experiments on the A549 lung cancer model with irradiation of particles with a laser in the near infrared range (about 730 nm) demonstrated the advantage of using combined nanoparticles compared to monotherapy (Nikolaeva et al. 2024; Sanarova et al. 2023).

The **goal of this study** was to investigate morphology, release and cytotoxic activity of micellar combination particles with GFT and a phthalocyanine photosensitizer in various tumor models.

Materials and Methods

Reagents

GFT (MSN Laboratories Private Limited), aluminum 1,8,15,22-tetrakis(phenylthio)-29H,31H-phthalocyanine chloride (Merck Life Science LLC), L-alpha-lecithin (Acros Organics), Kollidon 17PF (polyvinylpyrrolidone, PVP, BASF), P-188bio (BASF), chloroform (Vekton, Russia).

Preparation of micelles with GFT and APC

The chloroform solution of GFT, APC and L-alpha-lecithin was added portion wise to the aqueous solution of P188bio heated to ~60 °C and mixed/emulsified using a continuous flow of nitrogen gas. After completely removing chloroform, the solutions were dispersed and filtered using polyethersulfone filters with a decreasing pore diameter from 0.45 to 0.22 μm.

Determination of the particle size, polydispersity index (PDI), and charge

The average particle size and polydispersity index of the samples were determined by dynamic light scattering using a He-Ne laser (633 nm wavelength) at a scattering angle of 173, and the ζ-potential was established by the electrophoretic method. The measurements were carried out on a Zetasizer Nano-ZS 3600 analyzer (Malvern) using standard research protocols.

Determination of the efficiency of inclusion

The percent entrapment efficiency was measured indirectly by separating aqueous free drug in supernatant after high speed centrifugation (10,000 rpm). The amount of drug that was free was determined using UV spectrophotometry. GFT and APC were quantified using spectrophotometry at 338±3 and 717±3 nm wavelengths.

Microscopic examination

Samples of 10 μL were placed between glasses and analyzed on a Leica TCS SP 5 confocal microscope (Leica Microsystems GmbH) in transmitted light with excitation wavelength of 633 nm and recording at 650-770 nm. The resulting images were recorded using the LAS AF software. The analysis was performed using the equipment of the Center for Collective Use "New Materials and Technologies" of the Institute of Biochemical Physics with funding from the Ministry of Education and Science of the Russian Federation, project No. 122041400114-2.

In vitro release study

Release of the substances from the particles was studied *in vitro* by placing the samples into a dialysis insert (100 KD) of a 15 mL centrifuge tube (Jet Biofil) and immersing the tube in a phosphate-buffered saline solution (pH 7.4) containing 2% polysorbate 80. The tube was then placed in an orbital water bath and shaken at 37 C. The medium collected for analysis was replaced with fresh medium at specific intervals. Samples of 0.5 mL were taken at 1 h, 4 h, 12 and 24 h after the start of the experiment. GFT were quantified using spectrophotometry at 338±3. To confirm controlled photoinduced release, some samples were irradiated after 4 h with an LED source with a wavelength of 730 nm (according to the mode selected to study the cytotoxic activity).

Study of cytotoxic activity

Cytotoxic activity was studied on the cell lines of lung cancer NCI-H640, glioblastoma A 172, melanoma A 375, and breast cancer SK-BR-3 obtained from the Cell Line Bank of the Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation. The cell lines were cultured according to the conventional method (Susova et al. 2024) in RPMI-1640 medium containing 10% fetal calf serum, 10 mM HEPES (Sigma), 2 mM L-glutamine (Sigma), 40 ng/mL gentamicin (ICN, USA), amino acids, sodium pyruvate, and vitamin solution (PanEco), at 37 C in an atmosphere of 5% CO_2. The cells were maintained in the logarithmic growth phase by constant passage of the culture every 3-4 days. Versen solution was used to detach the adherent cultures from the plastic. MTT test was carried out according to the standard method (Abo Qoura et al. 2023) in the dose range of 0.1-20 μg/mL; the samples were irradiated 4 hours after addition of the drug with a LED source at 730 nm. Then the cells were incubated for 24 hours. The cytotoxicity of nanomaterials was studied per ISO SO 10993-5:2009 international test procedures for *in vitro* cytotoxicity. Cell viability was assessed by the ratio of the test sample absorbance to the control absorbance (average cells), expressed as a percentage.

Statistical analysis

Each experiment was conducted at least 3 times independently, and the results were presented as the mean ± standard deviation. The primary data were processed using one-way ANOVA analysis of variance using Microsoft Excel and GraphPad Prism 7.0 (GraphPad Software Inc.) software packages.

Results and Discussion

Characterization and study of micelle stability

Several experimental studies allowed us to select the composition and technology for obtaining a micellar model of combined particles with GFT and a photosensitizer containing poloxamer P188 and lecithin in a mass ratio of 10:1. Characteristics of the particles met the requirements for nanostructured dosage forms. Quality characteristics, such as inclusion efficiency, pH, particle size, ζ-potential, and PDI, were monitored for several months (Table 1) to determine the shelf life of this model. The samples were stored at +8 °C.

Table 1. Characteristics of the micellar model based on GFT and APC and the model stability study

Mass ratios of the substances		Quality characteristics	Shelf life, months			
			0	1	2	3
GFT: APC	1:2	Efficiency of GFT inclusion, %	87±4	86±2	86±4	85±3
		Efficiency of APC inclusion, %	97±3	96±4	98±5	97±6
GFT: P188	1:100	Particle size, nm	190±11	194±16	191±8	170±20
		ζ-potential, mV	-35±2.0	-34±1.8	-26±2.0	-27±2.5
GFT: lecitin	1:10	PDI	0.21±0.05	0.18±0.1	0.20±0.05	0.22±0.08
		pH	7.9±0.2	7.1±0.2	6.9±0.5	5.3±1.1

Note: GFT – gefitinib, APC – aluminum phthalocyanine, PDI – polydispersity index, P188 – poloxamer 188, results were presented as the mean ± standard deviation.

As shown in Table 1, no significant changes in most characteristics were observed during storage, but a sharp drop in the hydrogen index was noted 3 months after production, apparently due to peroxidation. Hence, the model composition was lyophilized for stability. A structure-forming agent PVP was added to form an easily soluble porous "tablet" during lyophilization. Also, PVP was dissolved directly in the micellar solution during preparation of the model composition.

None of the quality characteristics changed significantly after lyophilization. The particle size remained in the nanoscale; the ζ-potential was negative. PDI did not exceed 0.3, i.e. it had a fairly narrow distribution (Fig. 1).

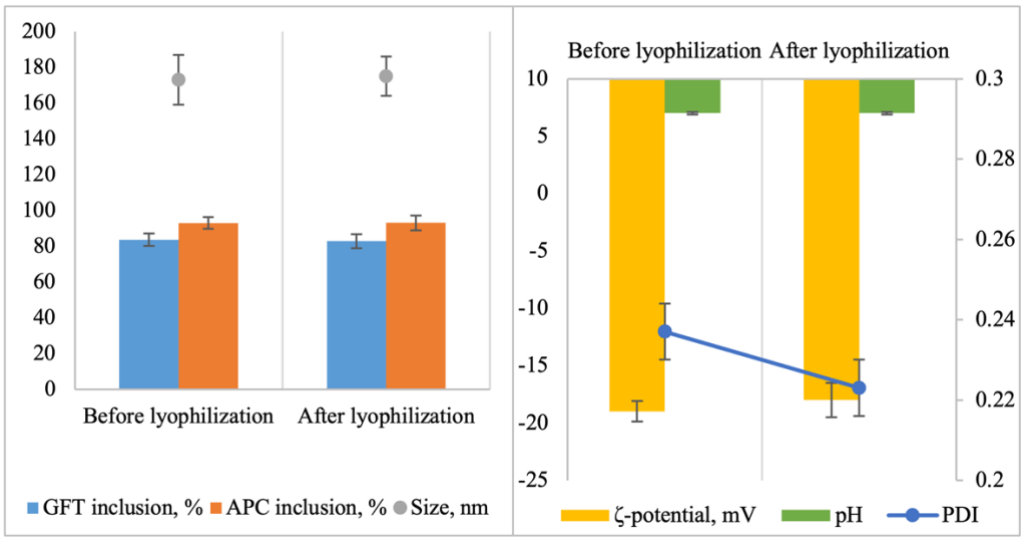


Figure 1. Changes in the main characteristics of the micellar model based on GFT and APC during lyophilization. *Note:* GFT – gefitinib, APC – aluminum phthalocyanine, PDI – polydispersity index, results were presented as the mean ± standard deviation.

Another essential characteristic of nanoparticles is their morphological structure, which determines the stable retention of active substances in the nanostructure and the release profile. Smaller particles have a high surface area to volume ratio, i.e. they have a larger area that will be exposed to the environment in which they are dissolved, and therefore they will degrade and release the drug faster (Singh 2009). Therefore, the samples were examined under a microscope before studying the kinetics of GFT and APC release from the selected model.

Electron microscopy of the morphology of the obtained nanoparticles showed that they have a spherical shape and nanoscale size (Fig. 2). Small size of the particles suggests that the release rate of the active substances will be quite high.

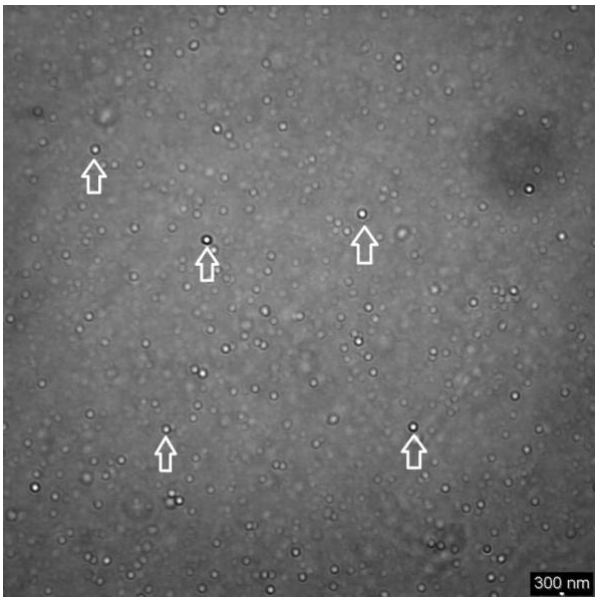


Figure 2. Micrograph of the micellar form based on GFT and APC.

In vitro release kinetics

At the next stage of the study, the release profile of the active substances was studied *in vitro* to prove the release modification, to predict the pharmacokinetics, and to confirm the controlled release. This analysis was conducted only for GFT, since APC was adsorbed on the dialysis insert.

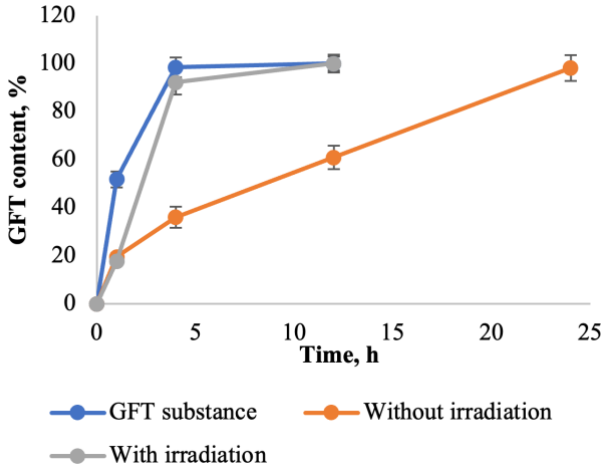


Figure 3. Study of the release kinetics of GFT substance and GFT from the micellar model *in vitro* without irradiation and with irradiation, 4 hours after the start of the experiment. *Note:* GFT – gefitinib, results were presented as the mean ± standard deviation.

The graph (Fig. 3) shows that the release of GFT without irradiation has a clear two-phase profile, with the "explosive" release reaching 36±4% observed for 4 hours. The two-phase profile is most likely associated with the release of GFT adsorbed on the outer shell of the nanoparticle ($y=3.7171x+12.42$, $r^2=0.9537$). Then, the polymer is destroyed and GFT is released with a uniform linear profile ($y=3.3152x+19.645$, $r^2=0.9929$). 50% of the encapsulated GFT is released from the micellar model (T1/2) within about 10.0 h.

Upon irradiation, the release profile changes and instant "explosive release" of GFT is observed with 92±5% level reached immediately after the exposure. Thus, the possibility of controlled, laser-induced release of GFT due to the presence of a photosensitizer in the model has been confirmed *in vitro*.

Antitumor effect in vitro

A study of cytotoxic activity was conducted on four tumor models in the dose range of 0.1-20.0 μg/mL for GFT (Table 2) to confirm the effectiveness and prospects of further research of the micelles with GFT and APC, as well as to identify the combined effect of GFT and photoirradiation.

Table 2. Study of cytotoxic activity of the micellar model based on GFT and APC in various tumor models

Product	IC_{50}, μg/mL			
	NCI-H640	A 172	A 375	SK-BR-3
Micelles based on GFT and APC	9.5±0.8	>20not installed	12.8±1.4	not installed
Micelles based on GFT and APC + irradiation	0.3±0.1	0.3±0.1	1.1±0.2	5.1±0.4
GFT substance	8.7±0.9	17.5±0.9	14.5±1.1	10.0±0.3

Note: GFT – gefitinib, APC – aluminum phthalocyanine, results were presented as the mean ± standard deviation.

As can be seen from the data in Table 2, the obtained model was effective in all the studied models. In two models (NCI-H640 and A 375), the activity without irradiation was comparable to the activity of the GFT substance, which simultaneously shows that this dosage form retains the activity of GFT, on the one hand, and that the photosensitizer is safe without photoexposure, on the other hand. The combined effect was confirmed in all models, being the most pronounced in the NCI-H640 lung cancer and A 172 glioblastoma model and suggesting potential for an expanded study of this formulation for the treatment of lung cancer and glioblastoma.

Over the past few decades, significant advances have been made in understanding the molecular basis of NSCLC, leading to the identification of driver gene alterations that have, in turn, changed the landscape of treatment for this disease through the introduction of tyrosine kinase inhibitors into chemotherapy regimens (Attili et al. 2023). However, first-generation inhibitors brought with them their own set of limitations, including the emergence of resistance mechanisms such as the p.T790M mutation (Attili et al. 2018).

Among the various strategies to overcome resistance, various nano- and microstructures as well as combination therapies have become widespread. For example, human albumin-based nanoparticles for delivery of both ibrutinib and hydroxychloroquine in a rat glioma model accumulate at the tumor site after intravenous injection, with improved overall survival observed in in vivo studies (Yang et al. 2023).

Our study is based on combination therapy using GFT and photodynamic therapy, but the main objective of the study is not combination therapy, but the creation of a targeted delivery system with stimulus-sensitive release, which we tried to achieve by introducing a photosensitizer into the micellar form.

In vitro data demonstrated the broad potential for further extended studies of these micelles *in vivo*, and release kinetics data provide the ability to predict pharmacokinetic parameters.

Conclusion

The micelles with GFT and a photosensitizer were obtained experimentally and their essential parameters were characterized. The *in vitro* experiments demonstrated modification of GFT release compared to the substance and the possibility of controlled release of the active substance under a photoirradiation stimulus. Release of GFT without irradiation has a clear two-phase profile, with the “explosive” release reaching 36% observed for 4 hours. After irradiation, the release rate immediately reaches 92%. The study of cytotoxic activity showed potential for in-depth research of micellar nanoparticles with GFT and a photosensitizer, especially concerning lung cancer and glioblastoma. Without photoirradiation, the activity of micelles was comparable to the activity of GFT, and with photoirradiation, cytotoxicity increased by 2-58 times.

Additional Information

Conflict of interest

The authors have declared that no competing interests exist.

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The authors have no support to report.

Data availability

All of the data that support the findings of this study are available in the main text

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