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Luminescent diagnostics of skin defects in the near-infrared range

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Abstract. Photodynamic therapy becomes a widely spread method due to cancer growth in the world. However, to detect tumors at early stages, it is necessary to carry out diagnostic measures in a timely manner. Our aim was to test the developed pharmaceutical composition, which can be used for external application in early fluorescent diagnostics even in the absence of visual changes, as well as for therapy effectiveness control. Pharmacokinetic studies on laboratory animals and volunteers were carried out. The results have shown that the dipotassium salt of Yb^{3+}-dimethoxyhematoporphyrin IX, which is highly soluble in water and stable in storage, is a promising marker for earlier diagnostics of tumors and can be used in dermatology, dentistry, gynecology, cosmetology, ear, nose, and throat diseases, veterinary, and in other areas of medicine. [DOI: 10.1117/1.JBO.22.9.098001]

Keywords: luminescent diagnostics; near-infrared range; tumors; ytterbium complexes; porphyrins; pharmaceutical composition.
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1 Introduction

In connection with cancer growth in the world, the photodynamic therapy using porphyrin and chlorine photosensitizers has become a widespread method. However, a timely diagnostic measure is necessary to detect tumors at an early stage. Proceeding from the several porphyrin compounds, the ytterbium porphyrin complexes of predominantly natural structure that have been previously proposed for malignant tumor diagnostics in the form of aqueous solutions or liposomes fit for this purpose.[1]

The most promising biomedical diagnostic research is the near-infrared (NIR) spectral range (700 to 1100 nm) because of the greater depth of photon penetration through biological tissues and minimal autofluorescence in this spectral range. Currently, the intensive research of nanoscale nonphototoxic photosensitizers based on lanthanide porphyrins complexes are carried out. Porphyrins complexes with erbium, neodymium, and ytterbium have 4f-luminescence in the NIR part of spectrum. The 4f-luminescence occurs due to intramolecular energy transfer from triplet porphyrin state located in the range of 12,500 to 13, 500 cm^{-1} to lower resonance levels of Er^{3+}, Nd^{3+}, and Yb^{3+} (6450, 11,500, and 10, 200 cm^{-1}, respectively; Fig. 1).[2,3]

Luminescence of Yb-ion itself is rather weak, but it is greatly enhanced in complexes with porphyrins due to the energy transfer from excited macrocycle to Yb^{3+} ion.[4,5]

The main photophysical properties of the ytterbium complex of 2,4-dimethoxyhematoporphyrin IX were investigated in the work process: electronic absorption spectra, lifetime and intensity of luminescence, and relative 4f-luminescence quantum yield. These properties were studied in various solvents [water, dimethyl sulfoxide (DMSO), etc.]. The absorption spectra of the initial porphyrin consist of an intensive fundamental Soret band 370 to 420 nm (C-band) and four Q-bands in 500- to 650-nm region. When complexation takes place, the Soret band becomes more intense and undergoes a slight bathochromic shift (8 to 12 nm). In addition, two bands are observed in 550- to 650-nm range (Fig. 2).

The spectral and kinetic luminescence characteristics of some metal complex samples are shown in Figs. 3 and 4, and one can see the characteristic for the rare earth ions luminescence line is narrow and quite bright. For Yb^{3+}-ion, it is located in the 975- to 985-nm IR range where the luminescence of biological tissues is practically absent.

Even before Yb-porphyrin complexes have been offered as diagnostic agents, lanthanide salts were used to treat various diseases. Zeng et al.[6] have studied absorption, distribution, and metabolism of salts in body. Thus, after intravenous injection, the highest content of ^{169}Yb was observed in endoplasmic reticulum and mitochondria and the least—in cell nucleus. Rare earth elements penetrate into liver quickly and are easily removed from it mainly with bile. ^{169}Yb is widely used as a diagnostic agent for scintigraphy of internal organs, as well as in cancer treatment of brain, liver, lungs, bones, heart, throat, and pelvis. Doses of radioactive isotopes applied for treatment are safe. When a drug based on ^{169}Yb in complex with diethylenetriaminepentaacetic acid is injected into the brain; it is completely removed from central nervous system tissues in 14 days later, and no anomalous phenomena in tissues are observed. Half-life of ^{169}Yb isotope is 31.8 days.

Also, the antimicrobial activity of Yb^{3+} ion, 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin free base and its ytterbium

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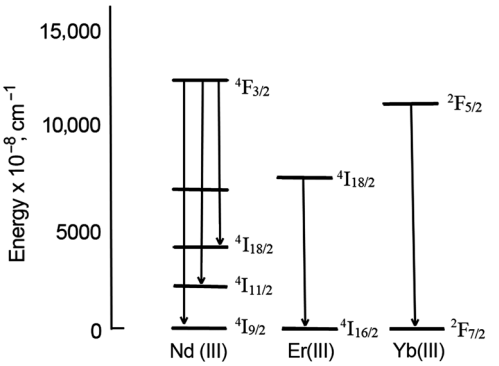

Fig. 1 Diagram of energy levels and luminescence spectra of Yb^{3+}, Er^{3+}, and Nd^{3+} ions.

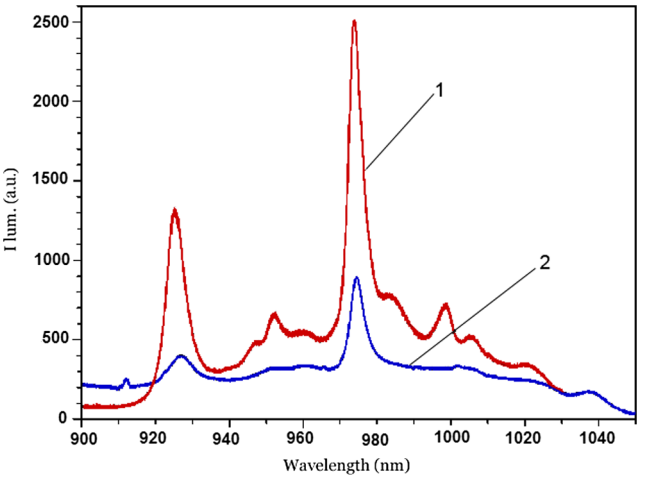

Fig. 3 Luminescence spectrum (in DMSO): 1—Yb-complex of 5,10,15,20-tetra[1-N-(*p*-fluorophenyl)-3-(*o*-chlorophenyl)pyrazol-4-yl] porphyrin and 2—Yb-complex of 2,4-dimethoxyhematoporphyrin IX.

complex was studied against *Staphylococcus aureus* using the stopped-flow microcalorimetry, wherein the Yb-complex showed the highest activity (as presumably synergetic effect of Yb^{3+} and porphyrin base) with $IC_{50} = 273$ mg/l.[7] Further studies were carried out on two cationic Yb^{3+}-complexes: 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin and 5,10,15,20-tetrakis(4-tolyl)porphyrin.[8] Their antibacterial activity was tested at cellular and intracellular levels against *Escherichia coli*. The binding character of Yb-complexes with DNA molecule was studied at the intracellular level by spectroscopy, and it was concluded that Yb-complex of 5,10,15,20-tetrakis(4-methoxyphenyl) porphyrin, which showed the higher activity, is a promising agent for an intercalating antimicrobial therapy.

At the end of the last century, we, together with German scientists, carried out studies on laboratory animals with Yb-porphyrin complexes as diagnostic markers, in which radioactive ^{169}Yb was used.[9] A comparative study of accumulation in healthy and malignant tissues of experimental animals was carried out on four Yb-complexes: 5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin, 5,10,15,20-tetrasulfophenylporphyrin, 5-phenyl-10,15,20-tris(4-sulfophenyl)porphyrin, and 2,4-dimethoxyhematoporphyrin IX dinatrium salt. It turned out that porphyrins having their composition both hydrophobic and hydrophilic residues, such as Yb-2,4-dimethoxyhematoporphyrin IX and unsymmetrical water-soluble 5-phenyl-10,15,20-tris(4-sulfophenyl)porphyrin, mainly accumulate in tumors; this result corresponds well to the published data.[10]

The composite nanoparticles on base of gold–silver nanocages and Yb-2,4-dimethoxyhematoporphyrin IX, combining plasmon resonance in the lowest biological tissues absorption region, porphyrin fluorescence in the visible spectrum region, and luminescence of Yb^{3+}-ion in the NIR range, have been also created.[11] Dipotassium salt of Yb-2,4-dimethoxyhematoporphyrin IX was first used for a functionalization of composite nanoparticles consisting of Au–Ag-nanocages covered with mesoporous silicon dioxide shell. A general scheme of composite nanoparticle synthesis consists of three main stages. At the first stage, silver nanocubes of 30 to 60 nm were synthesized, which are used as templates for producing gold–silver nanocages. At the second stage, a porous silicon dioxide nanoshell of controlled thickness (about 40 nm) is formed on the

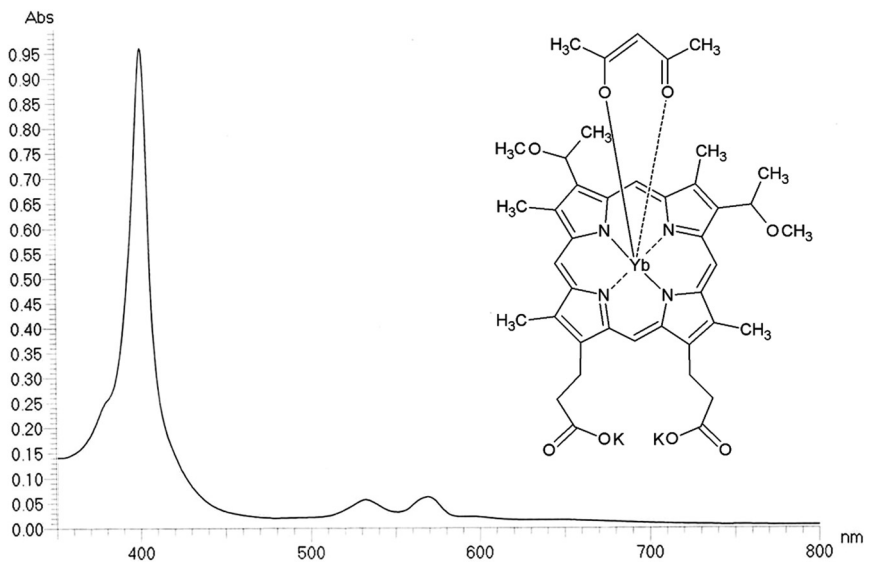

Fig. 2 Electronic absorption spectrum of dipotassium salt of ytterbium 2,4-dimethoxyhematoporphyrin IX complex (40% DMSO solution, complex concentration—10^{-5} M).

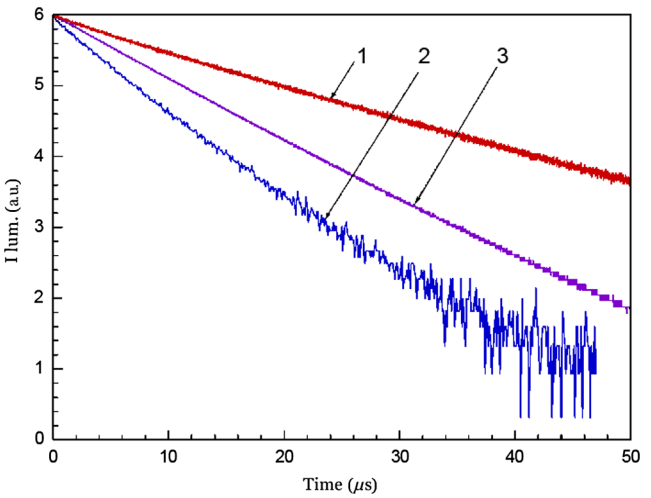

Fig. 4 Luminescence decay curves (in DMSO): 1—Yb-complex of 5,10,15,20-tetra[1-N-(*p*-fluorophenyl)-3-(*o*-chlorophenyl)pyrazol-4-yl] porphyrin; 2—Yb-complex of 5,10,15,20-tetra(*p*-carboxyphenyl)porphyrin; and 3—Yb-complex of 2,4-dimethoxyhematoporphyrin IX.

Au–Ag-nanocages. At the third stage, the obtained particles are aminated, functionalized by Yb-2,4-dimethoxyhematoporphyrin IX molecules, and stabilized by gum arabic.

Such nanostructures combine several important and promising properties—easily customizable cell plasmon resonance in 650- to 950-nm range,[12] convenience of porous silicon dioxide shell functionalization, and the existence of application experience in experimental oncology for Yb-2,4-dimethoxyhematoporphyrin IX drug with IR luminescence bands.[13]

Disadvantages of these nanocomposite particles are: (1) a laborious multistep chemical synthesis in the first place; (2) the construction of multifunctional nanoparticles (based on gold–silver nano-cages, coated with silicon dioxide and functionalized by Yb-2,4-dimethoxyhematoporphyrin IX) requires expensive reagents; and (3) a long time of accumulation in malignant tumors that is not less than 24 h.[14]

Yb^{3+}-ion luminescence in its complexes, including porphyrins, is known to be quenched by OH-oscillators vibrations; therefore, in 100% aqueous solutions, it has lower quantum yield values and luminescence lifetime. CH-oscillators possess the similar action, but in a less degree. All factors above indicate that to increase diagnostic potential of Yb-complexes, it is necessary as far as possible to isolate them from the quenching effect of water environment.

In this case, DMSO can be a promising solvent for Yb-2,4-dimethoxyhematoporphyrin IX and has unique biomedical and pharmacological properties: it penetrates through biological membranes, improves transport properties of drugs, and also stimulates the immune system.[15]

Figure 6 shows the emission spectra of Yb-2,4-dimethoxyhematoporphyrin IX luminescence in an aqueous solution at different DMSO concentrations. The nature of the specific spectrum reflects a polarity of environment in which ytterbium ion resides. Under conditions of lower polarity (solutions with growing concentration of DMSO), emission maxima are shifted to longer wavelengths of spectrum (so-called solvatochromism phenomenon).

From Fig. 5, one can see that the luminescence intensity significantly grows with an increase in the DMSO concentrations (more than 10 times in conversion from a purely aqueous

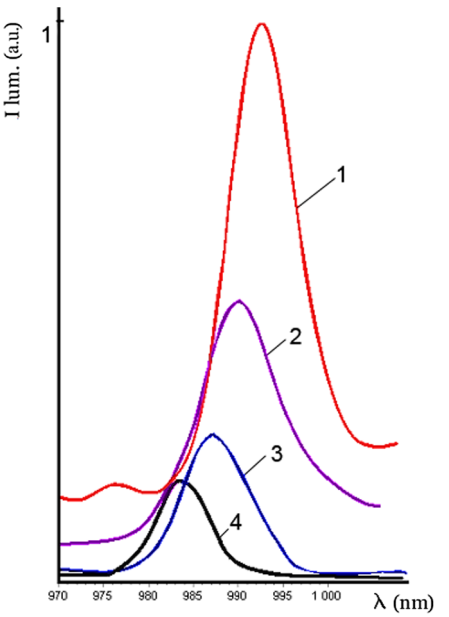

Fig. 5 Luminescence emission spectra of Yb-2,4-dimethoxyhematoporphyrin IX in aqueous solutions with different DMSO concentrations: 1–100% DMSO, 2–50% DMSO, 3–20% DMSO, and 4—a purely aqueous solution.

solution of Yb-2,4-dimethoxyhematoporphyrin IX to its 100% solution in DMSO), and the emission spectrum maximum shifts with almost 10 nm.

Changes in Yb-2,4-dimethoxyhematoporphyrin IX luminescence lifetime depending on DMSO concentration are shown in Fig. 6. For 100% solution of DMSO, the luminescence lifetime is about 22 μs, which is a significant value. Yb-2,4-dimethoxyhematoporphyrin IX substance in 20 to 30% DMSO solution that is allowed in medicine presents the practical interest for intravenous injections. For such DMSO concentrations, the luminescence lifetime is about 5 to 10 μs.[15]

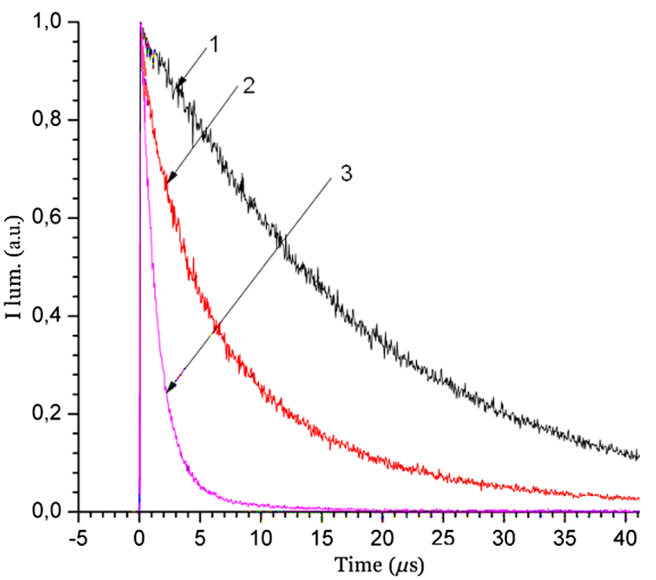

Fig. 6 Dependence of Yb-2,4-dimethoxyhematoporphyrin IX luminescence lifetime from DMSO concentrations: 1–100% DMSO, 2–20% DMSO, and 3—purely aqueous solution.

Table 1 Components of pharmaceutical compositions

No.	Yb-2,4-dimethoxy-hematoporphyrin IX (mg)	Solvent	Base	Additives	Mass percentage (w/w)
1	5	0.5 ml DMSO	9.5 ml Cremophor	—	0.05
2	6	0.5 ml $H_2O_{distilled}$	5.5 g CALGEL	1 mg N-methylglucosamine	0.1
3	5	0.5 ml $H_2O_{distilled}$	9.5 ml Cremophor	3 mg N-methyl-glucosamine, 2 drops glycerol	0.05
4	5	0.5 ml $H_2O_{distilled}$	9.0 ml Cremophor, 1 ml TIZOL	—	0.05
5	5	0.5 ml $H_2O_{distilled}$	9.5 ml TIZOL	—	0.05

As shown in Fig. 6, the luminescence lifetime increases to 22 μs in the conversion from a purely aqueous solution of Yb--2,4-dimethoxyhematoporphyrin IX to its 100% DMSO solution.

Due to the fact that ytterbium ion fluoresces in the NIR region (900 to 1050 nm) where a background fluorescence of own body tissues is practically absent, one can obtain information about the Yb-complexes accumulation in pathologically changed tissues both benign and malignant types, using fiber-laser spectrofluorimetry techniques. The heavy metal insertion in a porphyrin macrocycle harshly decreases a singlet oxygen yield[16] and hence minimizes the occurrence of adverse reactions in a body that is also caused by the low Yb-complexes toxicity. The porphyrin presence in pharmaceutical composition provides the metal complex preferential accumulation in pathologically altered tissues and mucous membranes.

2 Results and Discussion

Our aim was to test a pharmaceutical composition, which can be used for external application in early fluorescent diagnostics of pathologically changed skin and mucous membranes including malignant tumors, even in the absence of visual changes, as well as help to control the efficiency of therapy.

For a medical use purpose, amphiphilic pharmaceutical compositions based on Yb-2,4-dimethoxyhematoporphyrin IX with various gels (TIZOL, CALGEL, Cremophor, etc.) and additives (glycerol, N-methylglucosamine), as well as solutions based on DMSO (all components are approved for clinical use) were discovered.[17] The last solvent, in addition to a good skin penetration, also enhances the intensity and lifetime of luminescence.[15] Pharmaceutical compositions were used both for skin and mucous membranes application. Because of almost absent light toxicity of ytterbium porphyrin complexes, compositions applied to skin and mucous membranes do not have a negative influence on a living body in the form of side reactions, which are characteristic for photosensitizers.

Table 1 shows the components of developed compositions based on dipotassium salt of Yb-2,4-dimethoxyhematoporphyrin IX. Compositions 1, 3, 4, and 5 are used for skin application, 2—for pathologically changed mucous membranes application.

Along with acetylacetonate (acac), Yb-2,4-dimethoxyhematoporphyrin IX complex another low-toxic composition was created in the form of nanoparticles based on Yb(acac)-protoporphyrin IX dimethyl ester, which was placed in polymer shell based on Lexan, and an additional coordination complex trioctylphosphine oxide (TOPO) was inserted in complex structure, and nonionic detergent polyethyleneglycol ($n = 9, 10$) was also added in organic phase in addition to TOPO. Yb-complex conclusion in nanoparticles composition increases the stability of the complex due to an isolation from influence of aqueous medium, which quenches the Yb^{3+}-ion luminescence, and it leads to the diagnostic potential increase of Yb(acac)-protoporphyrin IX dimethyl ester. This composition possesses high lifetime values (for nanoparticles of 100 to 200 nm lifetime were

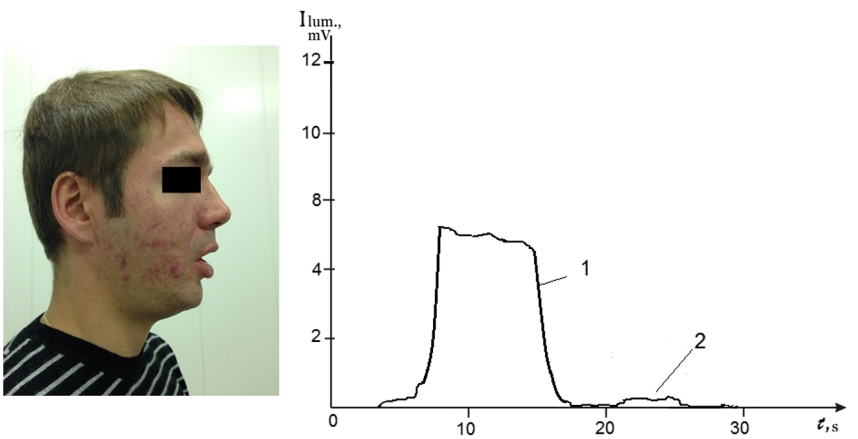

Fig. 7 Integrated luminescence intensity from papules surface and healthy skin (diagnosis Rosacea).

17 μs) and luminescence intensity in the NIR range, as well as good solubility in water, thereby allows one to reduce a drug dose and to provide a lower price for diagnostic procedures through use of available natural porphyrin.[14,18]

Previous experiments on animals were carried out with Yb-2,4-dimethoxyhematoporphyrin IX injection into the tail vein of mice line Balb/c with grafted Ehrlich carcinoma. Diagnostics (Yb-complex luminescence intensity measurement) was carried out *ex vivo* after 20 h of drug injection. The significant accumulation was shown in tumor tissues in comparison with normal tissues. These data allow one to solve the following tasks: (a) simplify a diagnostics process for pathologically changed skin and mucous membranes, which allows a doctor to carry out more in-depth studies when needed, including aiming biopsy for histological examinations; (b) facilitate a treatment monitoring due to the indicative decrease of luminescence, which confirms the effectiveness of treatment; (c) help to identify an occurrence of pathological processes in places of their localization that cannot be determined visually; and (d) significantly reduce an optimum time of drug accumulation in various tumors to values less than 1 h, which is very important for diagnostic tests in clinic on real patients.

The research results are shown in Figs. 7–10.

The luminescence intensity and, accordingly, the Yb-2,4-dimethoxyhematoporphyrin IX accumulation in various rash elements and rash healthy skin areas were investigated (Figs. 7 and 8) on a male patient, 31 years old, with diagnosis of Rosacea, papulo-pustules form. Herewith the luminescence intensity increase, drug accumulation was observed in inflammatory elements.

Similarly, the luminescence intensity and the complex accumulation were investigated (Fig. 9) on a male patient, 21 years old, with diagnosis Acne vulgaris. The luminescence intensity increase was also observed in inflammatory elements.

The same investigations were carried out (Fig. 10) on a female patient, 55 years old, with diagnosis vulvovaginal atrophy.

It should be noted that the gradual decrease of Yb-2,4-dimethoxyhematoporphyrin IX luminescence intensity to values typical for healthy tissues was observed for all patients during a treatment. Interesting, that some visually not changed skin areas revealed the increased luminescence in places, where fresh inflammatory elements have been appeared later (after 3 to 4 days).

Also, it should be noted that the developed pharmaceutical compositions can be used for theranostics purposes (simultaneously consistent use of diagnostics and therapy). This is explained by the fact that the residual fluorescence of Yb-2,4-dimethoxyhematoporphyrin IX base porphyrin remains in the red spectrum region.[18] A pharmaceutical composition in addition to main quantity of ytterbium porphyrin complex also

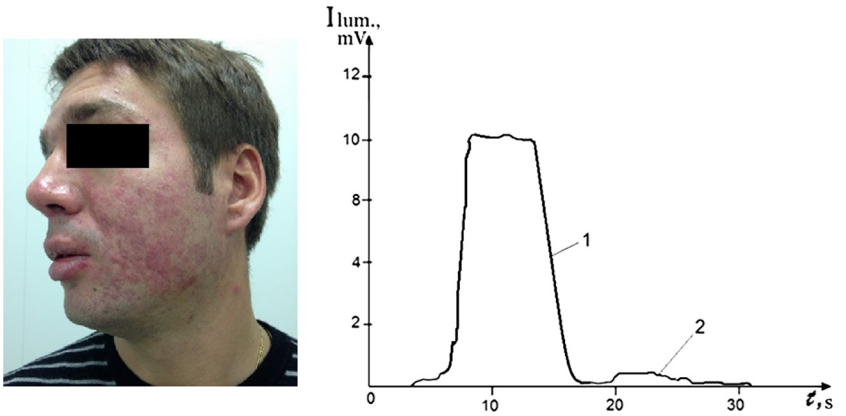

Fig. 8 Integrated luminescence intensity from pustules surface and healthy skin (diagnosis Rosacea).

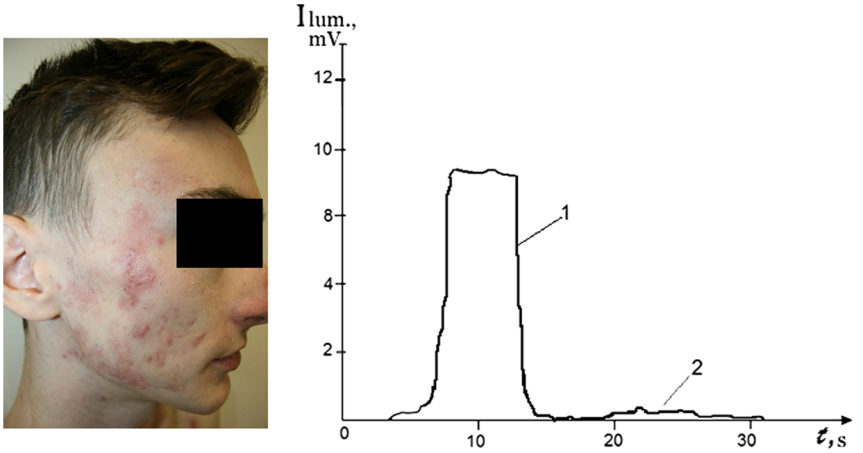

Fig. 9 Integrated luminescence intensity from pustules surface and healthy skin (diagnosis Acne vulgaris).

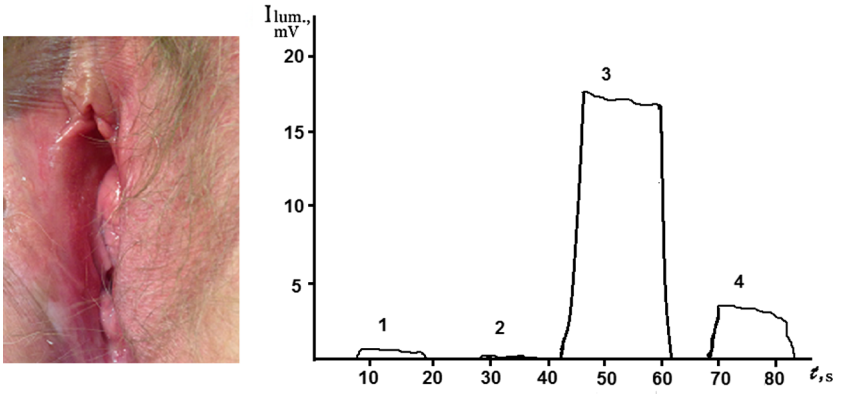

Fig. 10 Integrated luminescence intensity in the study of mucous membranes lesions depending on time signal accumulation when applying CALGEL composition (diagnosis vulvovaginal atrophy).

contains some amount of metal-free porphyrin, which under therapeutic laser irradiation at the wavelength of 630 nm generates singlet oxygen—a main agent for the photodynamic tumors therapy. This fact is confirmed by the presence of bands at wavelengths of 630 and 700 nm in Yb-2,4-dimethoxyhematoporphyrin IX emission spectrum. However, in this case, the quantum yield of a singlet oxygen generation is low and very large doses of therapeutic laser radiation may be required for photodynamic therapy procedures.

3 Conclusion

Ytterbium porphyrins complexes with fiber-laser spectrofluorimetry techniques use may be applied as diagnostic markers in pathologically changed tissues of both benign and malignant type. Under laser irradiation, ytterbium ion fluoresces in the NIR range where a background luminescence of body tissues is practically absent, and besides, these metal complexes have a low phototoxicity. The designed pharmaceutical compositions in the form of gels may be used for diagnostics and treatment monitoring of skin and mucous membranes diseases of both proliferative and inflammatory nature.

Disclosures

Before and during the experiments, animals were kept in vivarium following the rules of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes." Animal studies were performed in accordance with the Guide for the Use of Laboratory Animals. The gel in the pharmaceutical composition is approved for external use. Declaration of Conformity of the gel "FLUROSCAN" was issued by the Customs Union (EAC), No. POOC RU.0001.510608. The patent of Russian Federation No. 2617045 "Pharmaceutical composition for fluorescent diagnostics of pathological changes in skin and mucous membranes" was received. Pharmacokinetic studies were carried out on volunteers in State Scientific Center of Laser medicine FMBA. The authors have no relevant financial interests in this article and no potential conflicts of interest to disclose.

Acknowledgments

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