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Abstract

Photodynamic therapy implies a combined use of a photosensitizing medicament and low-intensity light to cause selective damage to the target tissue—tumor. As potential medicament, we use $Ru(II)(dcbpy)_2Cl_2$ complex, and in order to achieve better photosensitization properties, the Ru complex was attached to the

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Keywords (separated by '-')	Photodynamic therapy - Light controlled drug release - Metallo-drug delivery
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Light controllable TiO_2-Ru nanocomposite system encapsulated in phospholipid unilamellar vesicles for anti-cancer photodynamic therapy

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Abstract Photodynamic therapy implies a combined use of a photosensitizing medicament and low-intensity light to cause selective damage to the target tissue—tumor. As potential medicament, we use $Ru(II)(dcbpy)_2Cl_2$ complex, and in order to achieve better photosensitization properties, the Ru complex was attached to the nano carrier—TiO_2 nanoparticles. Additionally, this nanocomposite system was encapsulated in the phospholipid vesicles, which could be classified as small unilamellar vesicles, based on the technique of production. The complex-release tests were performed under light illumination, at pH 5, characteristic for tumor cells` interior and compared with the release pattern at pH 7, characteristic for the serum, i.e. physiological solution.

Keywords Photodynamic therapy · Light controlled drug release · Metallo-drug delivery

1 Introduction

Photodynamic therapy represents an alternative tumor-ablative, function-sparing and cost-effective oncologic approach (Dougherty et al. 1998). Usually, medicaments are delivered to diseased tissues by different types of carriers, which have the purpose to preserve medicament in the circulation and to minimize toxic side-effects (Hu et al. 2015). The light-induced medicament activation is based on the intrinsic optical properties of a medicament carrier and a medicament itself. In most cases, a nanoparticle (NP)-based medicament carrier or a

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medicament itself act as photosensitizers (PSs), by triggering free radical reactions in cells leading eventually to the cell death. As carriers, inorganic NPs have great potency for use, as they can act as PSs due to their distinctive optical absorption properties, transparency of the matrix to light absorption and chemical inertness. They can be easily attached to therapeutic medicament in the form of nanocomposite system (NCS), which can exhibit greater cytotoxicity (Nešić et al. 2017) and higher therapeutic effectiveness for cancer than the corresponding free drugs (Wang et al. 2015; Chen et al. 2011).

We used TiO_2 NPs as carrier because of their availability, minimal dark cytotoxicity at low concentrations and brief exposure (Hou et al. 2015). TiO_2 NPs also showed great chemical stability and minimal impact to the environment (Zhang et al. 2012). The photocatalytic killing effect to the tumor cells of the TiO_2 NPs had been confirmed, via the caspase-dependent apoptosis (Zhang et al. 2014).

The surface of TiO_2 can be modified and thus specifically designed for the function of drug carriers (Wang et al. 2015). As the second component of the system, $Ru(II)(dcbpy)_2Cl_2$ complex, that belongs to the second generation of metallo-drugs, can be easily attached to the TiO_2 surface via carboxyl groups (Savić et al. 2012), while the central metal ion remains free for the interaction with biomolecules. In the field of the development of anticancer drugs, it was proved that some Ru complexes could promote the intracellular formation of free radical species upon irradiation, thus photosensitizing capacity for PDT had been confirmed (Levina et al. 2009). The photoactive properties of the $Ru(II)(dcbpy)_2Cl_2$ complex had been confirmed in the nanocrystalline TiO_2-based solar cell (Nazeeruddin et al. 1999). Moreover, in our previous work we showed that this NCS which is conjugate of $Ru(II)(dcbpy)_2Cl_2$ complex and TiO_2 NPs, has cytotoxic effect on melanoma cells (Nešić et al. 2017), and that the complex release kinetics can be influenced by light of various wavelengths. Additionally, the system demonstrated light-tunable properties, regarding the cell cytotoxicity: the melanoma cell cytotoxicity increased upon UV light illumination, whereas visible light reduced the number of dead melanoma cells (Nešić et al. 2017).

In spite of initial success, there are several issues which are addressed in the present study. Firstly, the stability of the system in physiological conditions (for instance, stability in human sera during drug administration and transportation) is questionable, because there is the risk from the NCSs aggregation. Second question is whether is possible to affect the complex release properties when the system is encapsulated in the phospholipid vesicles, which should additionally prevent the complex leakage from the NCS, and potentially increase the cellular uptake of the NCS by tumor cells. To address the first issue, we have stabilized colloidal dispersion of TiO_2 NPs in physiological conditions, pH 7, by NP surface modification. Then, NCS was formed as described in our previous work (Nešić et al. 2016, 2017), and binding of Ru-complex to the surface of the TiO_2 NPs was confirmed by Fourier transform infrared (FTIR) spectroscopy. Secondly, NCS was encapsulated in the small unilamellar vesicules (SUVs), and for both systems, encapsulated and non-encapsulated, visible light photo responsive properties for potential controlled drug delivery were examined.

2 Materials and methods

2.1 Synthesis and characterization of transitional metal complex and NCS

Complex cis-dichlorobis(2,2′-bipyridyl-4,4′-dicarboxylic acid) ruthenium(II), was synthesized using the procedure described earlier (Nazeeruddin et al. 1999) and stored in the dark

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at −20 °C. Synthesized Ru(II) complex was characterized by UV–Vis spectrophotometry and by FTIR spectroscopy. Colloidal TiO_2 NPs pH 7 (d − 5 nm) were synthesized by the slightly modified method of Rajh et al. (2004).

Ethanol solution of complex was added to aqueous suspensions of TiO_2 NPs pH 7, estimating that the fraction of exposed Ti atoms on surface of TiO_2 NPs is 30% (Lin et al. 1997). The reaction mixture was incubated overnight in the dark at room temperature for the preparation of NCS. The stability of the NCS was checked by additional incubation with Bovine Serum Albumin at physiological conditions (phosphate buffer saline, pH 7), that was followed by ultra-centrifugation with extreme G force of 40,000× g, for 1 h (Beckman J2–21).

A commercial UV–Vis spectrometer (Perkin Elmer Lambda 35) was used for acquisition of the spectra of complex at room temperature. FTIR spectra of the synthesized complex and complex-TiO_2 NCS were recorded using Nicolet 380 FTIR spectrophotometer (Thermo Electron Corporation) in attenuated total reflection (ATR) mode. For each spectrum, 64 scans were performed, with a resolution of cm^{-1}, in the range of 400–4000 cm^{-1}.

2.2 Isolation of phospholipids and formation of SUVs

For isolation and preparation of SUVs we used egg yolk phospholipids. The phospholipids were extracted by the procedure for total lipid extraction from the egg yolk (Furusawa et al. 1999), and the phospholipids composition was confirmed by thin layer chromatography by the procedure described earlier (Davidson et al. 1998). SUVs were prepared by the procedure that had been used for encapsulation of TiO_2 NPs (Alonso et al. 1982), and the literature suggests that SUVs had diameter of around 30 nm.

2.3 Encapsulation of NCS in SUVs

The specific amount of formed NCS was additionally incubated overnight, with SUVs in 1:1 mass proportion, in dark and at room temperature. The SUV-NCS system that was formed was cross-examined, under identical conditions, as the free NCS.

2.4 Light stimuli complex release studies

To investigate the influence of red and UV light on the rate of complex release from NPs, we performed two separate tests, with the identical principle—samples consisting of 750 µL NCS solution or SUVs-NCS (750 µL + 750 µL) was placed into the dialysis cassette (Thermo Scientific Dialysis cassette, 7000 MWCO, 0.5–5 mL capacity). Then the cassettes were transferred into the beakers with 150 mL of phosphate buffer saline (PBS) solution. For these tests, we used PBS solutions with two pH level, pH 7 and pH 5. The samples were stirred in dark at room temperature, and for illumination we have applied the red light (the intensity of 80 µW) and UV light (120 µW). The source of red light was a CW He–Ne laser (Coherent, 2 mW, 632.8 nm) whereas we used UV light from UVC Hg-lamp (Philips, 25 W, 254 nm). The light intensities were measured with laser power meter NOVA II (Ophir) with UV enhanced silicon photodiode sensor PD300-UV with installed filter (CW power up to 300 mW). At the indicated time intervals, 500 µL of samples were removed from outer medium and replaced with equal volumes of PBS solution, and the aliquots were analyzed by measuring absorbance at 310 nm, which was specific for used complex. Concentration of drug released from composite matrix was calculated and plotted

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against the time. Non-irradiated NCS complex release profile served as control, for both tests.

3 Results and discussion

3.1 Characterization of transitional metal complex and complex-TiO_2 NCS

The transitional complex, Ru(II)$(dcbpy)_2Cl_2$, was selected because of its binding potential for the surface of TiO_2. This complex contains ligand with carboxyl groups, which has strong affinity for the TiO_2 NPs surface. To establish the end point of synthesis of the complex and binding of ligand to the $RuCl_3$ salts, we measured the relative intensities of the absorption maxima in 9 mM ethanol solution of the complex. The UV–Vis spectra of complex is shown in the Fig. 1a, and the absorption maxima measured (I) correspond well to the data from literature (II), (Nazeeruddin et al. 1999), and are presented in Table 1.

Four carboxyl groups on the Ru-complex can coordinate the Ti atoms on the surface of TiO_2 NPs in three modes forming bidentate, unidentate and bridging carboxylates (Nazeeruddin et al. 2003). In our previous work, we carried out surface modification of colloidal TiO_2 NPs (pH 3) with Ru complexes, discussed those binding options and concluded that in this system unidentate binding structure prevails (Nešić et al. 2017). Since the NCSs applied in this work were prepared by modified synthetic approach taking care about final pH of dispersion (pH 7) and particles stability in physiological conditions, a slightly different interaction between colloidal TiO_2 NPs (pH 7) and Ru(II) complexes could be expected.

The ATR-FTIR spectra of powdered samples of Ru(II) complex and NCS (colloidal TiO_2 NPs (pH 7) surface modified by Ru(II) complex) are shown in Fig. 1b. In FTIR spectrum of Ru(II) complex peaks characteristic for stretching vibrations of carboxylic groups ν_s(–COOH) at ~ 1700 and ~ 1540 cm^{-1} were clearly observed as well as peaks assigned to stretching vibrations of ν(CO) at 1215 and 1130 cm^{-1}. Finally, strong peak at 1014 cm^{-1} could be assigned to the deformation vibrations of carboxyl groups δ(O–CO–H). In the FTIR spectrum of NCS all previously mentioned peaks are of reduced intensities indicating the possible interaction of Ru(II) complexes and surface of colloidal TiO_2 NPs (pH 7). More precisely, appearance of new peaks at 1590 and 1365 cm^{-1} in FTIR spectrum of NCS and a significant decrease in the intensity of a peak assigned to stretching vibration of carboxylic groups at 1700 cm^{-1}, implied to the contribution of unidentate and bridging binding of Ru(II) complexes to an colloidal TiO_2 NPs (pH 7).

3.2 Complex release tests

In order to investigate the influence of light on the kinetics of complex release, as possible ways to preserve the medicament before it reaches the target tissue, and the possibilities to control the release rates, we performed separate tests, for two type of samples—SUVs encapsulated NCS and free NCS, in which we irradiated samples with red (632.8 nm) and UVC (254 nm) light. Along with illumination experiments, control experiments were performed, i.e. the kinetics of a drug release in the dark. Additionally, two pH values of dialysis solutions were used for the study of complex release properties of NCS: PBS with pH 5, and PBS medium of pH 7. The SUV-NCS sample was dialysed only against the PBS medium of pH 7, since the liposomal encapsulation should prevent leaking of the model drug—complex before it reaches the target tissue, i.e. in the serum/circulation. All the

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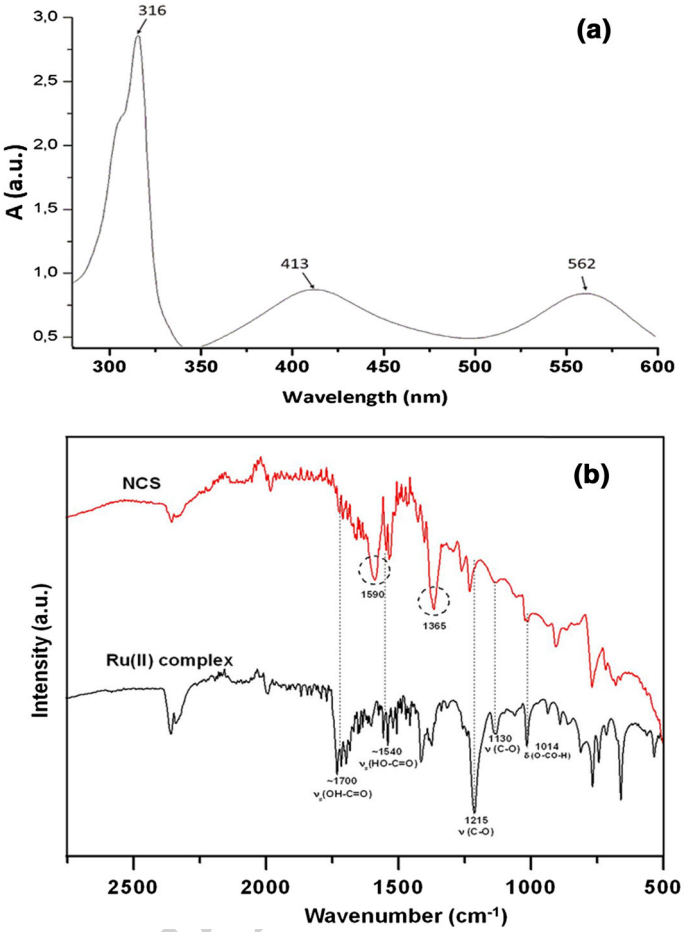

Fig. 1 UV-Vis spectra of complex Ru(II)$(dcbpy)_2Cl_2$ (**a**). The FTIR spectrum of complex and NCS (**b**)

Table 1 Spectral Data of the complex Ru(II)$(dcbpy)_2Cl_2$ in ethanol (concentration 9 mM)

	Wavelengths of the excitation at three characteristic absorption maxima, λ_{max} (nm) (absorption maxima ratio)		
I	562 (1.00)	413 (1.04)	316 (3.40)
II	565 (1.00)	414 (1.05)	316 (3.33)

studies were carried out in triplicate. The schematic diagram of experimental setup for the sample illumination with red light of NCS in pH 7 and pH 5 medium, is shown in Fig. 2, and obtained release curves from release tests are shown in Fig. 3.

All nine drug release profiles suggest a biphasic release process, with an initial burst phase followed by a lag period before the onset of degradation phase. At pH 7, the results obtained with red light illumination are as expected—the complex release rate is lower upon illumination of the NCS with red light. On the contrary, UV seems not to have any

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influence on the complex release rate. In contrast to the previous system, the surface of NPs used in this work is additionally modified, it seems that either higher UV power is needed to achieve comparable effects, or that the mechanism of complex release is in the present case different.

Also, the results obtained at pH 5 are quite unexpected, because there are no differences in the complex release rates in the dark and upon illumination. Apart from the unknown mechanism of the complex release when the surface of TiO_2 is modified, the difference in the release rate upon visible light illumination might also arise from the higher moiety of the protonated carboxylic acid residues, and hydration layer on the surface of TiO_2, which prevent re-binding of the complex to the NPs` surface once they are released.

Encapsulation of NCS in SUVs showed that irradiation, either with red or UV light, had similar impact to the release rates, as under all experimental conditions, the complex release from the conjugate NCS-SUV was less than 60% of total bound complex. This experiment is only preliminary, but it is possible that phospholipids absorb a major part of the applied light, both UV and visible, which explains the similarity with results of control experiments.

4 Conclusion

In this study we synthesized NCS which had shown promising light-controllable drug-release ability. NCS prepared in this way was extremely stable under physiological conditions, which enables in vivo experiments in the future. We demonstrated that, due to the presence of the Ru-complex in physiological conditions, the system had the ability to respond to red light by sustaining complex release, whereas the encapsulation in SUVs showed the potency to additionally preserve complex from release before it reaches tumor cells. Sustained release could decrease side effects and increase effectiveness, so this property is strongly favorable for drug delivery systems, and makes this NCS interesting for further investigation. Greater impact of red light on the sustained complex release at pH 7, is the advantageous property, because it opens possibility to keep the complex bound to the surface of nanoparticle with red light until the system reaches target tissue.

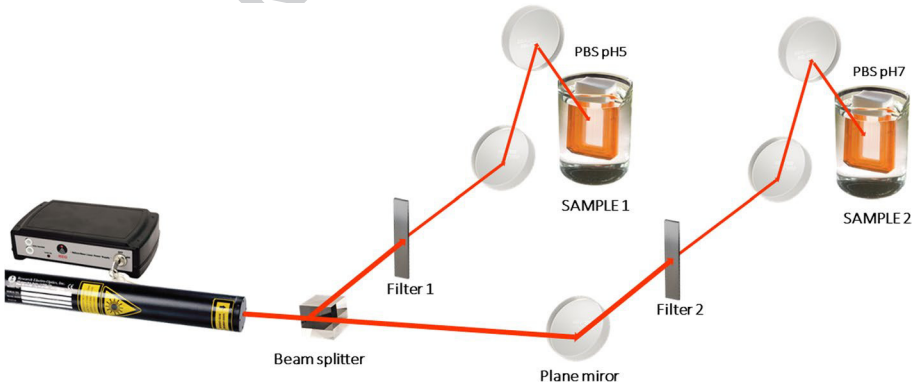

Fig. 2 Schematic diagram of the experimental setup: HeNe red laser beam is split by glass cube beam splitter into two beams and reflected by plane mirrors to the samples. The power of each beam is regulated by variable neutral density filter

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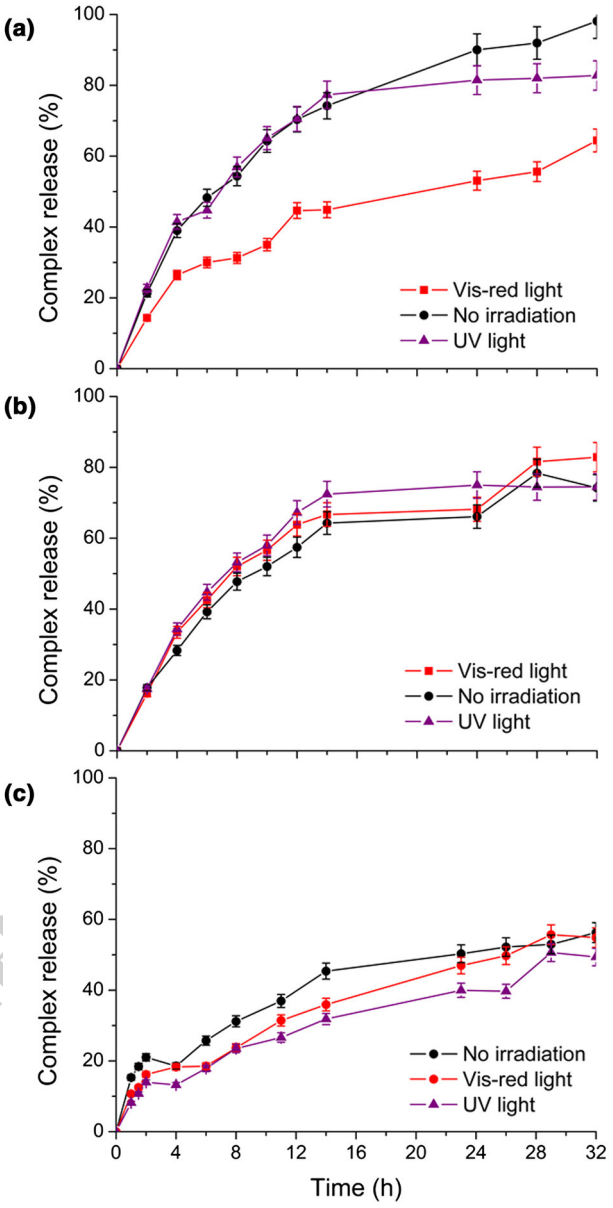

Fig. 3 Comparative complex release profiles of non-irradiated sample (annotated with "No irradiation"), samples irradiated with red light ("Vis-red light"), and samples irradiated with UV light ("UV light"). Briefly, the complex release test was carried out at the room temperature, and the system was monitored for 32 h. The complex release from the free NCS in the dissolution medium PBS of pH 7 is shown at **a** the complex release from the free NCS in the dissolution medium PBS of pH 5 is shown at **b** and the complex release from the conjugate SUV-NCS in the dissolution medium PBS of pH 7 is shown at **c**. The concentrations of the released complex are expressed as the percentage of the control experiments, i.e. of the free complex. Experiments are performed in triplicate and the mean ± SD are presented in graphs

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