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Synthesis, Characterisation and Biological Evaluation of the Polymeric Encapsulation of a Ru(II) Polypyridine Complex with Pluronic F-127 for Photodynamic Therapy Applications

Johannes Karges,^[a] Hui Chao,^{*[b]} and Gilles Gasser^{*[a]}

Abstract: The therapy of cancer remains a major challenge for modern medicine. Complementary to classical treatments, the use of photodynamic therapy (PDT) has received increasing attention over the last decades. Among the classes of PDT photosensitizers (PSs) investigated, Ru(II) polypyridine complexes are currently considered as a valuable option. To improve the water solubility of these lipophilic compounds and generate a drug delivery system, these complexes can be encapsulated into polymers. Herein, the physical encapsulation of the photoactive [Ru((*E,E'*)-4,4'-bis[*p*-methoxystyryl]-2,2'-bipyridine)₃][PF₆]₂ complex with the polymer Pluronic F-127 is presented. The resulting spherical particles were found to have a toxic effect in the micromolar range in human cervical carcinoma cells upon light irradiation (500 nm).

Introduction

The use of metal complexes in medicine has started to develop during the last century after the discovery of Salvarsan (mixture of 3-amino-4-hydroxyphenyl-arsenic(III) compounds) by Ehrlich *et al.* in 1912^[1] and cisplatin (*cis*-diamminodichloroplatinum(II)) by Rosenberg *et al.* in the 1960's.^[2] These compounds, which had/have a tremendous impact on human health, have promoted the development of other metal-based compounds.^[3] To date, metal complexes have received special attention in the treatment of cancer, one of the deadliest diseases worldwide. For example, the Pt(II)-containing chemotherapeutic drug cisplatin and its derivatives are very commonly used to treat this disease. Despite their undeniable success, these drugs are associated with severe side effects (e.g., nerve and kidney damage, nausea, vomiting, and bone marrow suppression) as well as an increasing number of resistance problems, limiting their clinical applications.^[4] As a complementary technique to the traditional medical treatments against cancer (i.e., surgery, chemotherapy, radiotherapy), photodynamic therapy (PDT) has received increasing attention over the last decades. It relies on the

combination of a photosensitizer (PS), light and oxygen. During a PDT treatment, the PS is selectively activated upon light irradiation to generate reactive oxygen species (ROS). These species can cause significant cell damage and ultimately trigger cell death.^[5] Metal complexes,^[6] and especially Ru(II) polypyridine complexes,^[7] are currently being investigated as PSs for PDT due to their ideal photophysical properties. One of such compounds, namely TLD-1433 from the group of McFarland, is currently in phase II clinical trial against bladder cancer.^[8] However, the majority of Ru(II) polypyridine complexes lack significant absorption in the phototherapeutic window (600-900 nm), which limits their application for PDT purposes.^[9] For this reason, research effort are devoted towards the development of compounds with absorption at these wavelengths.^[10] One possibility to reach this aim is to extend the aromatic system of the ligands bound to the Ru(II) centre. However, such synthetic modifications usually engenders a decrease of the water solubility of the generated compounds, limiting their applications.^[11] An additional limitation of the currently investigated and clinically applied PDT agents is their poor cancer cell selectivity, resulting in the use of high concentrations for a desired therapeutic outcome. To overcome this drawback, there is a need for the development of suitable drug delivery systems. To date, a variety of different delivery carriers for Ru(II) polypyridine complexes have been reported, including polymeric/physical encapsulations,^[12] loading into nanoparticles^[13], conjugation to carbon nanotubes,^[14] receptor-targeting moieties/peptides,^[15] antibodies,^[16] or metal-organic frameworks.^[17] However, the majority of these drug delivery systems are associated with either a tedious preparation, high price, poor water solubility or reduced therapeutic effect. There is therefore a need for the development of a cheap, easy-to-prepare and selective drug carrier. Among these techniques, the physical encapsulation of a compound into polymeric particles is known to be synthetically not challenging and to highly improve water solubility. It also allows to specifically target tissue thanks to the enhanced permeability and retention (EPR) effect,^[18] although this concept is currently controversially discussed.^[19]

Among others, poloxamers are investigated as a class of polymers carriers, which are not or only slowly biodegradable but biocompatible. These polymeric materials consist of a non-ionic triblock ABA structure with block A as hydrophilic poly(ethylene oxide) and block B as hydrophobic poly(propylene oxide). Based on this difference in water solubility, the polymeric material is able to self-assemble into spherical micelles, which can be loaded with hydrophobic compounds.^[20] Recently, Sadler *et al.* successfully encapsulated the [Ru(*p*-cymene)(1,2-dicarba-closo-dodecarborane-1,2-dithiolato)] complex for boron neutron capture therapy with the Pluronic P-123 polymer. The generated micelles were shown to have a decreased toxicity profile while having an increased selectivity towards cancer cells in comparison to non-

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cancerous cells.^[21] The group of Howard *et al.* has reported the encapsulation of $[\text{Ru}(4,7\text{-diphenyl-}1,10\text{-phenanthroline})_3]^{2+}$ with Poloxamer-407/Pluronic F-127 as a two-photon excited oxygen imaging agent in aqueous solution.^[22] Lemerrier *et al.* encapsulated the PDT PS $[\text{Ru}(1,10\text{-phenanthroline})_3]^{2+}$ derivatives into poly(D,L-lactide-co-glycolide) and Poloxamer 188/Pluronic F-68. They could show that their PS was slowly released from the particles and had the ability to generate a phototoxic effect in cancerous cells upon irradiation.^[23]

Encouraged by the promising results obtained by our group on the encapsulation of Ru(II)-based PDT PSs^[24], we report, in this article, the encapsulation of the lipophilic Ru(II) polypyridine complex $[\text{Ru}((E,E)\text{-}4,4'\text{-Bis}[p\text{-methoxystyryl}]\text{-}2,2'\text{-bipyridine})_3][\text{PF}_6]_2$ (Figure 1a), which we have recently reported as an effective PS^[10b] with the polymer Poloxamer-407/Pluronic F-127 (Figure 1b). The generated particles were found to have a spherical shape as characterised by dynamic light scattering and transmission electron microscopy. While stable in a biological environment, the particles were able to trigger cell death in human cervical carcinoma (HeLa) cells in the micromolar range upon irradiation at 500 nm. Interestingly, the cytotoxic effect of the particles could be correlated with their different loading ratios and particle sizes.

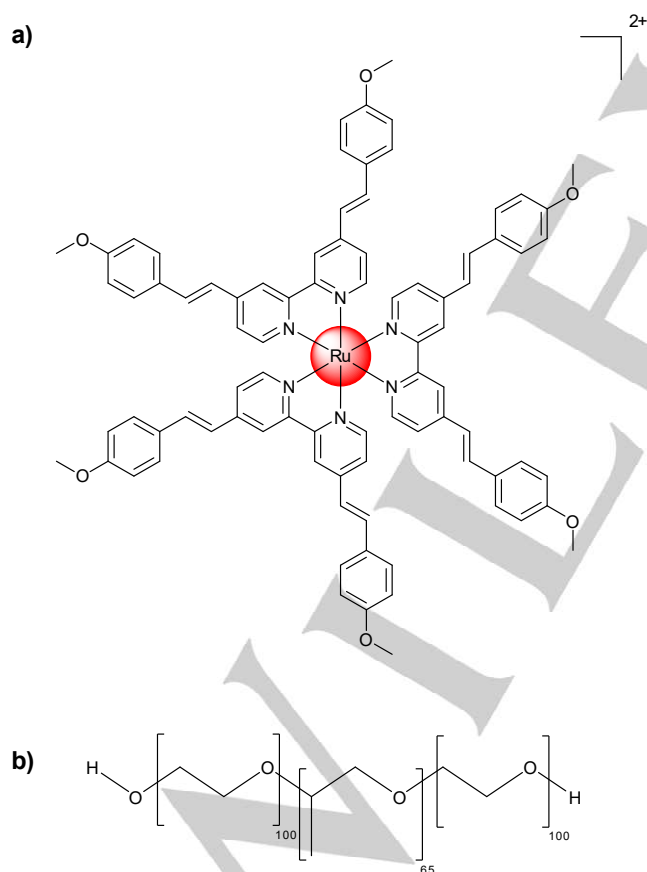


Figure 1. a) Chemical structure of **Ru**. The compound was isolated as a PF_6^- salt. b) Chemical structure of the block-polymer Pluronic F-127/Poloxamer-407.

Results and Discussion

Synthesis

The Ru(II) polypyridine complex $[\text{Ru}((E,E)\text{-}4,4'\text{-Bis}[p\text{-methoxystyryl}]\text{-}2,2'\text{-bipyridine})_3][\text{PF}_6]_2$ (**Ru**, Figure 1a) was synthesised as previously reported.^[10b] The purity of the compound was verified by HPLC (Figure S1) and elemental analysis. Due to the insolubility of **Ru** in H_2O , the compound was encapsulated using the polymer poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol), which is also known as Pluronic F-127/Poloxamer-407 ($M_n \sim 10000 - 12000$, Figure 1b). In this study, the effect of different loadings (2.5 : 97.5 – **Ru1** ; 5 : 95 – **Ru2**; 7.5 : 92.5 – **Ru3**; 10 : 90 – **Ru4**, wt% Ru : Pluronic F-127) of the Ru complex with the polymer was investigated. The encapsulation process was performed by mixing a DCM phase of the Ru(II) polypyridine complex with a H_2O phase of Pluronic F-127 in the presence of ultrasonic pulses, as previously published for the encapsulation of metal complexes.^[25] Following this, the DCM was evaporated and large aggregates were removed by size exclusion chromatography, resulting in a clear red aqueous solution.

Particle Characterisation

As only part of the Ru(II) polypyridine complex **Ru** could be encapsulated during the particles preparation process, the amount of encapsulated Ru complex inside the particles was determined by inductive coupled plasma mass spectrometry (ICP-MS, Table 1). As expected, the more Ru(II) complex was used during this process, the higher amount of this lipophilic compound was encapsulated.

Table 1. Ru concentration of the generated particles **Ru1-Ru4**.

	Loading ratio Ru : Pluronic F127	Theoretical Ru concentration	Experimentally determined Ru concentration	Yield
Ru1	2.5 % : 97.5 %	0.125 mg/mL	0.108 mg/mL	86 %
Ru2	5.0 % : 95.0 %	0.250 mg/mL	0.179 mg/mL	72 %
Ru3	7.5 % : 92.5 %	0.375 mg/mL	0.237 mg/mL	63 %
Ru4	10.0 % : 90.0 %	0.500 mg/mL	0.246 mg/mL	49 %

With the particles in hand, they were then characterised by dynamic light scattering (DLS) and transmission electron microscopy (TEM) measurements (Table 2). The results indicate that the generated particles are well defined with a polydispersity between 0.183-0.234 and an average size of 53-162 nm, as determined by DLS (Figure S2-S5) and 31-153 nm, as determined by TEM (Figure 2, Figure S6-S8). As expected, increasing the loading of the Ru(II) polypyridine complex during their synthesis resulted also in an overall larger particle size. The TEM images showed that the **Ru1-Ru4** particles have a spherical shape.

Table 2. Physical properties of the particles **Ru1-Ru4** determined by dynamic light scattering (DLS) in H_2O and transmission electron microscopy (TEM).

	DLS		TEM
	Average size	Polydispersity	Average size
Ru1	53 nm	0.183	31 ± 3 nm
Ru2	58 nm	0.217	46 ± 5 nm
Ru3	65 nm	0.196	56 ± 6 nm
Ru4	162 nm	0.234	153 ± 8 nm

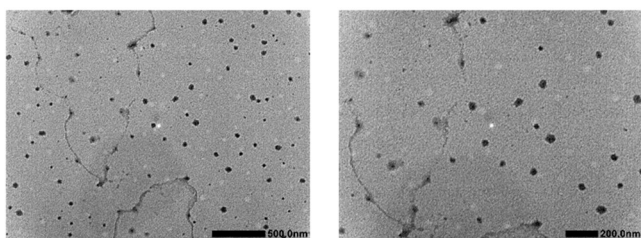


Figure 2. Representative TEM images of Ru3.

Photophysical evaluation

In order to verify that the photophysical properties of the complex are not significantly influenced by the encapsulation due to, for example, quenching effects, which would prevent the desired PDT outcome, the photophysical properties (Table S1) of **Ru1-Ru4** were investigated and compared to the complex alone (**Ru**). The absorption and emission spectra upon irradiation at 450 nm show no significant differences. Interestingly, the particles (**Ru1-Ru4**) show an increased luminescence quantum yield. This finding can be explained: the encapsulated Ru(II) polypyridyl complexes are surrounded by a lesser number of water molecules, which could potentially quench their luminescence. The ability to produce singlet oxygen (1O_2) was then investigated to confirm that oxygen is able to reach the compound and to interact with the excited state of the complex. For this purpose, the change in absorbance of the 1O_2 scavenger 1,3-diphenyl-isobenzofuran was time dependently monitored upon irradiation at 500 nm.^[26] The results (Table S1) confirm that the particles (**Ru1-Ru4**) are able to generate 1O_2 in a similar manner than the compound itself. Overall, the photophysical evaluation indicated that the encapsulation of the Ru(II) polypyridine complex did not influence its excited state behaviour. This finding is in agreement with that recently observed for the encapsulation of $[Ru(4,7\text{-diphenyl-1,10-phenanthroline})_3]^{2+}$ with the same polymer^[22] as well as the encapsulation $[Ru(2,2'\text{-bipyridine})_2(\text{dipyrido}[3,2\text{-}a:2',3'\text{-}c]\text{phenazine-7-hydroxymethyl})]^{2+}$ with a polylactide polymer.^[24]

Stability

As an important factor for biological applications, the stability of the polymeric particles under biological conditions was investigated as previous works have shown that this could be problematic.^[23, 27] For this purpose, the particles were incubated in H₂O and the cell medium DMEM and their absorption spectra as well as their size distribution were monitored in various time intervals (0, 2, 8, 12, 24, 48 h). As no significant changes were observed within 48 h (Figure S9-S20), the stability of the particles is confirmed. These findings are in agreement with stability studies of particles formed by the encapsulation of $[Ru(4,7\text{-diphenyl-1,10-phenanthroline})_3]^{2+}$ with the same polymer carrier.^[22]

Biological evaluation

After confirmation of the stability of the particles (**Ru1-Ru4**) in a biological environment, the effect these particles have on cancer cells was investigated. For this purpose, the compounds were incubated in human cervical carcinoma (HeLa) cells in the dark as well as exposed to a light irradiation at 500 nm (16.7 min, 10

J/cm²) and their cell viability measured (Table 3). All particle formulations were found to have no cytotoxic effect in the dark up to high micromolar concentrations ($IC_{50} > 500 \mu\text{M}$), as requested for a PDT agent. Upon light exposure, the compounds were found to be able to generate highly cytotoxic 1O_2 and therefore trigger cell death in the micromolar range ($IC_{50} = 93\text{-}261 \mu\text{M}$). Interestingly, the particle formulations **Ru1-Ru3** were found to have a stronger phototoxic effect than **Ru4**. Of note, **Ru** was found to have a drastically stronger cytotoxic effect than its corresponding nanoformulations.

Table 3. IC_{50} values (μM) in the dark and upon irradiation at 500 nm (16.7 min, 10 J/cm²) for the particles **Ru1-Ru4** in comparison to **Ru** and cisplatin in human cervical carcinoma (HeLa) cells. Average of three independent measurements.

	IC_{50} in the dark	IC_{50} upon irradiation	PI
Ru	>50	13.6 ± 0.9	>3.7
Ru1	>500	93 ± 8	>5.4
Ru2	>500	104 ± 11	>4.8
Ru3	>500	117 ± 12	>4.3
Ru4	>500	261 ± 23	>1.9
cisplatin	11.2 ± 1.1	-	-

To understand these results, the cellular uptake of the particles was investigated by incubating the compounds in HeLa cells and determining the amount of Ru inside the cells by ICP-MS. Interestingly, **Ru** has a much higher cellular uptake than the particle formulations (**Ru1-Ru4**). In addition, the particles with a smaller size were found to have a significantly higher cellular uptake than the larger ones. Overall, these experiments explain the superior phototoxic effect observed for **Ru** and the small particles.

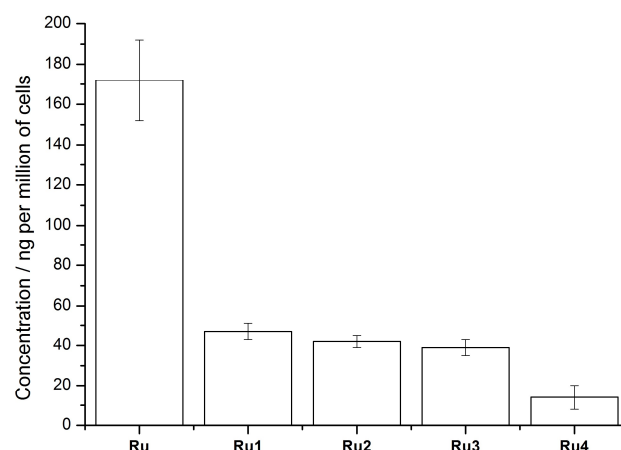


Figure 3. Comparison of the cellular uptake of **Ru** (50 μM) and its particle formulations **Ru1-Ru4** after a 12 h incubation in HeLa cells.

Conclusions

In summary, we have synthesised and characterised polymeric particles containing the photoactive Ru(II) polypyridine complex $[Ru((E,E')\text{-}4,4'\text{-bis}[p\text{-methoxystyryl}]\text{-}2,2'\text{-bipyridine})_3][PF_6]_2$ with different loading ratios of the compound within the polymer carrier Pluronic F-127. By increasing the amount of the Ru(II) polypyridine complex during the encapsulation, we observed that

the size of the generated particles is increased. Photophysical measurements showed that the particles are able to generate highly cytotoxic singlet oxygen. The particles were found to have a high stability in water and cell medium. While being non-toxic in the dark up to high concentrations, the particles had a phototoxic effect upon light irradiation at 500 nm in cancerous human cervical carcinoma cells in the micromolar range. Interestingly, thanks to ICP-MS measurements, the particles with a smaller size were found to have a significant higher cellular uptake, explaining their superior phototoxicity.

Experimental Section

Materials

Poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol) with the tradename Pluronic F127 ($M_n \sim 10000 - 12000$) was commercially obtained from Energy Chemical. Dulbecco's modified eagle medium (DMEM), fetal bovine serum (FBS) and penicillin were purchased from Invitrogen.

Instrumentation and methods

^1H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (δ 0.00) ppm using the residual proton solvent peaks as internal standards. Coupling constants (J) are reported in Hertz (Hz) and the multiplicity is abbreviated as follows: s (singlet), d (doublet). Elemental microanalyses were performed on a Thermo Flash 2000 elemental analyser. For analytic HPLC the following system has been used: 2 x Agilent G1361 1260 Prep Pump system with Agilent G7115A 1260 DAD WR Detector equipped with an Agilent Pursuit XRs 5C18 (100Å, C18 5 μm 250 x 4.6 mm) column and an Agilent G1364B 1260-FC fraction collector. The solvents (HPLC grade) were millipore water (0.1% TFA, solvent A) and acetonitrile (0.1% TFA, solvent B). The solvents (HPLC grade) were millipore water (0.1% TFA, solvent A) and acetonitrile (solvent B). Method: 0-3 minutes: isocratic 50% A (50% B); 3-17 minutes: linear gradient from 50% A (50% B) to 0% A (100% B). The flow rate was 1 mL/min and the chromatogram was detected at 250 nm. Inductive coupled plasma mass spectrometry (ICP-MS) experiments were carried out on an iCAP RQ ICP-MS instrument (Thermo Fisher).

Synthesis

$[\text{Ru}((E,E)\text{-}4,4'\text{-Bis}[\rho\text{-methoxystyryl}]\text{-}2,2'\text{-bipyridine})_3][\text{PF}_6]_2$ (**Ru**): The compound was synthesised as previously reported.^[10b] Purity was assessed by HPLC and elemental analysis. Elemental analysis calcd. for $\text{C}_{84}\text{H}_{72}\text{F}_{12}\text{N}_6\text{O}_6\text{P}_2\text{Ru}$ (%): C 61.05, H 4.39, N 5.09; found: C 61.17, H 4.44, N 5.21.

Particle preparation

A solution of $[\text{Ru}((E,E)\text{-}4,4'\text{-Bis}[\rho\text{-methoxystyryl}]\text{-}2,2'\text{-bipyridine})_3][\text{PF}_6]_2$ (**Ru**) in 0.5 mL DCM was added to a solution of Pluronic F-127 in 19.5 mL H_2O in different weight ratios (2.5 : 97.5 – **Ru1** ; 5 : 95 – **Ru2**; 7.5 : 92.5 – **Ru3**; 10 : 90 – **Ru4**). The two phases were vigorously mixed to generate an emulsion. The solution was further treated with ultrasonic pulses with a Scientz – II D ultrasonic homogenizer using a 10 min method ($t_{\text{sonication}} = 2$ s, Power = 15%, $t_{\text{break}} = 1$ s) while keeping the sample constantly at 25 °C. This method has been repeated a second time after a 5 min break. The DCM was removed by evaporation at 50 °C. Large aggregated were removed by size exclusion chromatography. After that a clear transparent solution in H_2O was obtained.

Particle characterisation

The amount of encapsulated complex was determined using ICP-MS. Each sample was digested using a 60% HNO_3 solution for three days, followed by a 30% H_2O_2 solution for an additional day. After that time, the sample was diluted to a solution of 2% HNO_3 in water. The Ru content was determined using an ICP-MS apparatus and comparing the results with the Ru references. The size and polydispersity of the particles was determined using dynamic light scattering (DLS) measurements with an Omni EliteSizer (Brookhaven). The size and morphology of the particles was determined by transmission electron microscopy (TEM) with a JEM-1400 Plus electron microscope (Jeol).

Spectroscopic measurements

The absorption of a sample was recorded on a Lambda 850 UV/VIS spectrometer (PerkinElmer) at room temperature. Emission spectra were recorded on a LS 55 fluorescence spectrometer (PerkinElmer) at room temperature. For the determination of the luminescence quantum yield, the samples were prepared with an absorbance of 0.2 at 450 nm in H_2O . This solution was irradiated at 450 nm and the emission signal measured. The luminescence quantum yields were determined by comparison with the reference $[\text{Ru}(\text{bipy})_3]\text{Cl}_2$ in acetonitrile ($\Phi_{\text{em}}=5.9\%$)^[28] applying the following formula:

$$\Phi_{\text{em,S}} = \Phi_{\text{em,R}} * (F_{\text{R}} / F_{\text{S}}) * (I_{\text{S}} / I_{\text{R}}) * (n_{\text{S}} / n_{\text{R}})^2$$

$$F = 1 - 10^{-A}$$

Φ_{em} = luminescence quantum yield, F = fraction of light absorbed, I = integrated emission intensities, n = refractive index, A = absorbance of the sample at irradiation wavelength, S = sample, R = reference.

Singlet oxygen measurements

The singlet oxygen production ($\Phi(^1\text{O}_2)$) was measured by monitoring the change of the absorbance of the $^1\text{O}_2$ scavenger 1,3-Diphenylisobenzofuran. The samples were prepared in a H_2O solution containing the complex with an absorbance of 0.2 at 500 nm and DPBF (30 μM). The samples were aerated and irradiated at 500 nm using different time intervals. The absorbance of the samples at 411 nm was measured during these time intervals with a Lambda 850 UV/VIS spectrometer (PerkinElmer). The difference in absorbance ($A_0 - A$) was calculated and plotted against the irradiation times. From the plot the slope of the linear regression was calculated as well as the absorbance correction factor determined. As reference for the measurement rose bengal ($\Phi(^1\text{O}_2)_{\text{rose bengal}} = 76\%$)^[29] in methanol was used. The singlet oxygen quantum yields were calculated applying the following formula:

$$\Phi(^1\text{O}_2)_\text{S} = \Phi(^1\text{O}_2)_\text{R} * (B_{\text{S}} / B_{\text{R}}) * (I_{\text{R}} / I_{\text{S}})$$

$$I = I_0 * (1 - 10^{-A})$$

$\Phi(^1\text{O}_2)$ = singlet oxygen quantum yield, B = slope of the linear regression of the plot of the areas of the singlet oxygen luminescence peaks against the irradiation intensity, I = absorbance correction factor, I_0 = light intensity of the irradiation source, A = absorbance of the sample at irradiation wavelength, S = sample, R = reference.

Stability measurements by UV/Vis spectroscopy

The stability of a sample was investigated upon incubation in water and the cell medium DMEM. In various time intervals (0, 2, 8, 12, 24, 48 h) the absorption of the samples was recorded with a Lambda 850 UV/VIS spectrometer (PerkinElmer).

Stability measurements by DLS

The stability of the sample was investigated upon incubation in water and the cell medium DMEM. In various time intervals (0, 2, 8, 12, 24, 48 h) the size distribution of the particles was recorded with an Omni EliteSizer (Brookhaven) apparatus.

Cell culture

Human cervical carcinoma (HeLa) cells were obtained from the American Type Culture Collection (Manassas, VA). The cells were cultured using DMEM media with addition of 10% FBS and 1% penstrep. The cells were

cultivated and maintained in a cell culture incubator at 37 °C with 5% CO₂ atmosphere. Before an experiment, the cells were passaged three times.

(Photo-)cytotoxicity

The cytotoxicity of a sample was accessed using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were seeded in 96 well plates (1000 cells per well in 100 µL of media) and allowed to adhere upon incubation for 24 h. The cells were treated with increasing concentrations of the compounds diluted in cell media achieving a total volume of 200 µL. All cells were incubated in the dark for 12 h. After this time the culture medium was refreshed. For the phototoxicity studies, the cells were exposed to a 500 nm LED irradiation (16.7 min, 10 J/cm²). The cells were grown in the incubator for additional 36 h. For the determination of the dark cytotoxicity, the cells were not irradiated and after the media exchange directly incubated for 36 h. After this time, the media was replaced with fresh media containing MTT (10 µL/well). After 4 h incubation, the absorption at 595 nm in each well was determined with a SpectraMax CMax Plus (Molecular Devices) absorbance microplate reader. The viability of the cells in each well was obtained by subtracting the average absorbance of the blank group. The obtained data was analysed with the GraphPad Prism software.

Cellular uptake

The cellular uptake of a sample was investigated by determining the Ru content inside the cells. The compound with a final concentration of 50 µM were incubated for 12 h at 37 °C on a cell culture dish with a density of ca. 6*10⁶ cells in 10 mL of media. After this time, the media was removed and the cells washed with cell media. The cells were trypsinised, harvested, centrifuged and resuspended. The number of cells on each dish was accurately counted. Each sample was the digested using a 60% HNO₃ solution for three days followed by a 30% H₂O₂ solution for an additional day. Each sample was diluted to solution of 2% HNO₃ in water. The Ru content was determined using an ICP-MS apparatus and comparing the results with the Ru references. The Ru content was then associated with the number of cells.

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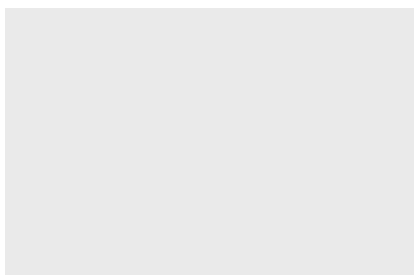
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FULL PAPER

Ru(II) polypyridine complexes are gaining attention as agents for photodynamic therapy. Due to the low water solubility of complexes with extended ligands, there is a need for delivery systems. Herein, the polymeric encapsulation with Pluronic F-127 is described. The photophysical properties as well as (photo-)cytotoxicity of the generated particles against cervical cancerous HeLa cells is reported.

**Photodynamic Therapy***J. Karges, H. Chao*, G. Gasser****Page No. – Page No.****Synthesis, Characterisation and Biological Evaluation of the Polymeric Encapsulation of a Ru(II) Polypyridine Complex with Pluronic F-127 for Photodynamic Therapy**

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