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New luminophor-activators based on (fluoro)quinolone antibacterials

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ABSTRACT

It was shown that (fluoro)quinolone antibiotics form strongly fluorescent solid-state complexes with Eu(III) and Tb(III) lanthanide ions, with a wavelength red-shift beneficial for applications to greenhouse-cover polymers. Complexes with optimal properties were prepared by the mechanical activation of fine-dispersed composite mixtures with the lanthanide salts. The spectral properties, photo-stability to UV-light, and compatibility with the polyethylene matrix were investigated. The formulation additives of the tablet forms of the antibiotic medicines did not quench the fluorescence from the lanthanide ions. Therefore, the outdated drug forms of the antibiotics can serve as cheap recyclable sources for the covering material of greenhouses. In addition, diphenylguanidine (DPG) was investigated as a coligand. DPG enhanced fluorescence of the fluoroquinolone complexes by decreasing the non-radiative energy loss through O–H vibration of H_2O.

1. Introduction

The rapid growth of the chemical industry causes problems related to the protection of natural ecosystems and water supplies from toxic chemicals. Environmental problems are associated with pharmaceutical wastes (counterfeited, overdue, or defective medicines) and overuse or misuse of the antibacterial agents in human and veterinary medicine. Residues of drugs and their metabolites affect the public health due to their presence in food or drinking water [1,2]. All pharmaceuticals and their metabolites are chemical substances with different degrees of toxicity and, consequently, potential carcinogens, mutagens, or allergens. The multi-drug resistance of microbes caused by the misuse of antibacterial agents is one of the most serious concerns at present [3–5]. One of the possible ways of reducing toxic chemicals from entering the environment and living organisms is to recycle them.

In this work, we have developed a new approach for the utilization of fluoroquinolone antibacterials (fqH) (Scheme 1, Table 1) that are synthetic drugs, widely used in human and veterinary medicine, and as growth promoters [3–8].

We have earlier investigated the complexation and the spectral-luminescent properties of some fqH complexes with lanthanides [9,10]. Most commonly, quinolones coordinate to the metal ions through ring carbonyl and carboxylate oxygen atoms [9–11]. Eu(III) and Tb(III) complexes with fqH are very efficient light converters under UV excitation, where the ligands act as antennas absorbing UV radiation and efficiently transferring energy to Ln(III) emitters [9,10]. The lanthanide complexes have characteristics that have a wide range of applications [12–14]. For instance, the levels of some lanthanide complexes with fqH in various environmental samples (water, food, urine, etc.) have been investigated [15–17].

Fluorescent polymer films for greenhouses that are commercially available by the name “Polisvetan” [12,18,19] can artificially increase the activity of blue–green pigments in plants and thereby promote photosynthesis. With the coordination compounds of Eu(III) salts incorporated into the polymer material, “Polisvetan” converts ultraviolet radiation into red light that is useful for plants.

This paper focused on studying the spectral properties of fqH lanthanide complexes, their photo-stability against UV-light, as well as their compatibility with the polyethylene (PE) matrix. Our results show that fluoroquinolone drugs can be used as lanthanide complexants for polymer material “Polisvetan” and recycled in the process of the film production.

2. Experimental

2.1. Materials

Tablet medications: “Negram” (nalidixic acid, KRKA, Slovenia), “Norbactin” (norfloxacin, Ranbaxy Laboratories Ltd, India) “Nolicin” (KRKA, Slovenia), “Ciprolet” (ciprofloxacin, Dr.REDDY’s Laboratories, India), “Tarivid” (ofloxacin, Hoechst Marion Roussel Ltd., Germany) were used. Low-density PE was purchased from

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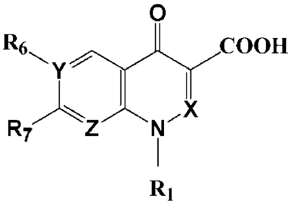
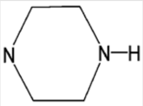
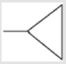
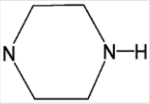
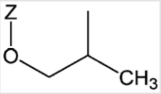


Scheme 1. Structure of quinolone and fluoroquinolone compounds with the substituents given in Table 1. The keto oxygen at C-4 and the carboxylic acid side chain at C-3 are present in all quinolone and fluoroquinolone antibacterials.

Table 1
Substituents of some commercial fqH

(Fluoro)quinolones	Substitutions					
	R_1	X	Y	R_6	R_7	Z
Nalidixic acid (nlqH)	$-C_2H_5$	CH	C	H	**CH_3**	N
Norfloxacin (nfqH)	$-C_2H_5$	CH	C	F		CH
Ciprofloxacin (cfqH)		CH	C	F		CH
Ofloxacin (ofqH)		CH	C	F		CR_1

Tomskneftechim, Russia. Diphenylguanidine (DPG) was purchased from Khimprom, Russia. Terbium (III) chloride hexahydrate, and europium (III) chloride hexahydrate were purchased from Aldrich Chem. Co. All reagents were of analytical reagent grade and distilled or deionized water was used.

2.2. Mechano-synthesis procedure

Mechano-chemical synthesis was conducted by the activation of the dry mixtures of the reagents in the laboratorial activator AGO-2. For obtaining lanthanide complexes, $EuCl_3 \cdot 6H_2O$ ($TbCl_3 \cdot 6H_2O$) and quinolones in the form of tablet in the mole ratio 1:3 as well as a ceramic nozzle, 12 ceramic balls of 10 mm diameter, were placed into thick-walled corundum barrels of 150 cm^3 volumes and were vibrated with a frequency of 50 Hz during 1–3 min at room temperature. A small amount of NaOH or water was added to the dry mixtures of the reagents to increase the speed of the reaction. After the mechanical treatment in the activator, the reaction was completed. Increasing of the activation time led to agglomeration of the synthesis products.

Products of mechano-chemical treatment were studied with fluorescent, infrared (IR) and Raman-spectroscopes and the products proved to be Ln (III) complexes with quinolones, not mechanical mixtures of the reagents. The luminescence intensity of the Eu(III) and Tb(III) complexes with tablet-form quinolones was at least 80–90% of the one of the individual compounds.

2.3. Incorporation of the lanthanide complexes in the polymer films

Polymer films of Eu(III) and/or Tb(III) with fqH formed highly homogenous films with thicknesses of about 0.5–1 mm by thermo-pressing techniques. The lanthanide complexes of fqH were incorporated in the polymer material by the hot pressing method at $t = 120–130\,^{\circ}C$. For this purpose, 1 g of the PE powder was thoroughly mixed with a luminophor additive ($c = 0.01–0.5\%$, w/w (luminophor mixture/PE)) and was pressed by a laboratory press.

2.4. UV-light exposure

The obtained film samples (2.3) were exposed to UV-irradiation with dose 10^{15} photon/cm^2 s, $\lambda_{Hg} = 366$ nm during several hours with continual registration of the fluorescence intensity ($\lambda = 615$ nm) at the maximum of the most intensive line of the $^5D_0$–$^7F_2$ transition of Eu(III).

2.5. Apparatus

The emission spectra of the europium, terbium, and gadolinium ion complexes were obtained on the SDL-1 (LOMO) spectrometer with the frequency measurement error being $\pm 3\,cm^{-1}$ with a DRSh-250 mercury lamp and "Tungsram" used as an excitation source and monochromatic light from the xenon lamp using the KSVU monochromator. The scale of the spectrometer wavelengths was verified using lines of the helium–neon sources and mercury lines, including duplicate 5769.6–5790.6 Å. Measurements were carried out at 300 and 77 K.

A Cary Eclipse Fluorescence Spectrophotometer (Varian, Australia) was used to measure excitation spectra and fluorescence lifetime. All measurements were carried out at 300 K. Emission and excitation slit widths were 5 nm and rates of 600 nm/min were used. Quoted lifetime is the averaged value of at least three independent measurements, each of which was obtained by monitoring the emission intensity at 615 nm after 6–8 different delay times with a gate time of 0.4 ms. The luminescence decay curves were fitted to an equation of the single- and double-exponential function.

IR spectra were recorded on a Shimadzu IRPrestige-21 IR spectrophotometer using KBr pellets. Raman spectra were recorded on a Bruker RFS 100/s spectrophotometer.

3. Results and discussion

3.1. IR, Raman, and luminescent spectroscopy

Under UV-irradiation, Ln(III) compounds with fqH obtained by the mechano-activation method emit a red and green light, characteristic for Eu(III) and Tb(III) ions, respectively. The appearance of strong red and green emission under UV-irradiation during mechano-synthesis allowed us to control the course of the reaction during the experiment, because of the effective transfer of excitation energy from $\pi\pi^*$ and $n\pi^*$ levels of fqH to the metastable $^5D_0$ level of Eu(III) and the $^5D_4$ level of Tb(III).

After the excitation of the complexes into the ligand's lowest-energy centred absorption band gives rise to the well-known structured emission of the Eu(III) and Tb(III) ions as shown in Fig. 1(a) for the Eu(III) complex with nfqH. The spectrum consists of the single line of the $^5D_0$–$^7F_0$ transition, three bands of the $^5D_0$–$^7F_1$ transition and five components of the $^5D_0$–$^7F_2$ transition. The spectrum is dominated by the $^5D_0$–$^7F_2$ transition; more than 60% of the total emission is centred on the 615 nm peak.

The characteristic splitting of the bands and intensities of the ^5D_j–^7F_j transitions ($j = 1$, 2) of the emission spectrum of the compounds is typical for the mononuclear compounds of Eu(III).

Table 2 shows fluorescence lifetimes measured for Eu(III) and Tb(III) complexes with (fluoro)quinolones and coligand DPG.