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Photophysics of Zinc (II) Phthalocyanine Polymer and Gel Formulation

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ABSTRACT

The photophysical properties of lipophilic phthalocyanines encapsulated into a polymer and two different gels were studied in order to predict their photosensitizing efficacy *in vivo*. Photophysical techniques for solid phase were adapted for light dispersing samples. Gel formulation of two tetrasubstituted phthalocyanines, tetra-*t*-butylphthalocyaninato zinc(II) (1), tetrakis(1,1-dimethyl-2-phthalimido)ethylphtalocyaninatozinc(II) (2) and two octasubstituted phthalocyanines, 2,3,9,10,16,17,23,24-octakis(decyloxy)phthalocyaninatozinc(II) (3) and 2,3,9,10,16,17,23,24-octakis[(*N*,*N*-dimethylamino)ethylsulfanyl] phthalocyaninatozinc(II) (4) were investigated for their possible use in photodynamic therapy for topical purposes. Supporting the fact that gel formulation improves the photophysical properties of phthalocyanines, singlet molecular oxygen quantum yield (Φ_Δ) values for 1–4 zinc(II) phthalocyaninates in Lutrol® F 127-Cremophor® RH 40 were 0.60, 0.60, 0.20 and 0.26, respectively. Permeation studies showed that no release of phthalocyanines occurs, thus indicating there should be no risk of generalized skin photosensitivity in areas other than the dye-deposition site.

INTRODUCTION

Photodynamic therapy (PDT) is a clinical treatment based on the systemic or local administration of a tumor-localizing and photosensitizing drug, which is then activated by irradiation with a proper visible light wavelength (1). Photosensitizing drugs act through the generation of singlet oxygen, which is believed to be the toxic agent responsible for destruction of the tumor cells. Topical PDT is an already-known treatment for nonmelanoma skin cancer and other skin diseases.

Diamagnetic metallophthalocyanines have been found to have high triplet yields and long lifetimes of the excited triplet state (2). Thus, these complexes are expected to show strong photochemical and photodynamic activity due to their having a higher efficiency in generating reactive oxygen species than that of other tetrapyrroles (3–5).

Topical 5-amino-levulinic acid PDT is effective for various malignant, premalignant and other skin disorders—acne vulgaris, dermatoses, mycosis—as well as in cosmetic dermatology and skin rejuvenation (6–10).

The therapeutic effects of PDT employing topical application of aluminum phthalocyanine chloride and a laser diode emitting at 670 nm in murine nonmelanoma skin carcinomas has been recently reported (11). Also, topical zinc phthalocyanine formulation in gel with or without monolein 5% was studied in an animal model (12). Topical PDT *in vivo* experiments demonstrated good accumulation and efficient photosensitizing properties of zinc octa-*n*-alkyl phthalocyanines after application in a tetrahydrofuran-azone formulation onto the dorsal skin of Balb/c mice (2). A silicon phthalocyanine photosensitizer Pc 4 is in phase I clinical trials for treatment of cutaneous cancers at the Case Western Reserve University (13).

Although metallophthalocyanines have interesting photodynamic properties, their solubility in aqueous media is far too low for direct application in PDT treatment. A convenient strategy to increase the biocompatibility and disperse water-insoluble liphophilic compounds is the micro and nanoencapsulation in vesicles, liposomes or polymeric capsules. This should be done in such a way that the interior is made lipophilic for allowing the solubilization of nonpolar compounds while their outside should be hydrophilic thus making them dispersible in aqueous media. The polymeric encapsulation represents an interesting choice among other alternatives, as the capsule shell can be made from several biocompatible polymers and with different degrees of cross-linking allowing the control of permeability and mechanical resistance (14–16).

Despite the relative simplicity of the technique, accurate dosimetry in PDT is complicated by multiple variables in drug formulation, delivery and duration of application in addition to light-specific parameters. Optimal disease-specific irradiance, wavelength and total dose characteristics have yet to be established and are subject to difficulties when comparing light sources. Many biological studies have been made in patients and experimental animals. However, photophysical studies of encapsulated metallophthalocyanines into polymeric or gels employed for topical administration have not yet been explored. Gels are microheterogeneous media showing many problems such as bubbles, inhomogeneous surface and translucent systems, factors that greatly disperse the light, and no

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standard references are known for fluorescence and singlet oxygen quantum yield determination.

The aim of this work was to present the PDT-relevant photophysical properties of four selected zinc(II) phthalocyanines encapsulated into polymers or gels (Fig. 1). In order to predict the efficacy *in vivo* of these systems, we have developed a method to study the photophysical properties of lipophilic phthalocyanines encapsulated into gels.

MATERIALS AND METHODS

Chemicals. All photosensitizers were synthezised in our laboratory according to the following previously reported procedures: tetra-*t*-butylphthalocyaninatozinc(II) (**1**) (3), tetrakis(1,1-dimethyl-2-phthalimido)ethylphtalocyaninatozinc(II) (**2**) (17), 2,3,9,10,16,17,23,24-octakis (decyloxy)phthalocyaninatozinc(II) (**3**) (4), 2,3,9,10,16,17,23,24-octakis[(*N*,*N*-dimethylamino)ethylsulfanyl]phthalocyaninatozinc (II) (**4**) (18,19) hydroxyaluminium tricarboxymonoamidephthalocyanine (AlTCPc) (20).

Lutrol® F 127 (polyoxyethylene-polyoxypropylene block polymer, the mass fraction of polyoxyethylene is *ca* 73%), Cremophor® RH 40 (polyoxyl 40 hydrogenated castor oil) and Solutol® HS 15 (polyethylene glycol 660 12-hydroxystearate) were a gift from BASF Argentina. Methylene blue (MB) was sourced from Fluka (Switzerland) and cresyl violet perchlorate (CV) from Aldrich Chemical Co. (St. Louis, MO). Polypropylene glycol was purchased from Anedra (Buenos Aires, Argentina). Dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), *N*,*N*-diethyl-1-4-nitrosoaniline and imidazol were obtained from Sigma-Aldrich (St. Louis, MO).

Membranes were kindly provided by Dr. Delia Bernik, INQUIMAE, Facultad de Ciencias Exactas, Universidad de Buenos Aires and Prof. José Dobrecky, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires.

All chemicals were of reagent grade and used without further purification. Distilled water treated in a Milli-Q system (Millipore) was utilized.

Sample preparation. Stock solutions of zinc (II) phthalocyanines were prepared in THF, stored at 4°C and carefully protected from ambient light. Dye concentration is indicated for each experiment.

Gel formulations:

1 *Cremophor® RH 40 25% wt/wt (hydrophilic gel)*.
2 *Cremophor®* RH 40 (25% wt/wt) was prepared by pouring the polymer into water at 60°C, under strong stirring. The stock solution of each dye dissolved in THF was then added and the mixture stirred to homogeneity while the temperature was kept at 60°C to remove the volatile solvent THF. The gel is formed as the solution cools down to room temperature.
3 *Lutrol® F 127 20%, polypropylene glycol 30% (gel with intermediate lipophilicity)*. The appropriate amount of Lutrol® F 127 is dissolved in polypropylene glycol at 70°C by stirring. Water was then added at the same temperature and stirring continued up to homogeneity.

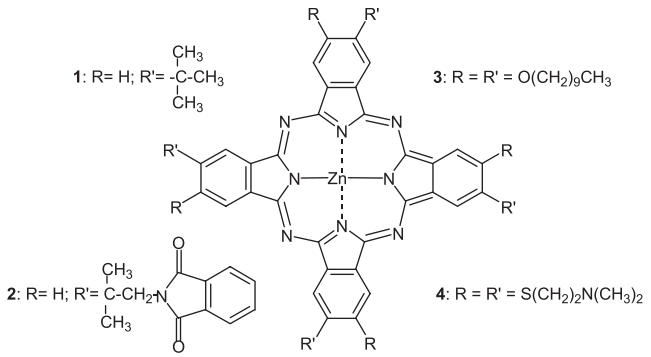

Figure 1. Chemical structure of phthalocyanines.

4 *Lutrol® F 127 15%, Cremophor® RH 40 10%, polypropylene glycol 15% (lipophilic gel)*. Polypropylene glycol was heated at 70°C, Cremophor® RH 40 added to the above reagent by stirring. After attaining homogeneity, Lutrol® F 127 was slowly added while stirring and followed by the addition of water. All reagents were heated at 70°C before utilization. The gel was left overnight at room temperature to eliminate bubbles.

Spectroscopic experiments. Electronic absorption spectra were determined with a Shimadzu UV-3101 PC spectrophotometer. Fluorescence spectra were monitored with a QuantaMaster Model QM-1 PTI spectrofluorometer and corrected for detector sensitivity and monochromator blaze angle by the software provided with the equipment.

Absorption and emission spectroscopy. Absorption and emission spectra and photochemical studies of phthalocyanines encapsulated into Cremophor® RH 40 were performed according to conventional methods for homogeneous media with a 10×10 mm quartz cuvette for fluorescence spectroscopy.

In the case of phthalocyanines incorporated in scattering media, all the absorption and emission experiments were performed using the same array of samples. They were spread on a home-made dispenser consisting of two glass slides. The top one has a hole to spread the samples to ensure all measurements are made at the same sample amount and thickness.

Optical spectra and absorbed photon flow for scattering media were recorded on a Shimadzu UV-3101 PC spectrophotometer fitted with an integrating sphere. $BaSO_4$ was used as a white standard to adjust the 100% reflectance level. Absorbance spectra were recorded for sample with dyes (A_2) and for gels free of dyes (A_1) according to the geometry recommended by Lagorio (21). The real absorbance spectra of the dyes were calculated according to Eq. (1):

$$A = -\log\left(1 - \frac{10^{-A_1} - 10^{-A_2}}{2}\right) \tag{1}$$

Equation (1) represents the dye absorbance without taking into account the contribution of the support.

Fluorescence emission spectra of scattering samples were obtained using the home-made dispenser at a front face arrangement. Emission spectra were collected at an excitation wavelength of 610 nm (Q-band) (absorbances were under 0.1) and recorded between 630 and 800 nm; a cutoff filter (Schott RG-630) at the emission monochromator was used to prevent the excitation reflected beam from reaching the detector. The emission spectrum of the reference for the fluorescence quantum yield calculation was also recorded between 630 and 800 nm exciting at 610 nm.

Fluorescence quantum yields. Relative fluorescence quantum yields (Φ_F) were determined by comparison with AlTCPc ($\Phi_F = 0.42$ in DMSO) (20) and CV ($\Phi_F = 0.60$ in microgranular cellulose) (22) as references. Quantum yields were calculated using Eq. (2) (5), where R and S refer to the reference and sample, respectively, I is the area under the emission spectrum, A is the sample absorbance at the excitation wavelength, and $(n_S/n_R)^2$ is the refractive index correction.

$$\Phi_F^S = \Phi_F^R \frac{I_{FS}(1 - 10^{-A_R})}{I_{FR}(1 - 10^{-A_S})} \left(\frac{n_S}{n_R}\right)^2 \tag{2}$$

Emission spectra using CV were excited at 505 nm and recorded between 515 and 800 nm. The emission beam was passed through a filter (Schott OG 515) to block reflected excited light. As reference and sample were excited at different wavelengths, emission spectra were corrected taking into account the response of the photomultiplier with wavelengths.

Singlet molecular oxygen quantum yield. Singlet oxygen photoproduction in gel-dye suspensions was quantified as follows. Five milligrams of gel formulation was prepared with the corresponding phthalocyanine and spread on a glass plate; following this, it was set into a 10×10 mm fluorescence quartz cuvette and fixed to the

window opposite site to the fluence incoming. The singlet oxygen monitor solutions composed of imidazol (8 mM) and *N*,*N*-diethyl-4-nitrosoaniline (40–50 μM) with pH = 7.0 (phosphate buffer 0.01 M), were air saturated and irradiated. The bleaching of nitrosoaniline was followed spectrophotometrically at 440 nm as a function of time and quantum yields were calculated using MB as a reference (Φ_Δ = 0.56) (23). The spectrophotometric measurements were detected at 90° of the excited beam. Chemical monitor bleaching rates were used as usual to calculate the singlet molecular oxygen photogeneration rates (24,25).

$$\Phi_\Delta^S = \Phi_\Delta^R \frac{V^S \cdot I_{aR}}{V^R \cdot I_{aS}} \quad (3)$$

where I_a is the intensity of the absorbed light, V is the singlet molecular oxygen photogeneration rate and the superscripts S and R stand for sample and reference, respectively.

Experiments were performed under polychromatic irradiation with a projector lamp (Philips 7748SEHJ, 24 V–250 W) and a cutoff filter at 610 nm (Schott RG 610). Determination of absolute singlet molecular quantum yields in suspensions requires calculation of the fraction of incident light absorbed by the dye (see below).

Fraction of incident light absorbed by gel-dye suspensions. Calculation of the fraction of incident light absorbed by dyes in scattering media was carried out with a standard spectrophotometer fitted with an integrating sphere. Diffuse reflectance (total, R, and nonspecular, R') and total transmittance (T) were measured in square 10 mm path length cells with four optical windows. The fraction of incident light absorbed (α) by dyes in gel suspensions was calculated by a method using an integrating sphere (26) according to the energy balance equation:

$$1 = T + R + L + \alpha$$

where L is the fraction of incoming light exiting the cell through the lateral windows and α is the fraction absorbed by the sample. The small fraction of the light exiting through the bottom of the cell and through the top surface of the suspension was neglected. Lateral losses required to calculate α are estimated as:

$$L = 2R'$$

under the assumption that the amount of light emerging from the lateral windows is the same as that of the light diffusing through the front window.

To correct for the possible absorption of light by the supporting material, measurements were performed on a suspension of the supported dye and for a blank consisting of a suspension of the same amount of support material.

The fraction of light absorbed by the dye and the reference is calculated as:

$$\alpha_{dye} = \alpha_{sample} - \alpha_{blank} \quad (4)$$

The absorbance spectrum of the dye can be calculated according to Eq. (5):

$$A = -\log(1 - \alpha_{dye}) \quad (5)$$

In the irradiation with polychromatic light within the wavelength interval λ_1–λ_2, once again using the same irradiation conditions for sample and reference and taking into account Eqs. (3) and (4), singlet oxygen quantum yields may be calculated as follows:

$$\Phi_\Delta^S = \Phi_\Delta^R \frac{V^S}{V^R} \cdot \frac{\int_{\lambda_1}^{\lambda_2} I_0(\lambda)\alpha_R(\lambda)d\lambda}{\int_{\lambda_1}^{\lambda_2} I_0(\lambda)\alpha_{dye}(\lambda)d\lambda} \quad (6)$$

where $I_0(\lambda)$ is the incident spectral photon flow (mol s^{-1} nm^{-1}). In our experiments, the wavelength interval was 610–800 nm. We assume that the incident intensity varies smoothly as the irradiation wavelength range is narrow, then I_0 is considered a constant value and cancelled in Eq. (6).

Dye permeation studies. Permeation experiments were made in a Franz diffusion cell (FDC) provided by PermeGear, USA (diameter = 25 mm, volume donor 20 mL). The Franz Cell apparatus is used in preclinical, *in vitro* studies to measure the enhanced percutaneous permeation of drugs and nutrient in delivery systems (27). Different membranes were utilized to study the release of phthalocyanines through the gel formulations. The membranes employed (MW cutoff 12000) were:

1 Hydrophilic porous polymeric membrane
2 *3M ™ CoTran™ 9728*: ethylene vinyl acetate (EVA) membrane
3 *3M ™ CoTran™ 9702*: controlled EVA membrane
4 *3M ™ CoTran™ 9711*: microporous polyethylene (PE) membrane
5 Skin male rat (WBN, weight of the specimen approaches 180–200 g, age of the rat ≈6–7 weeks, excised from abdominal fresh skin, depilated with an electric clipper)
6 Excised human skin from Caucasian patients who had undergone abdominal plastic surgery.

All the membranes except for the first are lipophilic with a pore size suitable for phthalocyanine molecular dimension. Membranes greased with the phthalocyanine-gel formulation were placed between two ground glass joints and sealed with a metal clamp. The receptor compartment was filled with a buffer solution containing 25% wt/wt of Solutol® HS 15 due to the high solubility of phthalocyanines in this medium (4).

Circulating 32 ± 1°C water through a FDC was employed to maintain skin physiological temperature (27). The acceptor fluid was mixed with a magnetic stirring bar at 500 rpm; experiments were performed overnight.

RESULTS AND DISCUSSION

Absorption spectra

The absorption spectra of zinc (II) phthalocyanines **1**–**4** in Cremophor® RH 40 at the 400–800 nm range were similar to those reported for homogeneous solutions (3–5). Table 1 shows the UV–Vis parameters of phthalocyanines **1**–**4** in homogeneous solutions.

The concentration dependence of the spectral properties was investigated upon excitation within the 500–800 nm Q-band. The strong tendency of **1**–**4** to aggregate is evidenced by the shape of the absorption spectra and the increase in the Q-band upon adding Cremophor® RH 40, thus indicating the induction of phthalocyanine monomerization. Figure 2 shows typical spectra of phthalocyanines **2** and **3** at different

Table 1. UV–Vis spectroscopic properties of **1**–**4** in homogeneous solutions.

Compound	**1***	**2***	**3†**	**4‡**
λ_{max} $Q(0–0)$ (nm)	678	676	673	704
ε_{max} $Q(0–0)$ (M^{-1} cm^{-1})	2.2 ± 0.1 × 10^5	1.8 ± 0.1 × 10^5	1.7 ± 0.3 × 10^5	1.1 ± 0.1 × 10^5

All parameters correspond to monomeric species. *In toluene (3); †in THF (4); ‡in THF (5).

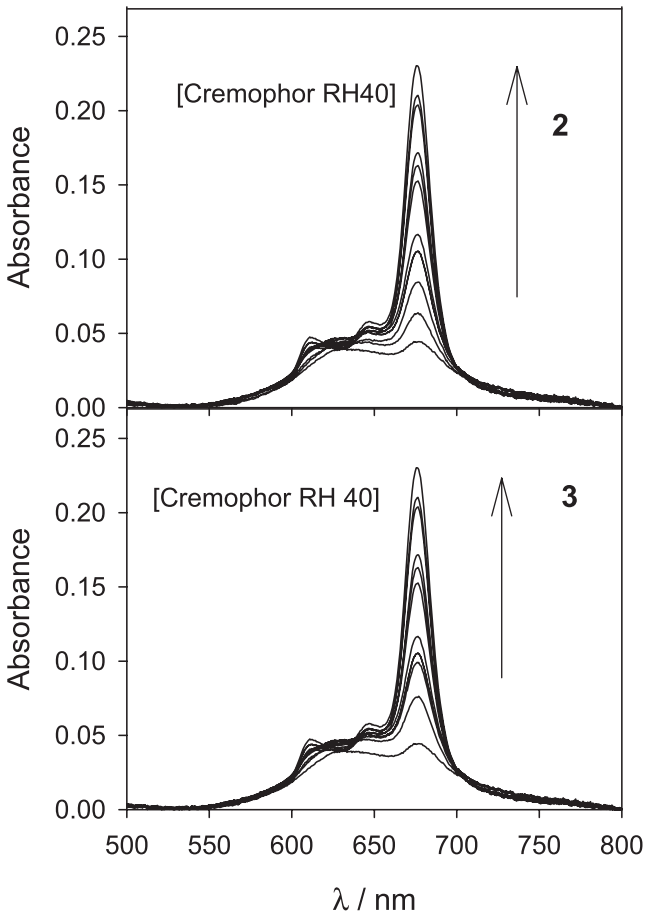

Figure 2. Absorption spectra of 2 and 3 in Cremophor® RH 40. [2] = 2.5×10^{-6} M; [3] = 9.0×10^{-7} M; [Cremophor® RH 40] = 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0 and 7.5% wt/wt.

Cremophor® RH 40 concentrations; a similar behavior is exhibited by phthalocyanines **1** and **4**.

When the phthalocyanines were encapsulated in scattering media such as gels, Lutrol® F 127 20%–polypropylene glycol 30%, Lutrol® F 127 15%–Cremophor® RH 40 10%–polypropylene glycol 15%, spectra were obtained according to Eqs. (1) and (5). Spectra of **1**–**4** in TFH, Cremophor® RH 40, Lutrol® F 127 and in the mixture of both matrices show neither significant wavelength shifts nor major modification in shape. These results were obtained either employing Eq. (1) or Eq. (5). The absorption spectra of compounds **1** and **2** are characteristic of the monomeric form (3,28). For **3** and **4** the shape of the spectra is typical of the presence of aggregates (4,29) (Fig. 3).

Fluorescence quantum yields

Fluorescence quantum yield measurements were performed employing AlTCPc in an homogeneous media (DMSO) as a reference and CV was added to each of the gel formulations studied. Different concentrations of CV were added and the sample corresponding to the monomer dye spectrum was used as a reference (22,30). Φ_F values (Table 2) obtained from both references were similar within 20% error.

The same behavior shown in absorption experiments was observed for Φ_F at an increasing concentration of Cremophor® RH 40 (Fig. 4). The addition of Cremophor® RH 40 increases fluorescence intensity at a given dye concentration, thus denoting that monomerization increases and that the monomer is the only fluorescent species.

Φ_F values (Table 2) show a strong tendency to aggregate for **3** and **4**. In all the matrices these phthalocyanines remain aggregated. The Lutrol® F 127 15%–Cremophor® RH 40 gel formulation induces further disaggregation of the phthalocyanines.

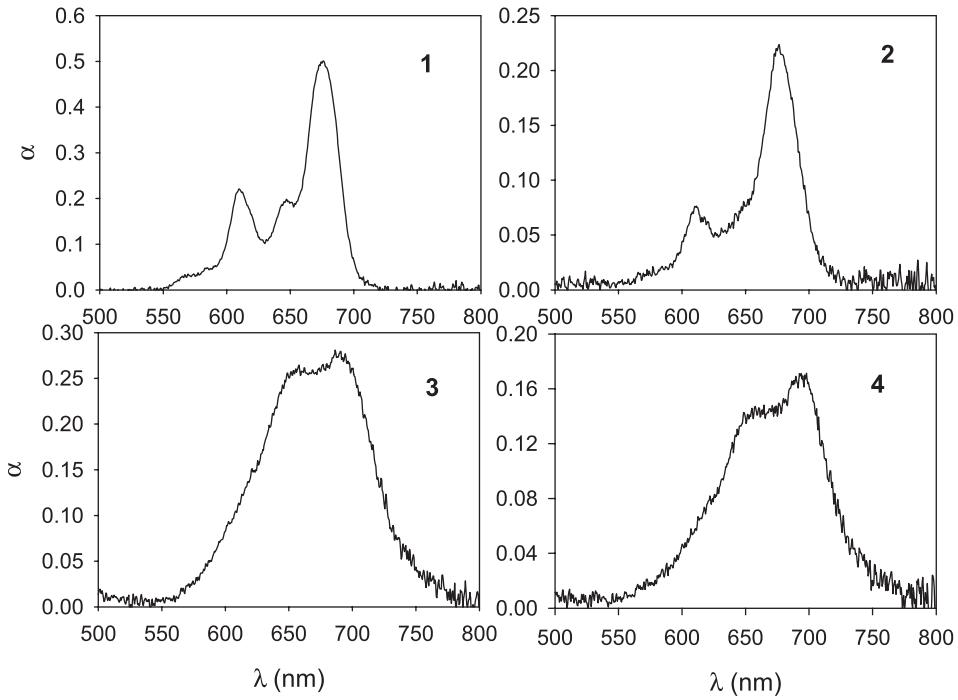

Figure 3. Absorption spectra: Fraction of the absorbed light (α) of **1**–**4** in Cremophor® RH 40- Lutrol® F 127. [Phthalocyanine] between 0.5 and 1.0 μM.

Table 2. Fluorescence quantum yields (Φ_F).

Pc/formulation	Φ_F* in homogeneous media	Φ_F Cremophor® RH 40	Φ_F Lutrol® F 127	Φ_F Lutrol® F 127–Cremophor® RH 40
1	0.33 ± 0.04*	0.20 ± 0.04	0.34 ± 0.04	0.34 ± 0.07
2	0.31 ± 0.03*	0.21 ± 0.04	0.34 ± 0.04	0.35 ± 0.06
3	0.28 ± 0.06‡	0.02 ± 0.06	0.01 ± 0.04	0.06 ± 0.03
4	0.26 ± 0.03§	0.02 ± 0.05	0.01 ± 0.05	0.04 ± 0.03

*Monomer values; †in toluene (3); ‡in THF (4); §in THF (5).

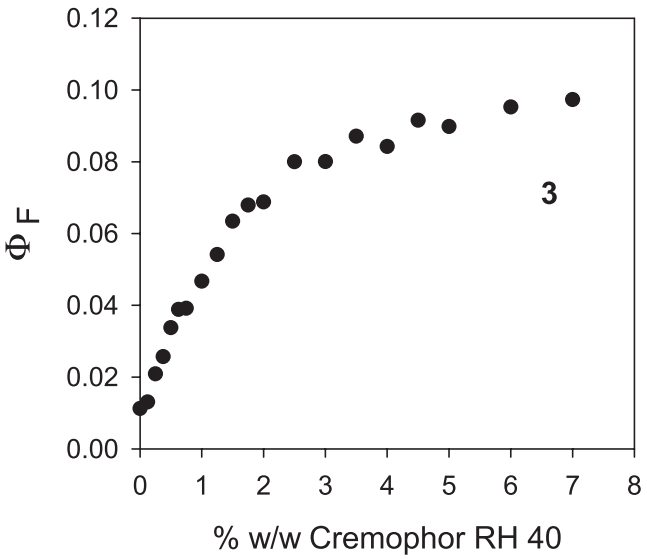

Figure 4. Fluorescence quantum yield of **3** at different Cremophor® RH 40 concentrations.

Singlet molecular oxygen quantum yield

These values (Table 3) were calculated against MB as a reference incorporated into different gel formulations at a concentration where only the monomer is present (0.1 μM). In all experiments samples were prepared with a phosphate buffer, pH = 7.0, instead of MilliQ water. Phthalocyanine concentrations between 0.5 and 1.0 μM were used. MB Φ_Δ value in gel was calculated using MB as a reference in a buffer solution.

Φ_Δ values (Table 3) for **3** and **4** show the tendency to aggregate in all the matrices. Photophysical characterization of **1**–**4** indicates that their aggregation degree is lower in lipophilic formulation than in Cremophor® RH 40 (hydrophilic gel).

Experimental errors are on the order of 25% due to factors such as medium heterogeneity greatly dispersing the light in samples. Besides experiments were performed at the minimum dye concentration in order to prevent aggregation, thus increasing the variability of the fraction of light absorbed by the sample and the reference sample (Eq. 6).

Dye permeation studies

In none of the permeation experiments was any phthalocyanine release observed. Besides, to improve epidermis permeation the skin pieces were transferred dermal side down into a petri dish which contained DMSO. However, the experiment was unsuccessful. To demonstrate that the formulation does not interfere with the drug release through the membrane, theophiline was encapsulated into the same carriers; after the experiment, 25% theophiline was observed on the acceptor compartment. These results agree with those reported by Kassab *et al.* (31) and Kaestner *et al.* (2) establishing that tetra and octasubstituted phthalocyanines used in topical applications *in vivo* are accumulated in the epidermis but do not reach the dermal layers.

Comparative spectroscopic studies of gel formulation spread on skin and on glass

Figure 5 shows the absorption and emission spectra of **1** (1.9×10^{-6} M) in Lutrol® F 127 15%, Cremophor® RH 40 10%, polypropylene glycol 15% gel formulation spread on rat skin and on glass. No difference in the absorption and emission spectra was observed in these conditions compared with **1** in solution. This akin behavior is a promising result to predict *in vivo* the efficiency of phthalocynine **1** formulation.

Preliminary experiments were carried out in order to study the photosensitization effect on human skin. The formulation described above was spread over human skin and irradiated with the same array as that employed for singlet oxygen experiments with approximately 3.8 J cm^{-2} light dose, and the absorption spectrum was then measured. After washing the skin with a phosphate buffer solution to rinse the phthalocyanine excess, a new absorption spectrum was taken (see Fig. 6) which shows a more disaggregated spectrum of **1** probably due

Table 3. Singlet molecular quantum yields (Φ_Δ).

Pc/formulation	Φ_Δ* in homogeneous media	Φ_Δ Cremophor® RH 40	Φ_Δ Lutrol® F 127	Φ_Δ Lutrol® F 127–Cremophor® RH 40
1	0.69 ± 0.13†	0.40 ± 0.10	0.90 ± 0.10	0.60 ± 0.10
2	0.66 ± 0.13†	0.60 ± 0.10	0.70 ± 0.10	0.60 ± 0.10
3	0.70 ± 0.10‡	0.13 ± 0.06	0.14 ± 0.06	0.20 ± 0.05
4	0.69 ± 0.05§	0.14 ± 0.05	0.19 ± 0.05	0.26 ± 0.05

*Monomer values; †in toluene (3); ‡in THF (4); §in THF (5).

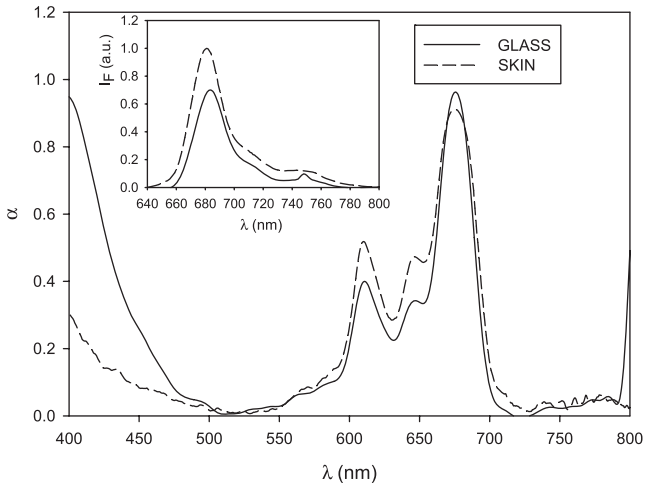

Figure 5. Fraction of the light absorbed (α) of **1** (1.9×10^{-6} M) in Cremophor® RH 40–Lutrol® F 127 on glass and on rat skin. Inset: fluorescence spectra of **1** (1.9×10^{-6} M) in Cremophor® RH 40–Lutrol® F 127 on glass and on rat skin.

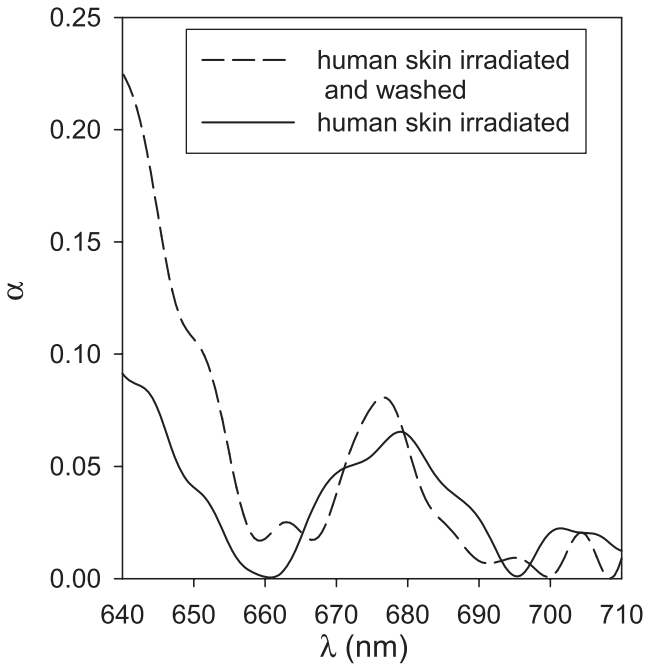

Figure 6. Fraction of the light absorbed (α) of **1** (1.9×10^{-6} M) in Cremophor® RH 40- Lutrol® F 127 on human skin after irradiation and on human skin after irradiation + washing.

to an increase in epidermis permeation on account of the photodynamic effect.

Herein we demonstrated that photophysical parameters *in vitro* can predict the *in vivo* skin behavior of a phthalocyanine formulation.

The photophysical properties of lipophilic phthalocyanines encapsulated into gels have been studied to our knowledge for the first time, in order to predict their efficacy *in vivo*. Photophysical techniques for solid phase were adapted for samples which present many problems such as bubbles, inhomogeneous surface and translucent systems, factors that greatly disperse the light.

In summary, gel formulation improves the photophysical properties of phthalocyanines. However, octasubstituted phthalocyanines **3** and **4** remain aggregated in spite of the lipophilic environment. Tetrasubstituted phthalocyanines **1** and **2** show a lower aggregation than that of octasubstituted dyes according to their absorption spectra, Φ_F and Φ_Δ values Nevertheless, **1**–**4** gel formulations are good photosensitizers to generate singlet molecular oxygen. As gel lipophilicity rises, Φ_F and Φ_Δ phthalocyanine values also increased (see Tables 2 and 3).

As a consequence of the permeation studies, there should be no risk of generalized skin photosensitivity in areas other than the dye deposition site. This is an advantage of topically applied sensitizers. Thus, zinc(II) phthalocyanines may be potential drugs for skin and epithelia disorders such as psoriasis, dermatitis and other conditions where multiple treatments are usually required.

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