

Photodynamic Therapy - Photosensitizers

Dr. Humberto Cabrera Morales

Instituto Venezolano de Investigaciones Científicas

The Abdus Salam International Centre for Theoretical Physics

Outline

1. Introduction
2. First generation photosensitizers
3. Second generation photosensitizers
4. Applications
5. Photodynamic therapy in dermatology
6. Conclusions

1. Introduction

The subcellular localization of sensitizers (lysosomes, mitochondria, and/or cell membranes) depends essentially on their nature and the cell line studied. Intracellular sites of photo damage do not necessarily correspond to the sensitizer binding site in cells, but relate to the PDT parameters involved, i.e. sensitizer concentration, incubation time, exposure time and laser power. The first photosensitizer used was a porphyrin derivative agent named hematoporphyrin derivative (HPD) and has become Photofrin® after purification. The approval of the FDA obtained in France (April 1996) after the USA (1995) and Japan (1994) promoted the synthesis and development of second generation photosensitizers.

1. Introduction

Principle. 2 agents act: photosensitizer (PS) and light.

PS must:

Have low toxicity in dark.

Accumulate in malignant tumors and not to accumulate in surrounding tissue at injection in blood.

Absorb light in some band near «therapeutic window» and initiate photochemical reactions resulting in cell destruction. One of ways: light energy is converted in excitation of oxygen molecules up to singlet state. Since the singlet oxygen is a very active radical, it initiates a chain of chemical reactions resulting in cell death.

Light source must:

Irradiate sufficient power in absorption band of PS. The best now is a diode laser.

Procedure. Inject PS into blood (intravenous way is better). Some time after irradiate tumor with sufficient dose.

1. Introduction

Ideal photosensitiser

Essential characteristics

- Pure chemical compound, not a mixture
- Efficient photosensitiser in situ
- Chemically stable
- Photostable
- Selective for target
- Intense, long-wavelength light absorption
- Non-toxic to host – rapidly excreted?
- Non-mutagenic in host

Desirable characteristics

- Aqueous solubility
- Easily formulated
- Short drug–light interval
- Straightforward synthesis/ease of scale-up

2. First generation photosensitizers

Haematoporphyrin derivative

Porphyrins are heteroaromatic compounds characterised by a tetrapyrrolic structure that consists of four pentagonal pyrroles linked by four methylene bridges, the porphine structure. It is characterised by an absorption spectrum having a specific band around 400 nm (Soret band) and usually four further absorption bands around 500-600 nm

Photofrin

Photofrin (Porfimer Sodium), a purified mixture of HPD

[1] T. Patrice, Photodynamic therapy, COMPREHENSIVE SERIES IN PHOTOCHEMISTRY & PHOTOBIOLOGY European Society for Photobiology (2003), **Chapter 1**, 8.

2. First generation photosensitizers

This first generation of photosensitizers present several deficiencies: the tumor selectivity is not as good as can be obtained with some of the newer sensitizers; the weak absorption in the near-infrared does not allow them to easily penetrate tissues (1 cm depth at most); they generally induce a strong and lasting (several weeks) skin photosensitization. Photofrin®, however, is safe and several clinical trials have been performed with this agent. Photofrin® was the first sensitizer to reach the market and was approved for specific clinical procedures by the government regulatory groups in several countries.

[1] T. Patrice, Photodynamic therapy, COMPREHENSIVE SERIES IN PHOTOCHEMISTRY & PHOTOBIOLOGY European Society for Photobiology (2003), **Chapter 1**, 8.

3. Second generation photosensitizers

1. 5-Aminolevulinic acid (ALA, Levulan@).

ALA is a hydrophilic molecule and, for this reason, it does not penetrate easily intact skin, cell membranes or biological barriers.

ALA is particularly efficient in dermatology for the treatment and the diagnosis of neoplastic skin tissues.

2. Chlorins

Unlike porphyrins, chlorins strongly absorb in the red (between 640 and 700 nm).

Chlorin e6 and derivative.

This hydrophilic sensitizer is mainly monomeric in a phosphate buffer solution, in which, at pH 7.4, it exhibits a main Soret peak at 402 nm and a strong peak in the red band at 654 nm. Its fluorescence is maximal at 675 nm with a life-time of 5.3 s

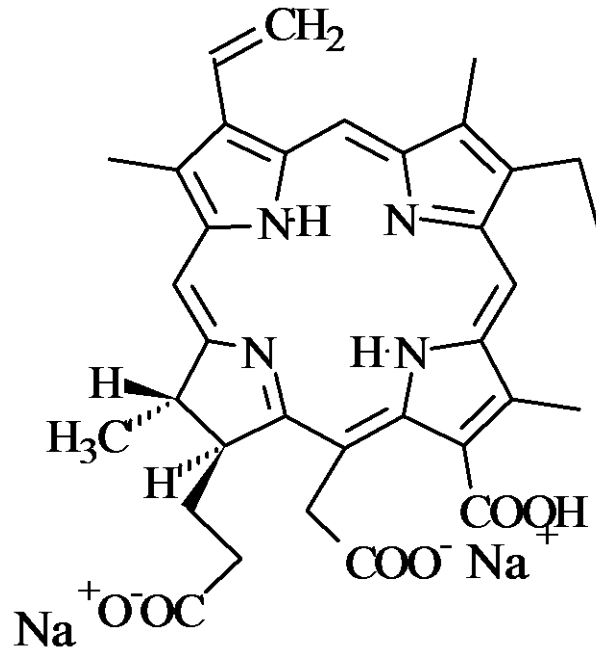
The Ce6 is localised in lysosomes where it induces damage after irradiation.

3. Second generation photosensitizers

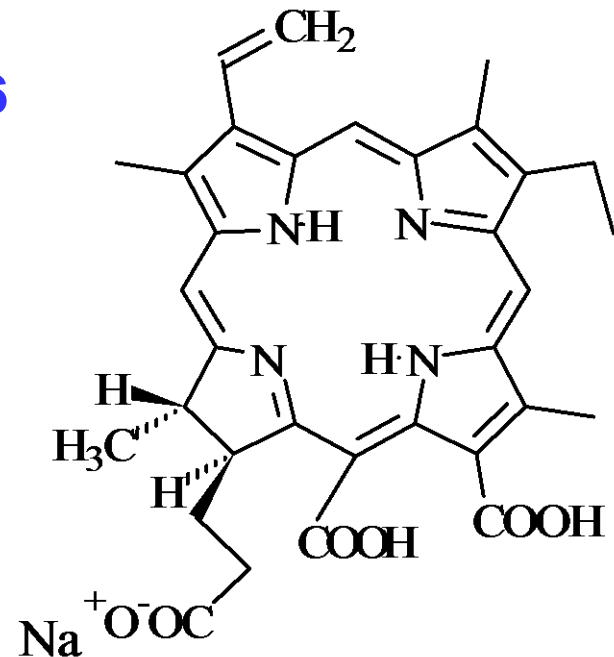
Photosensitizer RADACHORIN and PHOTOLON

Radachlorin (Ph) is a registered trade mark of a drug substance. It represents an aqueous solution of three chlorins, including sodium chlorin e_6 (90-95%), sodium chlorin p_6 (5-7%), and a third chlorin (1-5%). These chlorin constituents, "chlorin active substance", form 98% of the drug substance in dry weight. The drug substance Radachlorin is stored in form of 7% aqueous solution, we have found that this form provides the most shelf life (more 2 years).

e_6



p_6



3. Second generation photosensitizers

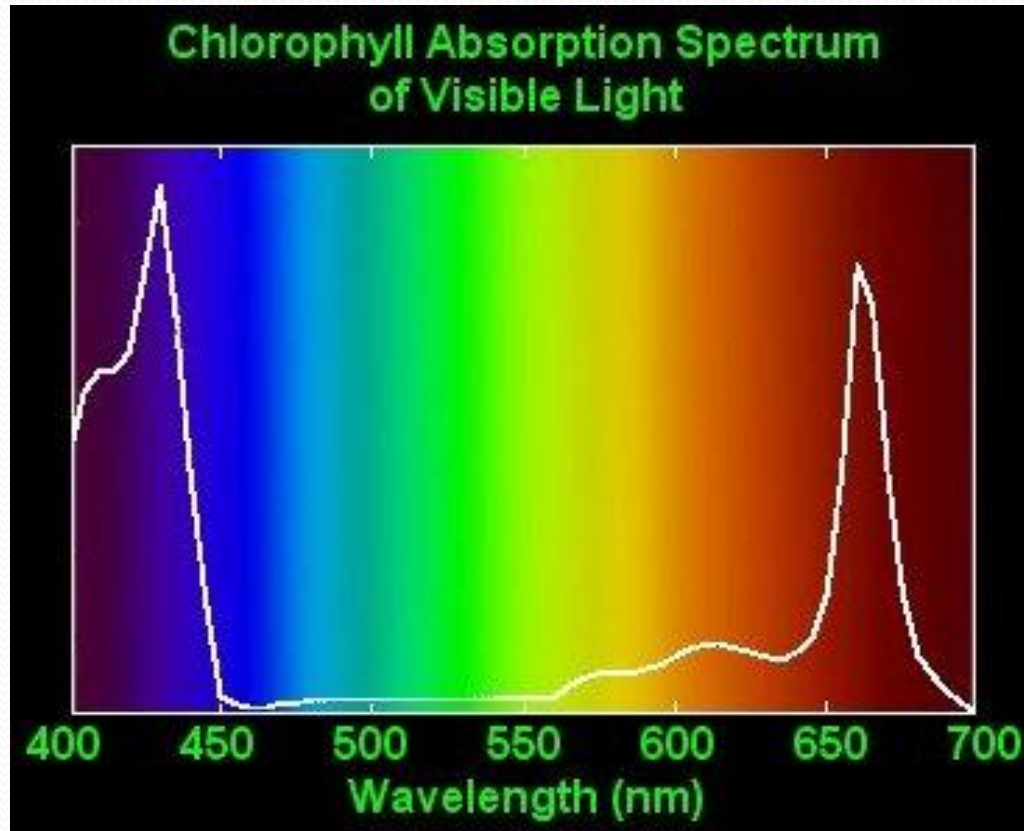


Fig. 1. Chlorophyll absorption spectrum

3. Second generation photosensitizers

Photophysical characteristics of Chlorin derivatives

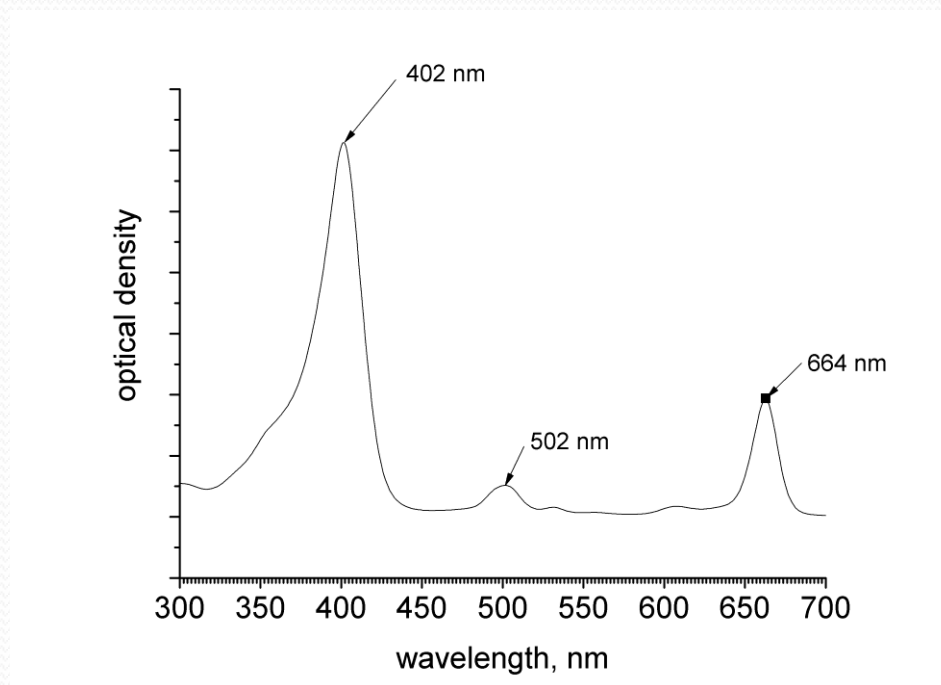


Figure 2. Typical absorption spectrum of Chlorin derivatives

3. Second generation photosensitizers

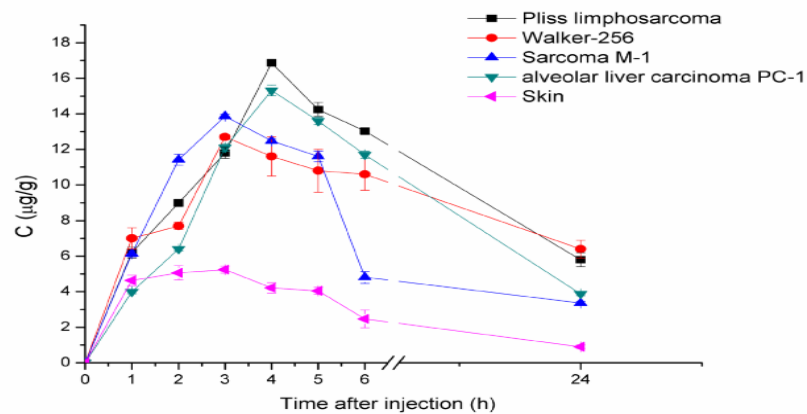


Fig 3. Accumulation of Photolon in different xenograft tumors and healthy skin of a rat.

3. Second generation photosensitizers

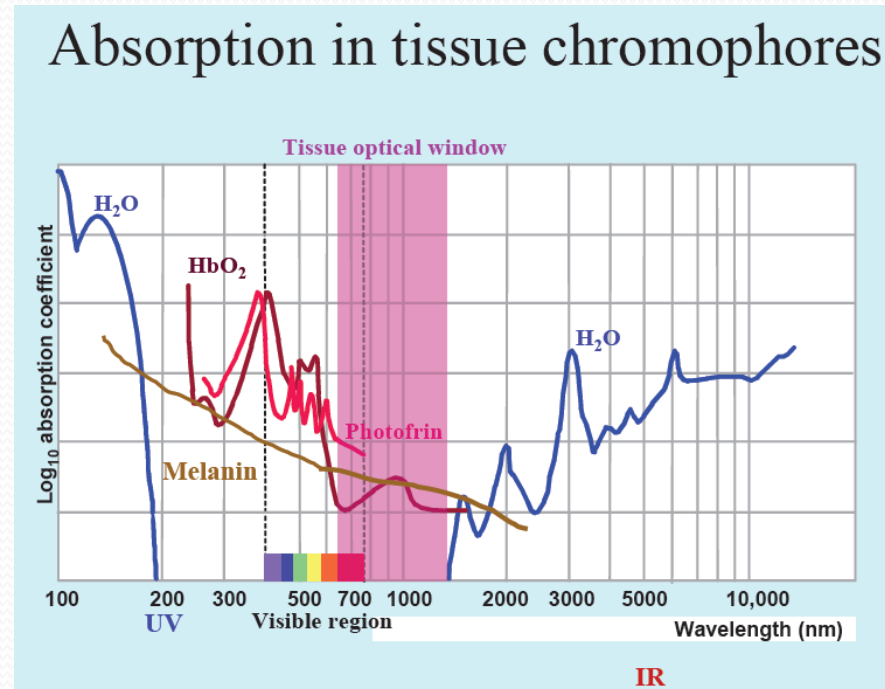


Figure 4. Absorption in tissue chromophores.

Longer wavelengths penetrate deeper.

3. Second generation photosensitizers

3. Purpurins

Purpurins have a strong absorption in the red, between 630 and 715 nm.

4. The benzoporphyrin derivative (BPD)

This chlorin (Verteporfin, Visudyne®) is synthesised from the protoporphyrin.

Its lipophilicity facilitates its association with the cell membrane. The main advantage of BPD is its strong absorption at 690 nm, promoting the tissue penetration of the light.

3. Second generation photosensitizers

5. Meta (Tetra) hydroxyphenylchlorin (m-THPC) and derivatives

m-THPC (temoporfin, Foscan) appears to be one of the most active Photosensitizing agents, requiring very low drug and light doses.

This sensitizer strongly absorbs in the red band with a maximal absorption at 652 nm

6. Phthalocyanines

Phthalocyanines are synthetic porphyrins.

Because of their very high molar absorption coefficient between 675 nm and 700 nm, some phthalocyanines are very potent photosensitizers.

3. Second generation photosensitizers

7. Texaphyrins

Texaphyrins are synthetic porphyrins, activated by deep tissue-penetrating red light, which are water soluble, tumor selective but rapidly cleared by the circulation

(Lu-TeX, Antrin, Lutrin, Optrin)

8. Bacteriochlorophyll a derivative agents.

Bacteriochlorophyll a is a natural pigment with an absorption band around 780 nm. At this wavelength, the penetration depth of light is approximately three times greater than that reached at 630 nm.

[1] T. Patrice, Photodynamic therapy, COMPREHENSIVE SERIES IN PHOTOCHEMISTRY & PHOTOBIOLOGY European Society for Photobiology (2003), **Chapter 1**, 8.

4. Applications

Cancer Therapy

- Microinvasive (early) endobronchial non-small-cell lung cancer.
- Other endobronchial lung tumors.
- Advanced, partially, or totally obstructing cancer of the esophagus.
- Other lung tumors, including mesothelioma.
- Early-stage esophageal cancer with Barrett's esophagus.
- Skin cancers.
- Breast cancer.
- Brain tumors.
- Colorectal tumors.
- Gynecologic malignancies: HPV-Human Papiloma Virus.

4. Applications

PDT for Other Diseases

- Cardiovascular (e.g., alternative to angioplasty).
- Chronic skin diseases [e.g., psoriasis].
- Autoimmune (e.g., rheumatoid arthritis).
- Macular degeneration.
- Antibacterial (wound healing, oral cavity).
- Antiviral (blood products, warts).
- Vaccines—especially anticancer vaccines.
- Endometriosis.
- Precancerous conditions: carcinoma in-situ and severe dysplasia in Barrett's; actinic keratoses (AK); cervical dysplasia; and so on.
- Neurosurgery.

5. Photodynamic therapy in dermatology

Uses for photodynamic therapy in dermatology include nonmelanoma skin cancer and its precursors, acne vulgaris, and photorejuvenation. Many other dermatologic entities have been treated with PDT, including psoriasis, lichen planus, lichen sclerosus, scleroderma, cutaneous T cell lymphoma, alopecia areata, verruca vulgaris, Darier's disease and tinea infections.

5. Photodynamic therapy in dermatology

As an example, consider PDT as a treatment for basal cell carcinoma (BCC). BCC is the most common form of skin cancer in humans.

Drug doses were injected intravenously at a dose of:

0.8-1.2 mg/kg (mean 1 mg/kg) body weight for Radachlorin®-PDT and 1.3-1.9 mg/kg (mean 1.6 mg/kg) body weight for Photolon®-PDT, drug-light interval 2-3 hours, light dose “ML-SP662” (662 nm, 2,5 W), 150-300 J/cm² (for Radachlorin®) or 100-250 J/cm² (for Photolon®)

<http://belmedpreparaty.com/eg/photolon.htm>

<http://www.radapharma.ru/main>

5. Photodynamic therapy in dermatology

The necrosis evolved during the first two weeks covering the total area of the tumor.

The lesions were totally removed after 5 weeks of the treatment with acceptable aesthetic results.

5. Photodynamic therapy in dermatology



Fig. 5. Photodynamic therapy illustration.

5. Photodynamic therapy in dermatology

Basal cell cancer of the skin treated with Photolon
(Patient :age 82)



Fig.6. Before PDT. Basal cell cancer There is a flat sore rising over the skin surface with erose edges and with scarce discharge.



Fig.7. 15 days after PDT. Partial tearing away of necrosis in the tumor zone. Surrounding skin is of usual color, no edema.

5. Photodynamic therapy in dermatology



Fig.8. 22 days after PDT. Partial tearing away of necrosis in the tumor zone. Surrounding skin is of usual color, no edema.



Fig.9. 6 weeks after PDT. Tearing away of necrosis in the tumor zone with edge epithelization of the wound.

5. Photodynamic therapy in dermatology



Fig.10. 75 days after PDT.



Fig.11. Before PDT.

5. Photodynamic therapy in dermatology



Fig.12. 15 days after PDT.



Fig.13. 34 days after PDT.



Fig.14. 68 days after PDT.

6. Conclusions

1. Most of the PDT drugs are porphyrin derivatives.
2. Other PDT drugs being investigated are phthalocyanines, naphthocyanines, chlorins, and tetrapyrins that absorb at longer wavelengths (in the red), providing a better penetration in tissues to allow for treatment of deeper tumors.
3. The mechanism of action is clearly linked to the intracellular localization of the sensitizers.
4. Besides cancer treatment, PDT also is useful for the treatment of a number of diseases such as cardiovascular disease, psoriasis, rheumatoid arthritis, and age-related macular degeneration.
5. Relatively selective and less invasive treatment regimen.
6. PDT has the advantage of avoiding surgery and its consequences.
7. PDT is very useful for multiple BCC.



Thanks for your attention