Photodiagnosis and Photodynamic Therapy 37 (2022) 102719

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Analysis and evaluation of the operational characteristics of a new photodynamic therapy device

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ARTICLE INFO

Keywords:
Absorption spectrum
Emission spectrum
Photosensitizer
LED technology
Photodynamic therapy (PDT)
LED device

ABSTRACT

One of the key aspects of photodynamic therapy is the light source that is used to irradiate the lesion to be treated. The devices used must ensure that their emission spectrum matches the absorption spectrum of the photosensitizer, so that treatment radiation is delivered only on the target area, without irradiating healthy tissue at superficial or deep levels. Irradiance values must be adequate in order to avoid thermal damage, exceed the oxygen replenishment rate and avoid long treatment times. Furthermore, the device should be user-friendly, inexpensive, and able to be adapted to different photosensitizers. We have developed an easy-to-use and highly customizable device based on LED technology. Its innovative geometric design allows radiation to be delivered to a small treatment surface, since the LEDs are arranged in three arms, the configuration of which directs their radiation on the treatment point. Different high-power color LEDs are disposed on the arms, and can be independently selected based on the most effective wavelengths for exciting the different photodynamic therapy photosensitizers. We have tested the prototype in 5 different patients (1 actinic keratose, 1 actinic cheilitis, 1 superficial basal cell carcinoma and 2 Bowen's disease) and after 1–2 sessions of total cumulative dose of 25–50 J / cm2, 100% clearance of lesions were obtained. Our device can be used by any professional in the field, whether for medical or research purposes. It facilitates the development of treatment protocols and trials with different photosensitizers.

1. Introduction

Traditional treatments for a wide variety of dermatologic lesions (eg, certain types of cancer, wounds, infections, and fungi) include hygiene measures and combined topical and systemic approaches. While the associated cure rates are high (75%−95%) [1], these approaches are not free from adverse effects, which are sometimes relevant (eg, gastrointestinal disorders, liver toxicity, hypersensitivity with skin involvement) and require long-term treatment (up to 6 months). In addition, treatment requires considerable self-discipline on the part of the patient and may interact with other medications [2].

As alternative to these traditional approaches appeared at the end of the 20th century and beginning of this century in the form of different types of light therapy [3,4] the known as photodynamic therapy (PDT). Technique consisting of the application of a photosensitizing drug or its precursor on the lesion or area to be treated. This chromophore makes the cells in which it is present sensitive to certain wavelengths of the electromagnetic spectrum, so that, when excited by them, a reaction is triggered that ends with its death.

Application of this technique requires 3 elements: oxygen, the photosensitive molecule (applied directly or induced by the photosensitizing agent supplied), and light [5].

On the one hand, we can select the photosensitizer. In dermatology, the most widely used photosensitizing agents are precursors of

; Abbreviation: PDT, Photodynamic Therapy; PpIX, Protoporphyrin IX; LED, Light Emitting Diode; BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma; UV, Ultraviolet.

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https://doi.org/10.1016/j.pdpdt.2022.102719
Received 15 September 2021; Received in revised form 19 December 2021; Accepted 7 January 2022
Available online 10 January 2022

protoporphyrin IX (PpIX) [5–7], a molecule whose absorption spectrum has an absolute maximum value of 409 nm (Soret band) [6, 8-10] and relative maximums of 509, 544, 548, and 634 nm (Q bands). In addition to porphyrin precursors, there are a large number of photosensitizing agents in use, many of which are based on the structures of tetrapyrroles [11], the pigments of life [12]. Examples include porphyrins, porphycenes, phthalocyanines, chlorins, pheophorbides, rose Bengal, and methylene blue, each of which is characterized by a specific absorption spectrum.

On the other hand, we can choose the light source for the treatment. Not all electromagnetic radiation on the visible spectrum (380 – 760 nm) can activate the photodynamic reaction, and the only useful bands are those that coincide with the absorption ranges of the photosensitive molecule, which depend on the photosensitizing agent selected for treatment. This determines the most appropriate wavelengths for treatment and, consequently, the optimal light treatment focused in used chromophores.

PDT was first applied using lasers [13], which enable short treatments (owing to their high degree of irradiation) of external application and high specificity. Lasers also enable internal treatment using endoscopy, given the possibility of using fiber optics as the light conductor. Consequently, for well-defined local treatment of lesions, we turn to laser technology, capable of limiting the radiation to the damaged area. However, as far as depth is concerned, the fact that it emits monochromatic light at around 630 nm means that it could affect healthy tissue in shallow, superficial lesions. This, together with the need for technical support, recalibration, and cost, is yet another drawback. As an alternative, new light sources have been developed which are cheaper, easy to use and maintain. We can cite the 300 W xenon arc discharge light generator filtered at the 630 ± 15 nm range (appropriate for PpIX) and irradiated between 55 and 158 mW / cm^2 for doses of 94–156 J / cm^2, a prototype lamp proposed by Morton et al. [14] 1995. In general, these types of filtered sources worsen the efficiency of the equipment, as well as increases the complexity in its design, with the addition that they are usually developed to treat lesions of a certain extension [13], with a not very selective definition (not the case of Paterson Lamp [14], which present a well define treatment field). They radiate both healthy and diseased tissue [15]. We can also cite the equipment proposed in 2006 by Moseley et al. [16], consisting of a matrix of AlGaInP **LED**s with an irradiance value of 12 mW / cm^2 for doses of 75 J / cm^2, which required exposure times close to 2 h, but allowed the self-treatment of the patients, so that when the photosensitizing drug was applied, they could leave the health center and self-irradiate after 4 h. A more recent proposal is, for example, that of Mordon et al. [17] in 2015, which presents a fiber optic-based fabric as a light source. Lastly, natural daylight has also been successfully adopted as the light source for some types of PDT in recent years [18].

All these contributions make clear the existence of a potential field of improvement for this technique, and the concern to achieve it. When using LED luminaires, there are not actual designs that concentrate light for a selective area with the consequent loosening of high-definition treatments and also, no LEDs devices are found capable of selectin output spectrum and irradiances depending on the photosensitizing drug used. Beyond the references indicated, the commercial panorama offers equipment (for example, Q-Med AB aktilite CL 128, OMNILUX Omnilux revive^2, MEDLight TrevioLux, Biofrontera BF-RhodoLED …), which generally have as drawbacks, the complexity of their design, size, and weight, which necessitate the use of a suitable support structure with multiple joints, this type of emitter is also hampered by the impossibility of applying local treatments without affecting a healthy surface or a damaged surface with different treatment requirements. In such cases, i.e., neighboring small lesions, the dose cannot be adapted as necessary, leading to over- or underexposure depending on the case.

For all this, considering that the state of the art in light-emitting diode (LED) technology makes it possible to develop sources with emission spectra adjusted to demand in the range running from UVC to near infrared. The objective of the present study is, first, to present a light source design based on LED technology that is inexpensive, requires minimum maintenance, is user-friendly, and can administer local treatment at the most effective wavelengths for the photosensitizer and the necessary depth of penetration at quantitatively and qualitatively appropriate doses. We also evaluate the operational characteristics of this approach and verify its effectiveness in a pilot study with 5 different patients.

2. Material and methods

The prototype light source (patent status: requested, in the last stages of the process) was manufactured according to the following specifications: a main body comprising a hollow cylinder measuring 15 cm in length and 4 cm in diameter and composed of plastic insulating material that acts as the handle; an aluminum component in the form of 3 arms set at 120° from each other and with 3 planes inclined at 160° on each arm; aluminum printed circuit boards and LEDs of different wavelengths. The first version of the prototype, namely Device A, mounted 405, 530 and 630 nm LEDs, later versions of it, that we named as Subsequent Devices, mounted other LEDs combinations selected from among the wavelengths capable of exciting the most common photosensitizers in the literature [405, 530, 630, 660, and 790 nm] among others. It is straightforward to adapt the basic design of the equipment to include more arms, so allowing the mounting of more LEDs of differing wavelengths with their individual concentrating lenses.

The printed circuit boards are connected in series by wavelength, thus generating 3 LED arrays (1 per arm) that are supplied by 3 different power supplies in order to enable independent control of each wavelength. The geometric configuration of the piece that supports the printed circuits on which the LEDs are mounted, and on these their concentrating lenses (20–25º), allows the treatment lamp to be focused on a different surface, being able to select specific areas of injury (up to 5 cm2). Consequently, specific treatments can be delivered to accurately defined areas. In addition to enabling the geometry of the construction, the metal material of the component dissipates the heat generated. The component in question is attached to the lower section of the main body by means of a screw. The power supplies supplying each of the arrays are controlled by their respective switches, which finish in a single cable that is connected to the mains supply. The design of the device can be seen in Figs. 1-3.

The radiation emitted by each of the LEDs of the light source was characterized independently by placing them on a simple aluminum printed circuit board with positive/negative supply connections and 2 fixing screws. In order to guarantee a power for measurement under working conditions, we used a double PROMAX FAC-662B power supply set at an intensity of 350 mA (Fig 3A). The measurements were taken in darkness in the laboratory after the stabilization of the light output of the emitters from its cold start to its steady state value fixed by the balance of self-generated heat and the heat-sinking capacity of the aluminum PCBs and body of the lamp. In our case, it means a 14 min time lapses producing a maximum of 6% of light output decrease from its cold start which can be consider negligible for the phototherapy treatment purpose. We use a clamp to place the emitter (central axis of emission) in front of the sensor (central axis of the entrance hole to the integrating sphere), with a distance between them of 6 cm (Fig 3A). Spectral irradiance was measured using a double-monochromator spectroradiometer (MACAM SR-2271, Irradian Co., Scotland, UK) connected via fiberoptics to an Ulbricht integrating sphere. The spectroradiometer was calibrated both for wavelength and for irradiance at the National Optics Center Madrid, Spain, using a certified UV–Vis calibration lamp.

Irradiance was assessed using the Device A at the treatment distance (Fig 1 and 3B). We made independent measurements by wavelength and finished by measuring with all the arrays running simultaneously (Fig 4).

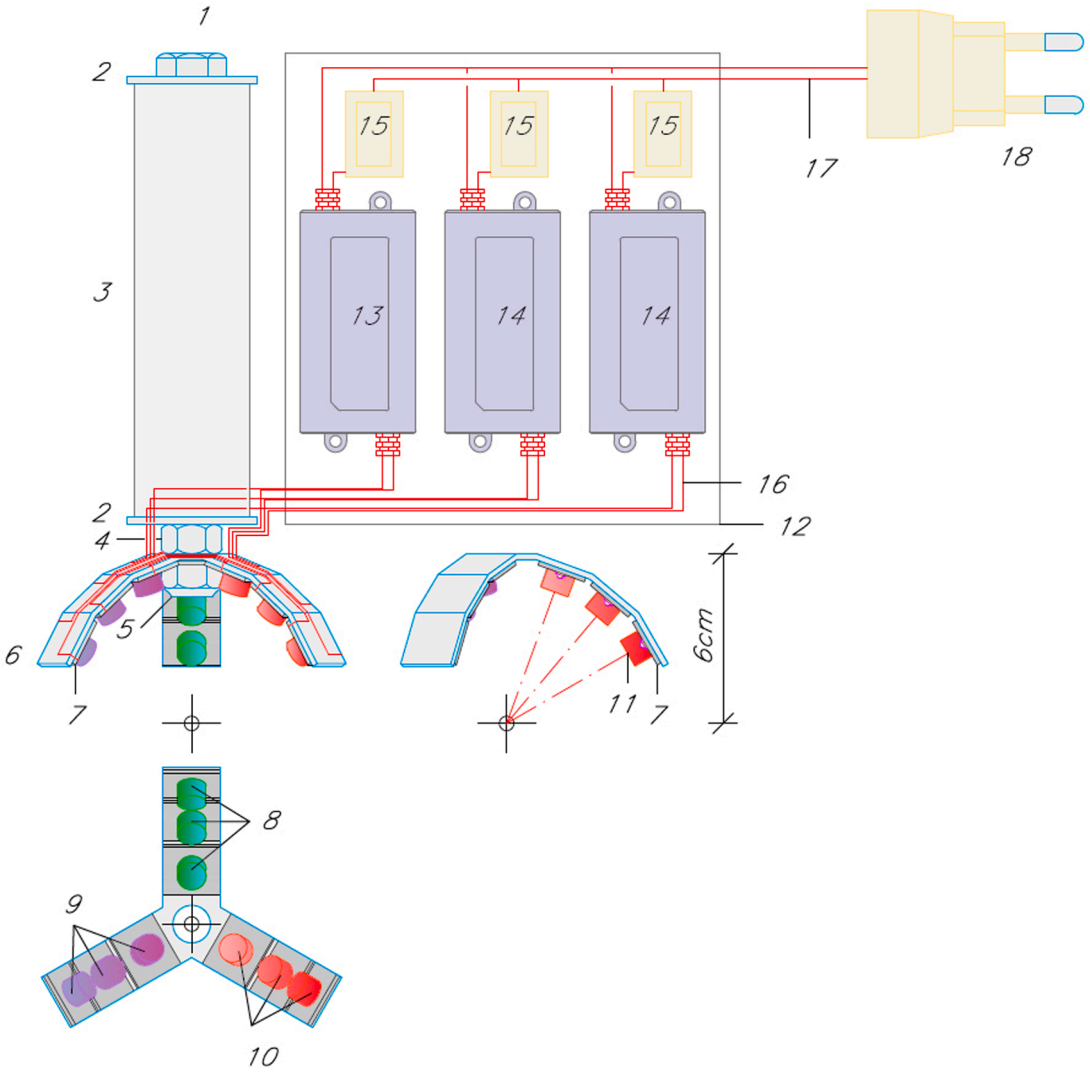

Fig. 1. Schematic representation of the light source for photodynamic therapy as set out in the present invention. 1. Body assembly screw – 3-arm aluminum component. 2. Body closing washer. 3. Arm made of plastic insulating material. 4. Positioning nut for the 3-arm aluminum component. 5. Self-locking assembly fixing nut. 6. Aluminum component with LED arrays arranged in 3 arms. 7. Printed circuit board for high-power LEDs. 8. High-power LED (405 nm). 9. High-power LED (630 nm). 10. High-power LED (530 nm). 11. Concentrating lens. 12. Insulated driver housing. 13. LED driver array (405 nm). 14. LED driver array (530 nm and 630 nm). 15. LED array on/off relay. 16. LED array DC supply cable. 17. Single-phase voltage (230 V – 50 Hz) AC supply cable. 18. Low-voltage mains plug (230 V – 50 Hz).

We performed a compatibility analysis of Device A (designed to work with porphyrins) and Subsequent Devices (which mounted LEDs with different wavelengths as previously in Device A) using different photosensitizers, some of which were approved for medical use and others for research purposes. To do so, we matched the emission spectrums with the absorption ones of some of the most commonly used photosensitizers in this type of therapy (Fig. 5).

The methodology followed was that shown in Table 1, with

Table 1
Preliminary results for PDT treatment in a group of 5 patients with different skin pre-cancer and non melanoma skin cancer in different body localizations. Proof-of-concept testing was carried out following a protocol inspired by the European guidelines for topical photodynamic therapy [19]. Methyl aminolevulinate cream was used and patients received 1 or 2 PDT sessions.

Patient number	Sex	Age (years)	Fitzpatrick skin Phototype	Cutaneous Condition	Location	Visual analogue scale-pain (VAS; 1–10)	Nº of sessions	Cumulative dose (J/cm^2)	Photobleach?	Clearance?
1	F	75	III	Actinic cheilitis	Upper lip	8	1	25	YES	YES
2	M	80	II	Actinic keratoses (cancerization field)	Left Temple	7	1	25	YES	YES
3	M	58	III	Superficial Basal Cell Carcinoma	Right supraclavicular area	4	2	50	YES	YES
4	F	77	III	Bowen Disease (SCC in situ)	Right leg	5	2	50	YES	YES
5	M	73	III	Bowen Disease	Left Hand dorsum	5	2	50	YES	YES

incubation of the photosensitizer for 3 h as set out in the clinical guidelines for PDT. The design of the study was supplemented by a various clinical test to evaluate the preliminary efficacy and tolerability of the Device A in a sample of 5 patients with localized lesions with clinical confirmation of 1 actinic keratosis field of cancerization, 1 actinic cheilitis, 1 superficial cell carcinoma and 2 Bowen diseases. Proof-of-concept testing was carried out following a protocol based on the European guidelines for topical photodynamic therapy [19]. The European for normal PDT Methyl aminolevulinate cream was used as the sensitizer (Metvix®, Galderma, Switzerland) and the patients were treated with 1 or 2 sessions of PDT (25–50 J/cm2 cumulative dose). Visual analogue scale-pain was assessed, and level of photobleaching and clearance was analyzed. The patient study was carried out in the University Hospital Ramón y Cajal from Madrid. Proof-of-concept testing with these patients was approved by the local ethics committees and the patients signed the inform consent for the study.

3. Results

The characterization of Device A (Fig. 2) LEDs yielded the following values: red LED (without concentrating lens), peak wavelength 632 nm with a spectral bandwidth of 17 nm (621 – 638 nm) and absolute irradiance up to 6.91 mW/cm^2; green LED (without concentrating lens), peak wavelength 522 nm with a spectral bandwidth of 36 nm (506 – 542 nm) and absolute irradiance up to 4.10 mW/cm^2; and a violet LED (without concentrating lens), peak wavelength 404 nm with a spectral bandwidth of 18 nm (395 – 413 nm) and absolute irradiance value up to 14.60 mW/cm^2 (Fig. 4).

The Device A characterization (concentrating lenses mounted on each LED) yielded the following values for irradiance delivered to the treatment area: red LED, 65.74 mW/cm^2; green LED, 24.48 mW/cm^2; and violet LED, 117.15 mW/cm^2 (Fig. 4).

Fig. 5 shows the findings from the study of the compatibility between the sources used here (Device A and Subsequent Devices) and the photosensitizers (porphyrin, chlorin, bacteriochlorin, methylene blue, and rose bengal). The Device A proved to be optimized for treatments based on PpIX precursors. Nevertheless, it also has suitable characteristics for use with the other photosensitizers by changing the used LEDs or by developing more arms in the device for a larger set of colors (Fig. 5).

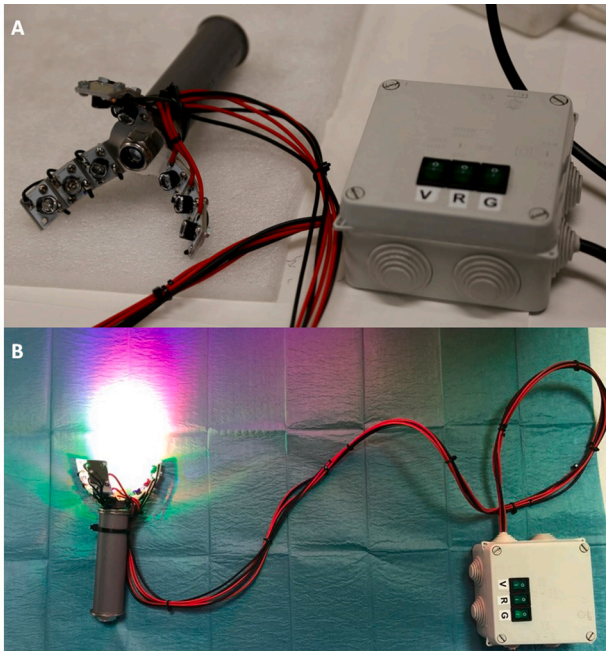

Fig. 2. A) Assembled prototype (Device A). B) Prototype (Device A) with Blue, Green and Red LEDs-on prior to illumination for Metvix PDT.

Table 1 shows the results of the first test with the Device A in a group of 5 patients who received PDT in the present study. In all of them, a strong photodynamic reaction was observed, which was the result of a long incubation period and of the light energy density (Table 1). In all of them, photobleach was observed using a Wood's light after treatment. The criteria was qualitative based on the presence of coral red fluorescence when the lesion was illuminated. After assimilating the photosensitizing drug (3 h after application), and prior to treatment, emission of coral red fluorescence was observed (transition from PpIX exited to basal state according to the fluorescence relaxation mechanism), after treatment the fluorescence disappeared (PpIX consumed by treatment). Patients 1 and 2, with needed only 1 PDT session showed highest painful treatment with level of 7–8 in the visual analogue scale. The rest showed pain level of 4–5. Two weeks after the first (in case of patients 1 and 2) or second session in patients 3–5 treated by this procedure the lesions were disappeared. The images of the serial treatment protocol in the patient 2 with an actinic cheilitis is shown in the Fig. 6 (A-C) as example of treatment with the device. Two weeks later lesion was disappeared (Fig. 6D).

4. Discussion

We propose a low-cost device, easy to use and customize, as shown in the prototype. The simplicity of its design and its components, together with its ease of assembly, allows the device to be customized for new applications without the need for major changes to the original proposal. It allows mounting diodes of other wavelengths and other types of lenses, as necessary, it even allows adding one or more additional arms, without this variation implying a conceptual change in the equipment and thus improving its versatility. A control system can be added by replacing the on / off buttons for each source with relays connected to the system's microcontroller, which will turn each arrangement on or off based on programmed parameters.

The ability to concentrate light in small regions of space, as well as to select the desired wavelengths, makes this source an apt tool to administer selective treatments to small lesions without the need to affect healthy tissue (both in depth and in lateral extent), and make it capable of individualizing the treatment in case of small lesions close to each other but with different needs (adapting irradiance, emission spectra and dose as required), without incurring in underexposing some or overexposing others.

When used as proposed in the present study, the Device A or the Subsequent Devices present a series of compatibilities depending on the photosensitizers used (Fig. 5). In the case of Device A, with porphyrins, emission/absorption peaks coincide at the wavelengths 404 nm/409 nm, 632 nm/634 nm, and, albeit to a lesser extent, emission at 522 nm with absorption at 509 and 544 nm. In the case of chlorins, emission/absorption peaks coincide at 404 nm/399 nm, and, again to a lesser extent, emission at 522 nm with absorption at 509 nm. With bacteriochlorins, the only wavelengths at which the emission/absorption peaks coincide are 404 nm/399 nm. In the case of methylene blue, the wavelengths coincide at an emission peak of 632 nm and an absorption spectrum between maximums of 615 and 670 nm. With rose bengal the emission/absorption peaks coincide partially at the wavelengths 522 nm/555 nm.

The use of high irradiance values close to 150 mW / cm^2 achieved by simultaneous operation of several of the matrices that make up our device, allows reducing treatment times. This value of 150 mW/cm^2 shall not be exceeded, above which thermal damage may occur [20]. In this sense, it is also important to note that such fluence values can exceed the oxygen replacement rate necessary for the correct development of the PDT reaction, and consequently, reduce the effectiveness of the treatment [21]. This is an aspect to consider in future studies.

Taking into account the operative characteristics revealed by our study, we propose our device as a light source for the management of

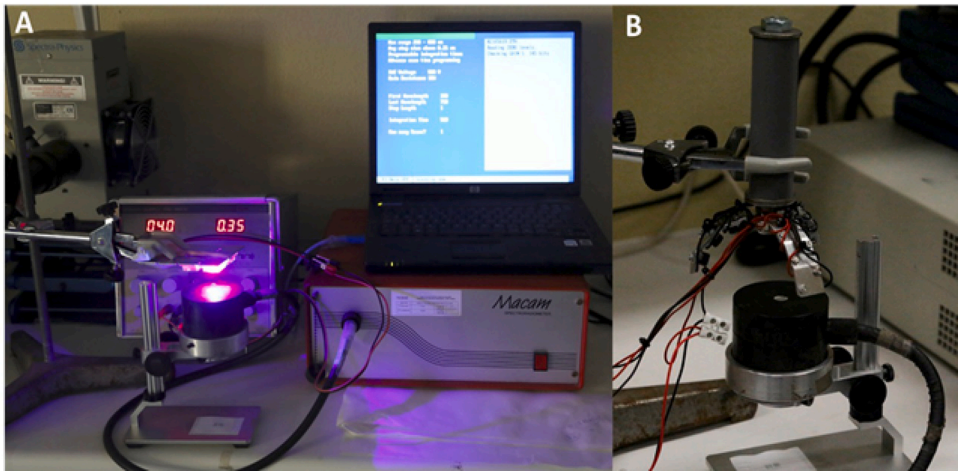

Fig. 3. A) Independent LED spectral characterization by means of a MACAM SR-2271 double-monochromator spectroradiometer, previous to their installation into the device. B) LED device spectral characterization on top of the Ulbricht integrating sphere connected to the spectroradiometer for lamp spectral and irradiance characterization.

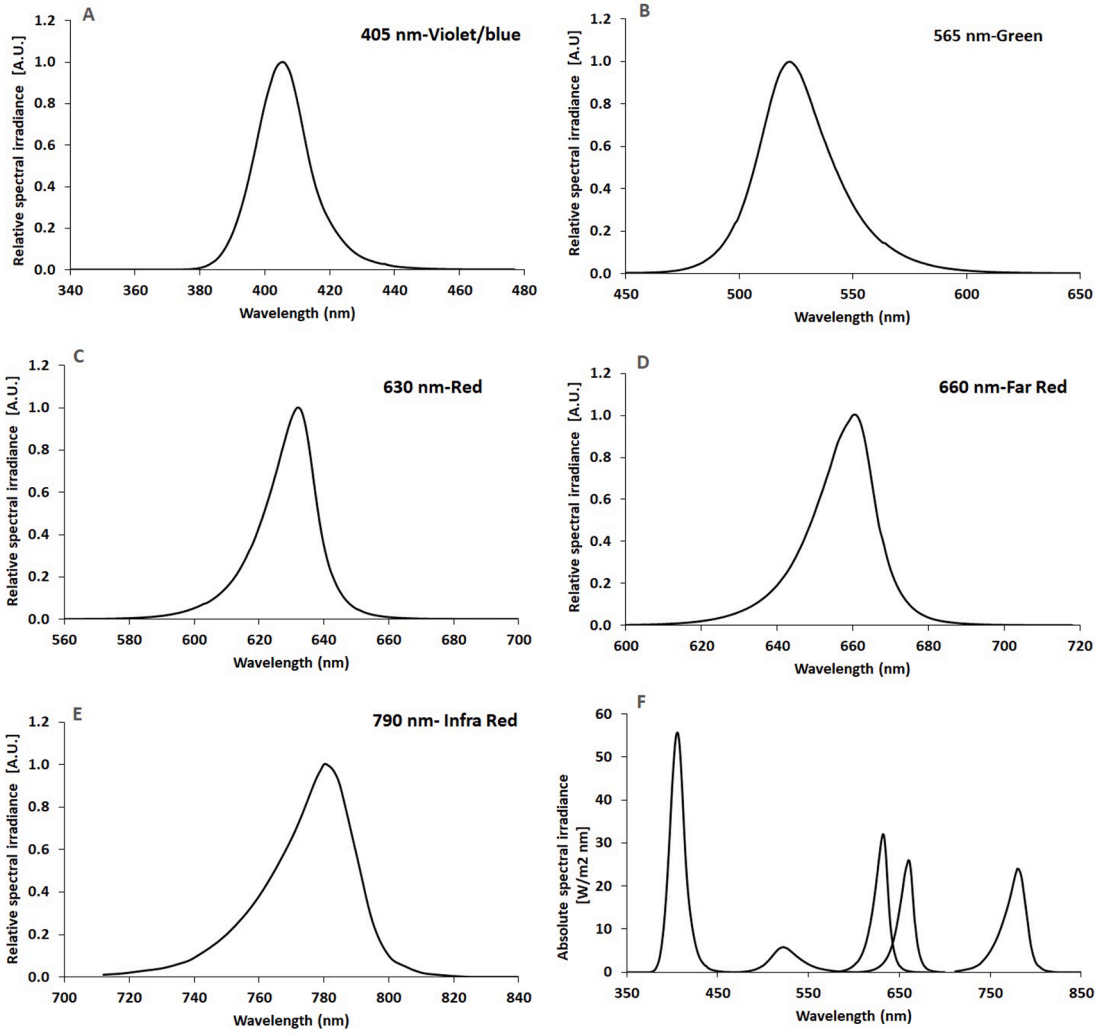

Fig. 4. Relative spectral irradiance for LEDS selected for photobiologic treatments: Device A) violet (405 nm), B) green (530 nm), C) red (630 nm). Subsequent Devices D) red (660 nm), E) infrared (790 nm). F) Absolute irradiance of the 5 types of LEDs included in a 3 arms prototype.

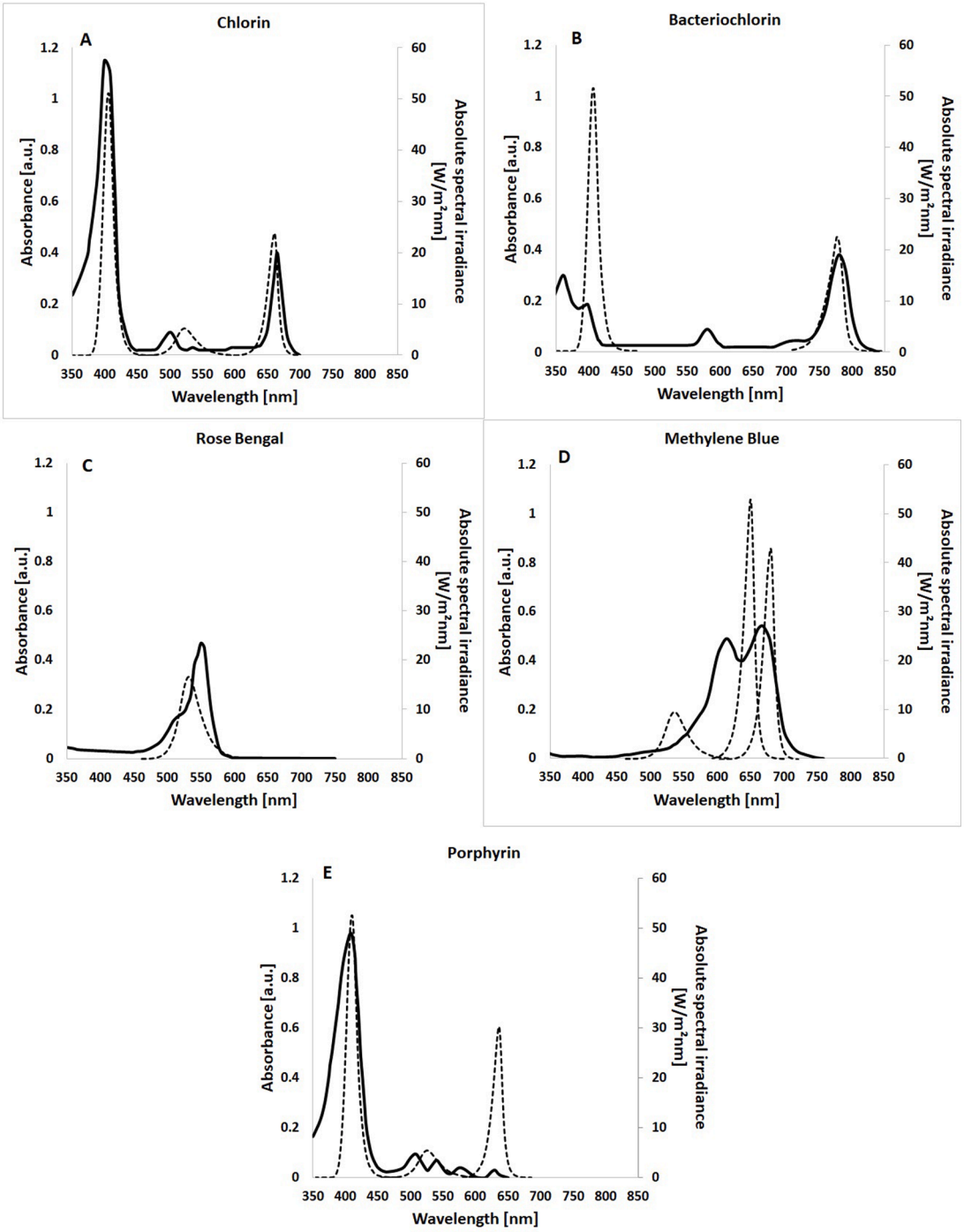

Fig. 5. Overlap of the absorption spectra of the various photosensitizers commonly used in therapy and the absolute irradiance of the source in configuration of Device A and Subsequent Devices (use of LEDs of 5 different wavelengths): A) Chlorine, 3 types of LEDs (violet / blue [405 nm], green [530 nm] and far red [660 nm]); B) Bacteriochlorins, 2 types of LEDs (violet / blue [405 nm] and infrared [790 nm]); C) Rose Bengal 1 type of LED (green [530 nm]), D) Methylene blue, 3 types of LED (green [530 nm], red [630 nm] and far red LED [660 nm]); and E) Porphyrins, 3 LED arms (violet / blue [405 nm], green [530 nm] and red [630 nm]).

lesions such as actinic keratosis, Bowen's disease, basal cell carcinoma and onychomycosis, among others. The parameters of the PDT in each case will need to be studied.

Device applications are not limited to those listed above. It can also be applied in PDT in many other ways, for example, treatment of psoriasis using oral aminolevulinic acid (3 – 6 h) as a photosensitizer, with an array of 404 nm to deliver a dose of 20 J/cm^2 [22]. Furthermore, given that no clear protocols have been developed to determine optimal irradiance values, wavelengths, type and dose of photosensitizers, or dosage [23] according to the lesion and its parameters (eg, lateral extent, depth, location) [24,25], the versatility, ease of manufacture, and low cost of the device we propose makes it a tool with enormous potential in this field.

Our preliminary results for the patients treated show that the tolerability and adverse effects profile to be similar to those of standard PDT with other high-intensity LED devices (Q-Med AB aktilite CL 128, Biofrontera BF-RhodoLED) that are currently being used in application of the technique, with the advantage over these, that given the greater irradiance of our device, the times necessary to apply the treatment dose are shorter and consequently the time that the patient has to endure the

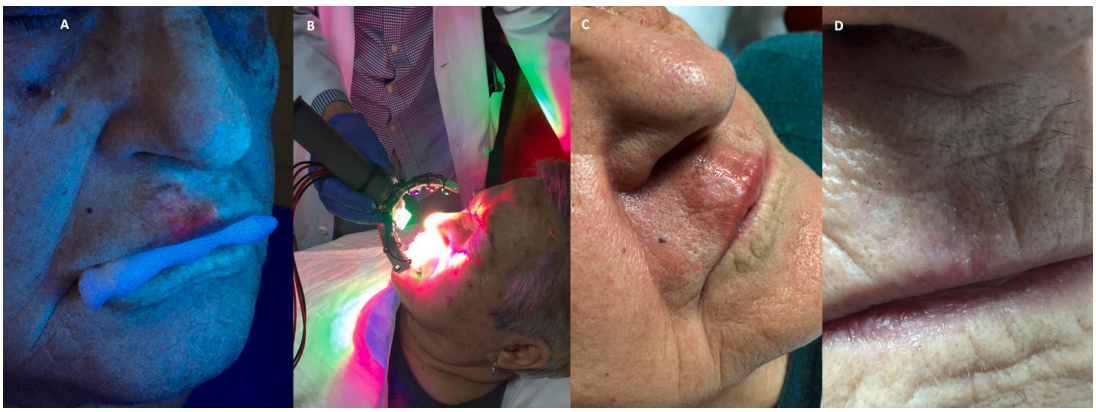

Fig. 6. Series of images in an example of Actinic cheilitis treatment with MAL-PDT in one patient of the study. A) UV image of the patient face with fluorescence of protoporphyrin IX in the upper lip lesions. B) Subsequent illumination with Device A using a violet/ blue (405 nm), green (560 nm) and red (630 nm) treatment combination. C) Outcome just after irradiation of the lesion. D) Image of the upper lip after 2 weeks of treatment with 100% resolution of the lesions.

pain (in none of the cases treated, the pain has exceeded a threshold value that would require early termination of treatment). While assessment of efficacy was not the primary objective of our study, we found the device to be 100% effective for localized lesions with the appropriate indication (actinic keratosis, basal cell carcinoma, and Bowen disease). Treatment with this experimental device proved to be practical and easy to apply given the short duration of the session and the maneuverability of the LED light.

5. Conclusions

A novel design of light for PDT is presented with demonstrated clinical effectiveness in a set of patients with pre-cancer and skin cancer lesions. This new LED based light source is cost friendly, easily manufactured and can be customized, either by changing the wavelengths of the LED arrays or adding more arms (as many as 6). Its design makes it possible to administer treatments that are highly accurate in terms of both lateral extent and depth of the lesion to be treated without damaging adjacent healthy skin, and without affecting any other nearby lesions that have has other treatment requirements. This all gives the device enormous potential for PDT treatments and as a research tool.

CRediT authorship contribution statement

Enrique Navarrete-de Gálvez: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **José Aguilera:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Pablo Fonda-Pascual:** Writing – review & editing, Validation, Investigation, Conceptualization. **María Victoria de Gálvez:** Funding acquisition, Investigation, Writing – review & editing. **José Ramón de Andrés-Díaz:** Writing – review & editing, Supervision, Methodology. **Santiago Vidal-Asensi:** . **Enrique Herrera-Acosta:** Investigation, Supervision, Writing – review & editing. **Alfonso Gago-Calderon:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

Non declared.

Acknowledgments

This work has been supported by the project no. PID2020–117224RB-100 of State Programs of Generation of Knowledge and Scientific and Technological Strengthening of the System from the Spanish Ministry of Science and Innovation. This work is part of the research of the Institute of Biomedicine of Málaga (IBIMA) and the Junta de Andalucía working group CTS-162.

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