Topical Review

Quantum dot light-emitting diodes as light sources in photomedicine: photodynamic therapy and photobiomodulation

Manuel A Trian A1, Adriana A Restrepo1, Raymond J Lanzafame1, Peter Palomaki2 and Yajie Dong2,3,4

1 NanoScience Technology Center, University of Central Florida, Orlando, FL 32826, United States of America
2 QLEDcures LLC, Orlando, FL 32826, United States of America
3 Department of Materials Science and Engineering, University of Central Florida, Orlando, FL 32816, United States of America
4 College of Optics and Photonics, University of Central Florida, Orlando, FL 32816, United States of America

E-mail: Yajie.Dong@ucf.edu

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Abstract

Widespread clinical adoption of photodynamic therapy (PDT) and photobiomodulation (PBM) has been limited due to the lack of a suitable commercial light source. Cost-effective quantum dot light-emitting diodes (QLEDs) promise to be an ideal light source nicely fitting into this niche, not only complying with desired form factors—flexibility, lightweight, and uniform large area illumination—but with narrow emission spectrum and high power density at clinically relevant deep red wavelengths. This paper is intended to provide a review on the development of QLEDs as a photomedical light source, specifically, for PDT and PBM. First, we introduce the potential of QLEDs as light sources in the photomedical field, briefly describe the mechanisms and benefits of both PDT and PBM phototherapies, and present the unique features of flexible QLEDs (FQLEDs) over conventional and commercial light sources. Then, the pioneering work and state-of-the-art research using QLEDs and organic light emitting diodes (OLEDs) for photomedicine are presented. The performance of QLEDs/OLEDs used in photomedical studies and latest progress on QLEDs are also summarized. Ultimately, we discuss the materials and design strategies for fabrication of efficient and stable FQLEDs, and present the basic requirements for near future introduction of FQLEDs into the healthcare and photomedicine markets. This review is expected to be comprehensive and useful to the scientific community interested in developing lightweight and flexible light sources for photomedicine and/or exploring novel applications for OLED/QLED based lighting devices.

1. Introduction

Quantum dot light emitting diodes (QLEDs) are attracting much attention due to their properties highly desirable for the display and lighting industries, and most recently in the photomedicine field. Such properties comprise emission wavelength tunability (by controlling the quantum dot size), high color purity or narrow emission bandwidth, wide color gamut and high power density [1–3]. Besides the optoelectronic properties, solution-processed QLEDs also offer simple/low-cost processing and high stability of the active quantum dot (QD) materials [4, 5]. Indeed, inkjet printing [6], direct photolithography [7] and transfer printing [8] have been proposed for film deposition of colloidal QDs, with inkjet printing being the most attractive technique to date for scalability and patterning of devices due to features such as on-demand jetting and flexible substrate capability [9, 10]. Solution process development to make flexible QLEDs (FQLEDs) on plastic-based substrates also creates an opportunity for cost-effective high-volume manufacturing through roll to roll (R2R) processing [11]. Overall, QLEDs are recognized as the next-generation display technology, due to its capacity of 100% Rec. 2020 color gamut, high efficiency and low cost of manufacturing [2, 12]. However, the unsatisfactory stability of the devices is still a current challenge impeding the full entry of QLEDs into the display and lighting industries.
Simultaneously, the world is witnessing the dawn of a new generation of flexible and wearable electronics, where displays for information input/output and large-area flexible light sources are key components of wearable healthcare medical device systems. In the first family of devices, FQLEDs could be integrated as input/output displays to make smart pressure sensitive displays, light-based biosensors, flexible printed circuit boards (FPCBs) and beyond [5]. The topic of this review focuses on the second family, where FQLEDs are proposed as wearable light sources for applications in emerging photomedical therapies, i.e. photodynamic therapy (PDT) and photobiomodulation (PBM), also known as low level light therapy (LLLT). Particularly, the efficacy of bright, deep-red QLEDs as a light source for photomedicine has been proved through PDT and PBM in vitro studies, resulting in performance comparable to that of commercial LED arrays [13, 14]. The main factor preventing wide adoption of photomedical therapies is the fundamental limitations of commercial and mainstream light sources, such as bulkiness and high cost of laser systems, and poor flexibility/irradiance uniformity of LED arrays. Fortunately, with the parallel advance of organic light emitting diodes (OLEDs) technology, low-cost FQLEDs have created an unprecedented opportunity to boost the wide adoption of photomedicine for healthcare management of cancer, acute and chronic wounds, inflammation, antimicrobial resistance and beyond. This growing technology is expected to greatly simplify the light source setup, lower the overall treatment cost and enhance the life quality of patients, consequently allowing treatment in small or low-resource clinics and ambulatory or ‘at-home’ treatment modalities.

Below we briefly describe the mechanisms and benefits of both phototherapies (PDT and PBM) and present the unique features of FQLEDs over conventional and commercial light sources. Then, the pioneering work and state-of-the-art research using QLEDs or OLEDs for photomedicine are discussed. The performance of QLEDs/OLEDs used in photomedical studies and latest progress on QLEDs are also summarized. Ultimately, we discuss the materials and design strategies for fabrication of efficient and stable FQLEDs, and present the basic requirements for near future introduction of FQLEDs into the healthcare and photomedicine markets.

2. Photodynamic therapy (PDT) and photobiomodulation (PBM)

Photomedicine has evolved to such an extent that it is now a full-fledged field of medical science. This developing field includes two important branches: (1) study and treatment of diseases caused by light exposure and (2) diagnosis and therapy using light for detecting and curing disease, respectively [15]. In particular, phototherapy involves the interaction between light and a specific chromophore in the biological tissue in order to obtain beneficial physiological effects. This interaction starts with light absorption by either an endogenous (naturally occurring) or exogenous (added from outside) chromophore, and is followed by transformation of light energy into chemical, kinetic or heat energy. Photodynamic therapy (PDT) and low level light therapy (LLLT), currently known as photobiomodulation (PBM), are two growing fields of application for phototherapies of high relevance.

Particularly, the mechanism for PDT requires the combined effect of light (usually long wavelength red light), a photosensitizing dye and molecular oxygen to produce a highly reactive type of oxygen (mainly singlet oxygen), which consequently kills and destroys unwanted cells and tissues. The mechanism of action for PDT in cancer cells is represented in figure 1(a). As depicted, there are two pathways for generation of reactive oxygen species (ROS) after excitation of the dye. Type I mechanism involves electron transfer and ion radical formation, which reacts with ground state oxygen to produce superoxide anion, hydrogen peroxide and hydroxyl radical. Type II mechanism involves direct energy transfer from the triplet excited state \((T_1)\) of the dye to ground state oxygen, producing singlet oxygen as illustrated. Type I and type II processes occur simultaneously, however type II is the dominant process in PDT and it is catalytic [17]. The Jablonski diagram from figure 1(b) depicts the photophysical mechanism for generation of singlet oxygen. Energy transfer to ground state oxygen is only possible if a sensitizer is in the same triplet state multiplicity, or occupies \(T_1\) as the ground state oxygen.

The dye sensitizers for PDT are exogenous chromophores administered either systemically, locally, or topically to a patient bearing a lesion. Red light in the 600–700 nm range falls into the ‘therapeutic window’ for PDT clinical treatment, since it can penetrate the epidermis and dermis without being absorbed by water and oxygenated hemoglobin [16, 18–20]. Accordingly, PDT has been adopted for treatment of cancer and other diseases characterized by unwanted tissues and cells [21], including the antimicrobial photodynamic therapy (aPDT) approach to prevent the growth of disease-causing microorganisms. The aPDT has been proposed as an alternative approach that can inactivate pathogens efficiently without the risk of inducing resistances, as there is an increasing number of pathogens reported to be resistant to commonly used antibiotics and antisepsics [22]; 10 million deaths per year by 2050 have been estimated [23].

On the other hand, PBM treatment induces beneficial clinical effects such as: reduction of pain, inflammation and edema [24–26]; promotion of wound healing and nerve regeneration [27–32]; prevention of
tissue damage [29, 32]; hair growth [33–35]; and influences the host response to different disease conditions, including infection and sepsis [36–38]. For instance, PBM can improve diabetic wound healing in patients with chronic wounds due to impaired wound healing. Its basic mechanism consists of exposure to low levels of deep red or NIR light and consequent absorption by cytochrome c oxidase, which leads to a cascade of effects: increased ATP production, modulation of reactive oxygen species (ROS) and induction of transcription factors [39] (represented in figure 1(c)). Therefore, increased cell proliferation and migration, modulation in the levels of cytokines, growth factors, inflammatory mediators, and increased tissue oxygenation are expected with PBM treatment. Enzyme/protein cytochrome c oxidase is an endogenous chromophore present in the mitochondria with absorption in a wavelength range of 620–900 nm. In general, red and near-infrared light penetrates deeper than green or blue light into biological tissue and are expected to stimulate cell proliferation [40]. The penetration depth of UV, visible and NIR light into the skin is illustrated in figure 1(d) [16].

A discussion of wavelength, light dosimetry and related parameters is complex and beyond the scope of this review. Photobiomodulation therapies (PBMT) are based on the observation that photostimulatory effects are generally observed at fluences between 1–10 J cm$^{-2}$, while photoinhibitory effects are typically observed at higher fluences, typically in the range of 20 J cm$^{-2}$ or higher [16, 25, 26, 31, 32, 41]. The literature is quite variable regarding recommendations for ideal treatment of the wide variety of diseases or conditions treated with PDT and PBM. The World Association for Light Treatment (WALT) [42] elaborated updated guidelines for clinical treatment of tendinopathies and arthritic conditions with PBMT regimens. Irradiance in the range of 10–100 mW cm$^{-2}$ are typically reported as being effective for stimulation of tissue repair, reduction of inflammation in superficial tendinopathies, reducing joint pain, and facilitating wound healing [19]. A range of 5–50 mW cm$^{-2}$, measured at the target tissue depth has also been found to produce successful tissue repair [41] and anti-inflammatory effects [43]. Despite the fact that 10 mW cm$^{-2}$ is a floor value commonly mentioned in the PBM literature, in vitro and in vivo studies using lower irradiance (e.g. ~5–8 mW cm$^{-2}$) [25, 30–32, 41, 44, 45] have produced positive results. The recommended approach for successful PBMT is to define the irradiation parameters (i.e. wavelength, irradiated or treatment area, irradiance, etc) first, and then define the irradiation time, instead of relying only on dose parameters such as energy (J) or fluence (J cm$^{-2}$). Irradiation times vary from a few seconds to many minutes. Being able to
target tissues at depth is an important concern in order to get the right amount of energy to the specific target. The time course over which light is delivered is also important. Mathematical reciprocity of exposure time and irradiance to achieve a specific light fluence can be ineffective or be deleterious [41].

In the case of clinical PDT regimes, a fluence rate between 10–200 mW cm$^{-2}$ has typically been used when employing wavelengths between 630–800 nm [19]. A high fluence rate was normally chosen in an effort to minimize treatment times and avoid overheating of tissue [19]. Certainly, the efficacy, fluence, and fluence rate strongly depend on the photosensitizer and specific application [46]. Nevertheless, subsequent studies showed an important correlation between oxygen depletion and fluence rate and the biological confirmation of reduced efficacy at a high fluence rate [47–51]. These observations motivated the use of low fluence rates or light fractionation with dark intervals. Consequently, a significant reduction in the fluence rate has demonstrated effects where cell repair and molecular responses to oxidative stress become important. In addition, the mechanism of cell death can also change from necrosis to apoptosis through metronomic photodynamic therapy (mPDT), which involves long treatment times at low fluence rates (~0.1–6 mW cm$^{-2}$) [52, 53] along with continuous and slow administration of the photosensitizer. Selective tumor cell killing through apoptosis is preferred for treating brain tumors.

It is highly important to note that fluence rate and irradiance are not the same, even though they have the same units (mW cm$^{-2}$) and are often misused in the literature. The irradiance only corresponds to the incident power on an area at the targeted tissue surface. The fluence rate considers the power incident from all directions being delivered inside a small sphere onto the cross-sectional area of the sphere, including absorption and scattering effects, and therefore light delivery inside tissue volume. Accordingly, irradiance is mainly used for topical administration of light to body surfaces, such as in the treatment of skin disorders (dermatology) and the oral cavity. The fluence rate is most often used in the PDT field for applications such as interstitial or intraoperative PDT treatments, which use optical fibers with different types of diffusers (i.e. frontal, cylindrical and spherical) inside the body. Considering the characteristics of planar QLEDs and superficial illuminated areas discussed in the present review, the optical power density output of this light source type is calculated in the next section as the irradiance ‘at skin’ when the QLED is in direct contact with the target.

3. Comparison of available photomedical light sources

PDT and PBM have been already proved as effective noninvasive or minimally invasive phototherapies [19], nevertheless, one critical factor limiting their widespread adoption and acceptance is the commercial availability of a suitable light source. In order to fulfill the general requirements for both PDT and PBM, such a light source must have: a narrow emission spectrum matching the absorption peaks of photosensitizers; high enough power density for sufficient excitation; low heat radiation to avoid pain in patients; and flexible form factors with homogeneous emission. Though there is a wide variety of light sources applied in photomedicine, herein we only discuss and compare the characteristics of light sources commonly used or proposed for PDT and PBM to date, i.e. lasers, LEDs, OLEDs and QLEDs.

Among these light sources, lasers (either crystalline media, diode, gas or liquid lasers) have been largely used in medical specialties such as dermatology, dentistry, ophthalmology and surgery, depending on the wavelength and power output required. A major advantage ascribed to lasers is that coherent light can be easily coupled into flexible optical fibers for light delivery inside the body, via endoscopes or transcutaneous insertion of fibers through needles [15]. However, the fundamental limitations preventing wide adoption of laser based PDT and PBM can be listed as follows: (1) equipment, operation, and staff trained for laser operation are expensive and limit the adoption in small clinics or hospitals; (2) bulky systems coupled to lenses and optical fibers, safety equipment, and small irradiation areas (leading to long-time procedures) limit the practical application; and (3) multiple visits of the patient to the hospital for daily session therapy may be necessary, but are impractical in many situations.

Inorganic light emitting diodes (LEDs) gained wide acceptance in the field of photomedicine after their introduction in the lighting industry. For the last decade, the use of LEDs in medical applications has increased due to their wide wavelength coverage, highly stable output power, considerably low cost (when compared to an equivalent laser source) [54] and capability to illuminate large areas of the body using LED arrays. Nevertheless, this breakthrough of LEDs with respect to lasers is not sufficient to meet the current needs for widespread application of PDT and PBM, since bulky LED arrays lack flexible form factors, and the irradiated area is unhomogeneous due to the point-source nature of LEDs [55].

Consequently with the emergence and development of OLEDs for the display industry, OLEDs were proposed for photomedical applications in 2009 [56] since flexible, thin-flat OLEDs could potentially offer new intrinsic features ideal for the photomedicine field, such as wearability, lightweight and uniform large area illumination. PDT treatment results were also reported in pilot preliminary studies [57], but the
research was largely abandoned in favor of LEDs later, partly due to the relatively low power density and broad emission spectra of OLEDs falling out of the desirable range for photomedicine.

Ultimately, the demonstration of QLEDs as effective light sources for PDT and PBM [13, 14] present a more promising future, since they can meet the features mentioned for flexible OLEDs and additionally overcome the low power density and broad emission spectrum limitations of OLEDs. In figure 2, the emission spectrum of a common QLED is compared with the spectra of standard OLED, LED and laser. In contrast to OLEDs, QLEDs show narrow emission bandwidth and high brightness in the deep red region, which can simultaneously guarantee deep tissue penetration and sufficient energy for molecular excitation; this will eventually generate additional benefits for the comfort of patients as shorter therapy times and pain relief. In addition, the unique advantages related to the quantum dot emissive materials such as color emission tunability, stability and easy processability result of great interest for practical and low cost application of QLEDs. The recent QLED photomedicine work has attracted considerable enthusiasm from the medical and lighting communities and also stimulated the revival of early OLED photomedicine studies, leading to recent demonstration of flexible microcavity OLED for PBM [58] and PDT [59] in-vitro studies. In table 1, the characteristics of the available light sources and QLEDs are summarized and compared in terms of the photomedical requirements. FWHM is the full width at half maximum of the emission spectrum, and power density is the optical power delivered per unit area normally given in milliwatts per square centimeter (mW cm$^{-2}$), herein the latter is more widely discussed for clarity. The power density has radiometric units and is used in photomedicine rather than the luminance (cd m$^{-2}$), which is generally used to refer to the luminous intensity per unit area (photometric units) of a light source in the display and lighting fields.

The power density is normally obtained as the measured power divided by the measured beam area of the light source. However, the approximate power density of a QLED can also be obtained from the measured luminance. First, luminance is converted to radiance $R$ (W cm$^{-2}$sr) using the following equation:

$$ R = L / [K \cdot V(\lambda)] \rightarrow V(\lambda) = 1.019e^{-285.4(\lambda-0.559)^2} $$

where $V(\lambda)$ is the luminous efficiency function calculated as an empirical function of the wavelength, and $K$ is a constant (683 lm W$^{-1}$). $V(\lambda)$ gives the spectral response of the human eye to visible light, and has a maximum value (equal to 1) at 555 nm, the wavelength at which the human eye is most sensitive to light. Though this equation is for monochromatic light, this also provides a good approach by using the peak emission wavelength when the light source has a unimodal and narrow emission spectrum. Once the

| Table 1. Characteristics and comparison of different light sources proposed for photomedicine. |
|---------------------------------------------------------|
| Lasers | LEDs array | OLEDs | QLEDs |
| Power density (mW cm$^{-2}$) | >100 | 10–100 | <10 | 10–25$^a$ |
| FWHM | <5 | 15–20 | >30 | 20–30 |
| Eye safety | Goggles/trained user | Safe | Safe | Safe |
| Cost | $$$$$ | $ | $ | $ |
| Flexible | No | No | Yes | Yes |
| Homogeneous/lightweight | No | No | Yes | Yes |

$^a$On-glass QLED with 16 mm$^2$ pixel.
Table 2. Equivalent luminance to optical power density output of 10 mW cm$^{-2}$ at different wavelengths.

| Wavelength (nm) | 620  | 630  | 640  | 650  | 660  | 670  |
|----------------|------|------|------|------|------|------|
| Luminance (cd m$^{-2}$) | 7660 | 5256 | 3406 | 2085 | 1205 | 658  |

As can be noticed in table 2, the luminance increases as the wavelength approaches 555 nm at constant power density, since luminance is a photometric quantity and takes into account the eye sensitivity.

**4. Developmental history of QLEDs/OLEDs in photomedicine**

Since QLEDs and OLEDs belong to the same 'family', and QLEDs have made rapid progress following OLED development, herein the discussion about QLEDs application in photomedicine also involves the developmental history of OLEDs in this field. In the first section, the pioneering work in PDT and subsequent studies (until 2015) using rigid OLEDs are discussed. The following section is dedicated to the QLED-based PDT and PBM studies carried out by our group. And in the final section, the OLED-based studies revived after the introduction of QLEDs are discussed. The timeline shown in figure 3 summarizes the PDT and PBM studies using OLEDs and QLEDs from 2009 to the present.

**4.1. Pioneering and subsequent photomedical studies using rigid OLEDs**

OLEDs were proposed for the first time by Samuel's group as an alternative light source for PDT in 2009 [57]. This was an open pilot study of ambulatory PDT using a low-irradiance OLED in the treatment of nonmelanoma skin cancer. Eight patients with Bowen's disease and four with superficial basal cell carcinoma (<2 cm in diameter) were recruited. Two treatments were administered 1 month apart following the application of aminolevulinic acid (ALA) for 4 h. At the 1 year follow-up, seven of the 12 patients remained clear, with four of the non-responders demonstrating peripheral margin failure. Before and after PDT treatment pictures (figure 4(c)) show successful clearance of lesion. The fluence per session applied with OLED source was in the range of 45–60 J cm$^{-2}$, with an average irradiance of 5 mW cm$^{-2}$. Whereas the fluence applied with an Aktilite inorganic LED source (used for routine PDT) was 75 J cm$^{-2}$, corresponding to average irradiance of 80 mW cm$^{-2}$. In general, the total fluence per session must be similar when
comparing treatments with different light sources, so that the results obtained can be compared. Since each light source can have different power density, plus different decay during operation, different time per session must be calculated in order to obtain approximately the same fluence in J cm$^{-2}$. This OLED-based pilot study demonstrated that this strategy is more convenient for ‘home PDT’ and less painful than conventional PDT with inorganic LEDs, eliminating the need for analgesia or skin cooling. Nevertheless, the broad red-light emission spectrum shown in figure 4(a) (550–750 nm with peak at 620 nm) and preliminary setup with rigid OLED patch (figure 4(b)), demanded more research in order to improve the characteristics of the light source and validate its efficacy on photomedical therapies.

After a significant period of 5–6 years, two OLED-based photomedical studies were published in 2015. One of these studies by Anders group addressed the first use of OLED-based PBM to stimulate wound healing [60]. In vitro (human dermal fibroblasts) and in vivo (genetic, diabetic rat) models were used to investigate the effects of OLED irradiation (the emission spectrum with peak at 623 nm is shown in figure 4(d)) on cellular function and cutaneous wound healing, respectively. In summary, the in vitro experiment under OLED irradiation increased total ATP concentration, metabolic activity and cell proliferation, compared to untreated controls. As for the in vivo experiment, the treatments with OLED and laser (635 ± 5 nm) had comparable effects on enhancing diabetic wound healing, based on the total histological scores of bar chart in figure 4(e) and the percentages of wound closure of figures 4(f). For both studies, the power density and fluence were $\leq 10$ mW cm$^{-2}$ and $\leq 5$ J cm$^{-2}$, respectively. The comparable effects obtained from OLED and laser treatments, suggested that low-cost OLED could be a feasible alternative to replace conventional light sources, especially for ambulatory purposes. However, it is worth noting that simultaneous effects could mask important individual effects at specific wavelengths, since the electroluminescence (EL) spectrum of the on-glass OLED used in this work was very broad (560–770 nm).

Later, Guo et al [61] published on OLED based PDT for glioma mouse models. Gliomas are the most common form of the primary brain tumors, presenting challenges of resistance to chemo and radiation

**Figure 4.** Pioneering works on OLED based PDT: (a) EL spectrum of OLED system shown in (b) and used for ALA assisted PDT; (c) before and after PDT treatment (12 months follow-up) showing successful clearance of lesion on patients with Bowen’s disease. (a–c) [61] John Wiley & Sons. [Copyright © 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim]. (d) EL spectrum of OLED with emission peak at 623 nm used to stimulate cellular function and cutaneous wound healing in genetic, diabetic rat model; (e) total histological score based on epithelium, cellular content, collagen deposition, vascularity and granulation tissue in the wound, obtained with OLED and laser irradiation (10 mW cm$^{-2}$; 5 J cm$^{-2}$ daily for a total of 7 d). (f) Percentage of wound closure in control, OLED and laser treated wounds, AUC is the area under the curve. (d–f) [61] John Wiley & Sons. [Copyright © 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim]. (g) EL spectrum of OLED with emission peak at 626 nm for PDT treatment in nude mouse model of human glioblastoma with single dose of ALA; h) picture shows mouse undergoing OLED based PDT treatment; i) Plot of tumour post-light luminescence intensity and total survival days of all mice with brain tumours including control (○) and PDT (●) groups. (g–i) Reprinted from [62], Copyright (2015), with permission from Elsevier.
therapy, and treatment side effects. These authors demonstrated the feasibility of single drug dose ALA-PDT at low-fluence rate (3 mW cm\(^{-2}\), 40 J cm\(^{-2}\)) and long treatment time (3.7 h) using an OLED panel.

Figure 4(g) shows the EL spectrum of the OLED used for PDT treatment in nude mouse model of human glioblastoma, and figure 4(h) is a picture of mouse undergoing OLED based PDT. Tumor volume was measured using bioluminescent imaging and the animal survival time was recorded. The response of PDT treated animals with controlled pre- and post-light tumor volume, promised longer survival time than the controls, as can be concluded from the data plotted in figure 4(i). In summary, authors demonstrated the feasibility of OLED based mPDT in small animals without anesthetization. OLED rigidity, broad EL spectrum with shoulder at ~680 nm (far from the Q-bands absorption of photosensitizer, PpIX) and small sample size suggested further studies with improved light source and larger sample size of the experiment.

Although new results were obtained for in-vitro and in-vivo studies in PBM and PDT, these last works did not add results with improved performance of OLEDs. In general, rigid OLEDs (typically on-glass) with broad emission spectra were used and irradiance was preferred in a range of 3–10 mW cm\(^{-2}\). Since the measured irradiance counts for the whole wavelength range, less power is delivered at the peak wavelength or desired wavelength, which could result in short tissue penetration and reduced energy for excitation of the photosensitizer.

4.2. QLED-based photomedical studies

Later in 2017, QLEDs were proposed by our group for application in both phototherapies, PDT and PBM [13, 62] for the first time. The multilayer structure, EL spectrum, luminance-voltage and current efficiency–current density characteristics of the ultrabright deep-red QLED used in both studies are shown in figures 5(a), (b) and (c), respectively. A setup of cell cultures with the 4 pixels (16 mm\(^2\) each) red QLED lighting underneath is shown in figure 5(d). For PBM testing, three cell lines were cultured: a human epithelial cell line (HEp-2 cells) and two fibroblast cell lines from mouse (L929 and 3T3). Irradiation of the culture wells was performed to deliver 4 J cm\(^{-2}\) in 10 min at ~8 mW cm\(^{-2}\). Cell metabolism was assessed by MTT assay 24 h post-treatment, the experimental data are not presented here. The QLED based PBM increased the cell metabolism for the three cell lines HEp-2, L929 and 3T3, by 27.9, 26 and 12.5% over the control systems, respectively. Although the peak wavelength of QLEDs used in this initial study (620 nm) was away from 660 nm (preferred for PBM), the results were comparable to parallel LED based PBM with emission peak at 670 nm. As for PDT test, 3D cultures of A431 cells (human cell line used in cancer-associated biomedical study) were photosensitized by administration of ALA, leading to accumulation of protoporphyrin IX (PpIX) prior to light activation. The 3D cultures were labelled using fluorescent vital-dye 24 h after PDT treatment as observed in figure 5(e). The images correspond to control cells with no light treatment, cells with LED based PDT and cells with QLED based PDT, from left to right. Both QLED and LED sources achieved photo-destruction of 3D tumor nodules. The quantitative image processing of multiple replicates revealed a slightly higher efficacy for QLED based PDT, with residual tumor viabilities of 0.61 ± 0.04 for LEDs and 0.53 ± 0.08 for QLEDs.

Subsequently in 2018, QLEDs were also used for in-vitro study of PBM based wound healing using a ‘2D scratch model’ [63]. Cultures of HEp-2 and L929 cells with a confluent monolayer were scored to leave a scratch of approx. 0.4–0.5 mm in width. Then, the irradiation was performed with a QLED emitting at 626 nm to deliver either 2 J cm\(^{-2}\) in 5 min or 4 J cm\(^{-2}\) in 10 min at ~8 mW cm\(^{-2}\). The closure rate ratio results at 24 h demonstrated for first time the promotion of cell migration by QLED based PBM, suggesting the potential of QLEDs for impaired wound healing treatments.

The most recent work on QLEDs for photomedicine was also published by our group in 2018 [14]. revealing QLED based PDT can effectively kill Methicillin-resistant S. aureus (MRSA), an antibiotic-resistant bacterium. MRSA bacterium was treated with 10 μM photofrin and 100 mM potassium iodide, and then illuminated with QLEDs powered by a simple battery pack (two 3 V coin cells as observed in inset of figure 5(h)). Remarkably, the survival fraction of MRSA dropped to less than 10\(^{-6}\) after 1 h illumination as shown in figure 5(h). Synthesis of QDs emitting at different wavelengths (625, 631 and 646 nm) was also carried out. Figure 5(g) shows the photoluminescence (PL) spectra of QDs matching in a wide wavelength range with the absorbance spectra of photosensitizers (PSs), by simply tuning the QD size during synthesis. These PSs widely used for PDT cancer treatment are Porfimer sodium (Photofrin\(^\text{®}\)), aminolevulinic acid (ALA), and temoporfin, with Photofrin\(^\text{®}\) being the most widely used first generation photosensitizer [17]. ALA is a topical porphyrin precursor that leads to the local accumulation of the endogenous photosensitizer protoporphyrin IX (PpIX) with no significant prolonged phototoxicity [18, 64]. In addition, this study demonstrated FQLEDs with external quantum efficiency (EQE) of 8.2% and luminance over 20 000 cd m\(^{-2}\) at driving voltage of 6 V. The device photograph, multilayer structure, EL spectrum and J–L–V characteristics of the flexible red QLED are shown in figures 5(f), (i) and (j), respectively. The potential application of these FQLEDs as wearable devices for PDT treatment of oral cancer and diabetic wound repair was discussed.
Recently, our group improved the performance of the FQLEDs by using a more conductive indium tin oxide (ITO) on polyethylene naphthalate (PEN) substrate, new treatment conditions of the substrate and double barrier lamination (top and bottom) for encapsulation of the devices [65].

The J–L–V characteristics of the new FQLEDs with large pixel of 8 mm$^2$ is shown in figure 5(k). A peak luminance of 42,214 cd m$^{-2}$ (power density output ~71 mW cm$^{-2}$ at 627 nm) was reached at only 5.8 V, largely fitting the power density requirement for application in low-irradiance PDT and PBM (~3–10 mW cm$^{-2}$).

4.3. Revival of OLED-based studies

Following the introduction of QLEDs based photomedicine, the Choi group at KAIST, a leading flexible OLED team, initiated work on OLED based PBM and published the in-vitro wound healing effects of PBM using flexible OLEDs for the first time [67]. This work investigated the effects of an OLED PBM patch on cultured normal human fibroblasts (3–9 J cm$^{-2}$). In general, positive effects were found since the in-vitro experiment effectively stimulated fibroblast proliferation (over 58% of control) and enhanced fibroblast migration (over 46% of control). Using the microcavity effect, the peak emission wavelength of the OLED was controlled over the 600–700 nm range by adjusting the thickness of the hole transport layer (HTL), while
maintaining similar power density (<10 mW cm$^{-2}$). Finally, the almost uniform cell metabolic activity at different peak wavelength and fluence, suggests that more specific wavelength (narrower emission spectrum) is needed in order to develop optimal PBM devices for wound healing, since the proliferation and migration effects can depend on small differences in wavelength.

In 2018 [68], the same group conducted a cell migration test to investigate the OLED PBM effect on keratinocyte cells (main cells of the human epidermis). The wearable OLED PBM patch with total thickness of ~1.1 mm (including battery thickness) was intended to make direct contact with the human body. 630 nm and 650 nm OLEDs showed improved wound healing by 9.9% and 31.5% (compared to the control group) 12 h after irradiation with total fluence of 3 J cm$^{-2}$ (5 mW cm$^{-2}$ for 10 min). Thus, confirming that peak emission at 650 nm is more effective in keratinocyte wound-healing promotion than a shorter wavelength.

Most recently in 2019, Jeon et al [58] presented sandwich-structured transferable free-form OLEDs (STOLEDs) as wearable and disposable light sources for skin wound photomedicine. The adhesive transferable STOLED (10 µm) with ultrathin barriers on top and bottom is depicted in figure 6(a), and photographs of red OLEDs with 2 × 2 arrays transferred onto textile are shown in figure 6(b). The red-emitting STOLEDs were used to test the wound healing effect in a keratinocyte based 2D model, a skin equivalent model and an organ culture model. Figures 6(c) and (d) show the in vitro wound healing effect using keratinocytes based 2D model, and images obtained from cell migration test using a scratch-wound healing assay. The organ culture model consisted in a rat skin cryo-wound model irradiated with a 670 nm STOLED, evolution of reference and irradiated wounds is shown in figure 6(e). Finally, authors found 26% and 32% increase of cell proliferation and migration after irradiation of keratinocytes, respectively, 39% increase of epidermis thickness in the skin equivalent model, 14% skin area increase and 21% re-epithelialization improvement in the organ culture models. Authors concluded that irradiation at 670 nm for 10 min was the best condition for wound healing in terms of the keratinocyte response, and poor response resulting from longer irradiation time was attributed to a biphasic response [69]. Further studies considering the total wound healing effect of different models (in vitro and in vivo) are needed, as cell proliferation seems to be suppressed under long irradiation time but cell migration can be increased at either short or long irradiation time depending on the wavelength.

In the same year, Samuel group revisited the OLED photomedicine topic by proposing flexible top-emitting OLEDs for antimicrobial PDT [59]. The flexible red OLED used a p-i-n (p-doped, intrinsic, n-doped) structure to enable enhanced conductivity of the transport layers and subsequent low driving voltage; a cross-sectional structure of the device is shown in figure 6(f). Spectral tuning was achieved by varying the HTL thickness through the microcavity effect. Then a 4 cm$^2$ flexible OLED was designed to perform aPDT testing; a device photograph, V-J-irradiance characteristics and operational lifetime test of the large-area OLED are shown in figures 6(h), (i) and (k), respectively. Spectral overlap of the OLED EL spectrum and the absorption spectrum of the photosensitizer methylene blue (MB) is shown is figure 6(j). Finally, the OLED PDT experiments for killing S. aureus were performed with on-glass and flexible OLEDs. For both types of device, the combination of the OLEDs with MB (5 µg/mL) showed more than 99% killing of bacteria at optical density (OD) 0.001 for 3 h of illumination (from bar charts in figure 6(g)). Comparative experiments with other types of light source (laser or inorganic LED) and the use of state-of-the-art photosensitizers will be important to further validate the performance of OLED-based aPDT studies.

The performance and actual progress of OLED devices used in the last two photomedical studies is discussed in the following section.

5. Performance of OLEDs and QLEDs proposed for photomedicine

The photomedical studies from Samuel’s and Choi’s groups in 2019 [58, 59] represent the state-of-the-art OLED-based work, with latest advances in performance of the devices. In comparison to early OLED-based studies, they reported advances in flexibility, form factors, emission bandwidth and emission wavelength tunability of the OLEDs. Both groups reported red-emitting flexible OLEDs and controlled the peak emission wavelength over a wide range using the microcavity effect; the microcavity effect was originally used in OLEDs to optimize the light extraction.

In particular, Samuel’s group [59] reported a 4 cm$^2$ flexible OLED with power density output of 9.85 mW cm$^{-2}$ (at 3.82 V), emission uniformity variation from ~2.78 to 4.22 %, and 13 h of stable emission (<1% intensity decay) at initial irradiance of 7.75 mW cm$^{-2}$. Thus, exceeding the maximum operating time of 6 h required for their experiments. While this work showed relatively high-power density at long peak emission wavelength (737 nm) compared to other reported OLEDs used in photomedicine, the results suggests further improvements of the EL spectrum bandwidth and shelf-life of the devices (dark spots after 10 d of encapsulation). It is worth noting that a broad EL spectrum can lead to undesirable synergistic effects of different wavelengths or low energy for molecular excitation at a desirable wavelength. The performance
Figure 6. (a) Cross sectional scheme of sandwich-structure transferable OLED (STOLED). (b) Photo of a large-area red free-form OLED with a $2 \times 2$ array on textile and same device working (light on); (c) bar charts of keratinocyte cell proliferation test 72 h after light irradiation, and migration test 12 h after light irradiation. Bars correspond to control sample and samples under OLEDs radiation with peak wavelengths at 630, 650, 670 and 690 nm; (d) migrated cell images 12 h after light irradiation for control, 650 nm and 670 nm (10 min irradiation). (e) Effect of irradiating rat skin with a 670 nm STOLED on organ culture in the cryo-wound model. Thin lines indicate the length of initial wounds, while thick lines indicate the length of re-epithelialization. Reproduced from \cite{60}. CC BY 4.0. (f) Device structure of flexible p-i-n OLED used in antibacterial PDT for killing S. aureus. (g) The bar charts show the fraction of bacteria alive for a range of conditions of illumination and photosensitizer (methylene blue or MB) concentrations. Control corresponds to sample with no light and no photosensitizer. (h) Photo and (i) V–J-irradiance characteristics of the 4 cm$^2$ flexible OLED; (j) emission spectrum of the 4 cm$^2$ flexible OLED (with peak wavelength at 737 nm) and absorption spectrum of MB; (k) 4 cm$^2$ flexible OLED driven at a constant current density of 25 mA cm$^{-2}$ for the operational lifetime test. (f–k) Reproduced from \cite{60}. CC BY 4.0.

details of the red OLED such as turn-on voltage, efficiency and FWHM of the EL spectrum were not reported for this work.

Meanwhile, Choi’s group \cite{58} reported a red-emitting flexible OLED with advantages such as long operating life (>150 h at 4000 cd m$^{-2}$ in air) and multiple free forms due to its ultra-thin sandwich structure (10 µm). A long operating life in air and water environments was enabled by using transfer barriers with low water vapor transmission rate (WVTR) ($10^{-6}$ g m$^{-2}$ d$^{-1}$). The free-standing transferable OLEDs had the same efficiency performance on cylindrical-shaped materials and on textile and paper. In addition, the red OLED with peak emission wavelength at 629 nm had a much narrower FWHM (34 nm) in comparison with conventional OLEDs. Nevertheless, its peak luminance of 13 040 cd m$^{-2}$ was still below the luminance of red QLEDs with similar peak emission wavelength (a pixel size is not specified). The efficiency presented by the authors corresponds to the current efficiency (CE) (peak of 21.6 cd A$^{-1}$) which is more useful for display application (photometric parameter), herein, the EQE is used to compare the efficiency of QLED devices (see table 3). In general, the existing OLEDs with either fluorescent or phosphorescent emitters cannot achieve high brightness at deep red wavelengths due to significant efficiency roll-off at high current density \cite{70} and the lack of efficient deep red emitters with narrow emission spectra \cite{71}.

On the other hand, QLEDs can simultaneously guarantee narrow emission spectrum and emission wavelength tunability only through the synthesis of the QDs, eliminating the need for additional strategies during the design of the device. High efficiency and low efficiency roll-off is achieved by tailoring the core/shell structure of the QDs and balanced charge injection of the device. The performance and fabrication
Table 3. J–L–V parameters of QLEDs and OLED proposed for PDT and PBM.

| QLEDs       | Pixel size (mm$^2$) | $V_{on}$ (V) | $\lambda_{peak}$/FWHM (nm) | $L_{max}$ (cd m$^{-2}$) | EQE$_{max}$ % | Fabrication/substrate                        |
|-------------|---------------------|-------------|-----------------------------|--------------------------|---------------|-----------------------------------------------|
| Dong et al  | ~1.0                | 1.7         | 620/22                      | 165 000 (5.8 V)          | ~20           | Spin coating and Vacuum evap./rigid glass     |
| Triana et al| 0.8                 | 1.8         | 622/24                      | 75 444 (7.7 V)           | 3.1           | Spin coating/rigid glass                      |
| Chen et al  | 0.8                 | 1.9         | 630/28                      | 20 000 (6 V)             | 8.2           | Spin coating and Vacuum evap./flex. PEN       |
| Chen et al  | 0.8                 | 2.0         | 629/25                      | 146 000 (8 V)            | ~6.0          | Spin coating/rigid glass                      |
| Triana et al| 8.0                 | 1.9         | 627/29                      | 42 214 (5.8 V)           | 8.3           | Spin coating and Vacuum evap./flex. PEN       |
| OLED        | —                   | —           | 629/34                      | 13 040                   | —             | Vacuum evap./flex. PET                        |

Techniques of the red-emitting QLEDs proposed by our group for photomedical application are also summarized in Table 3. The on-glass inverted red QLED with ultrahigh brightness reported in 2015 [66] have the fundamental structure of the devices tested for PDT and PBM studies. As shown in Table 3, the EL spectrum of this QLED can have a FWHM as narrow as 22 nm and high peak brightness of 165 000 cd m$^{-2}$ reached at 5.8 V corresponding to pixel size of ~1 mm$^2$. Although the half lifetime ($T_{50}$) at initial luminance of 100 cd m$^{-2}$ for these QLEDs (~7225 h) is below the luminance requirement for display application, the correlated lifetime for the devices working at initial power density $\leq$ 10 mW m$^{-2}$ is more than enough for PDT and PBM. The irradiation time for low-irradiance treatment normally does not exceed 6 h. Fabrication of on-glass QLEDs used in PDT and PBM reported to date [13, 14] has minor modifications. The hybrid organic-inorganic devices are fabricated inside an N$_2$ filled glove-box, using a combination of solution process and vacuum evaporation techniques as follows. Briefly, the ITO on-glass substrates are cleaned and treated inside an oxygen plasma chamber. After the plasma treatment, a ZnO:Cs$_2$CO$_3$ solution and the QDs solution are sequentially spin-coated on the substrates. Unlike the original process, a mix of ZnO nanoparticles (NPs) and Cs$_2$CO$_3$ is coated as the electron injection and transport layer, i.e. one single layer instead of a bilayer. The ZnO NPs and the CdSe-ZnS-CdZnS core–shell–shell QDs are synthesized using a precipitation method [74] and the hot injection route [75], respectively. Finally, a Spiro-2NPB layer (100 nm), a HAT-CN layer (20 nm) and the Al electrode (100 nm) are thermally evaporated under high vacuum as the HTL, hole injection layer (HIL) and anode, respectively. All the devices are encapsulated using a glass cover with UV-curable epoxy and a getter sheet before characterization and medical testing outside the glove-box.

Motivated for lower cost and simpler fabrication process, our group has also developed all-solution processed QLEDs with high brightness by spin-coating. The first device of this type was reported in 2018 [72], having a peak brightness of 75 444 cd m$^{-2}$ (at 7.7 V) and peak EQE of 3.1%, as presented in Table 3. Essentially, the difference with the previous hybrid device is that the HTL and the HIL were solution-processed polymers: poly-TPD and PEDOT:PSS respectively. Enhanced coverage of uniform hydrophilic PEDOT:PSS based HIL on hydrophobic poly-TPD was enabled by doping PEDOT:PSS with non-ionic surfactant Triton X-100.

Subsequently, the performance of this QLED was improved by imprinting speckle image holography (SIH) structures on the poly-TPD HTL surface [73]. The QLED with imprinted random grating structures reached a luminance of up to 146 000 Cd m$^{-2}$ at 8 V, with peak EQE approximately two times higher than that of previous device with planar architecture (see Table 3). It was found that the imprinting method simultaneously helps extracting the trapped photons via the SIH structure and also improves the device performance through an imprinting-induced film-compression mechanism. Though these bright all-solution processed QLEDs have not yet been used in photomedical testing, they are preferred for a more cost-effective photomedical treatment.

Most recently, FQLEDs using similar structure as the on-glass hybrid QLED were also developed by our group. For the first flexible QLED, a PEN film with conductive transparent ITO (~45 $\Omega$/sq.) and silicon nitride barrier layer was used as the substrate [14]. After deposition of the multilayer QLED, a flexible moisture getter and a barrier film developed by the Holst Centre [76] were sequentially laminated for top encapsulation. The top barrier film consisted in an organic coating for planarization (OCP) stacked between two inorganic layers of amorphous hydrogenated silicon nitride (SiN). The peak EQE of this QLED was 8.2%, and a luminance of 20 000 cd m$^{-2}$ could be reached at driving voltage of 6 V. Later, a flexible red QLED [65] with higher peak luminance of 42 214 cd m$^{-2}$ (power density output ~ 71 mW cm$^{-2}$ at 5.8 V), long shelf-life and high peak EQE of 8.3% was developed. Most importantly, this performance was demonstrated...
for large pixel of 8 mm², in contrast to performance normally measured with 1 mm² pixel. In this case, the flexible ITO on PEN substrate had a much lower sheet resistance (~6 Ω/sq.) but no barrier layer. Therefore, additional bottom lamination with barrier film (from Holst Centre) was needed for full encapsulation of the device. These devices could be stored for long time (≥1 month) either in inert atmosphere or in vacuum sealed bags, and could hold 80% of the initial luminance after 1 week out of glove-box. Finally, it is worth noting that all the QLEDs reported in table 3 had a very low turn on voltage (1.7–2.0 V) and low efficiency roll-off. In particular, the flexible QLED with high brightness only exhibited 9.6% decrease with respect to the maximum EQE when luminance of 20 000 cd m⁻² (power density output ~34 mW cm⁻²) was reached at 4.5 V. Overall, this is a low voltage that can be supplied from a small battery for practical photomedical treatment. Further improvement of the encapsulation to make the FQLEDs more stable in air environment is expected to boost its introduction as disposable light sources for ambulatory treatment in PDT and PBM.

6. Latest progress on rigid and flexible QLEDs

Since the first QLED was reported [77], continuous research has been made to significantly improve the efficiency, peak brightness and lifetime of QLEDs. Here the latest advance on record QLEDs and application status are briefly discussed. Although QDs are always present as the emissive materials, QLEDs can have either a forward (regular) or inverted structure, and can be classified as top-emitting or bottom-emitting devices depending on the transparency of the electrodes. In a simple way, the top electrode in forward and inverted QLEDs is the cathode and the anode, respectively. Inverted QLEDs normally utilizes metal oxides as efficient electron transport and electron injection layers. In addition, QLEDs can be made by solution processing or a combination of solution process and vacuum evaporation. Here the QLEDs made by combination of solution-processing and thermal evaporation techniques are called hybrid devices. Our group and Li et al early reported record hybrid inverted QLEDs, with EQE above 20% and 6% and ultrahigh brightness of 165 000 and 460 000 cd m⁻² for red [66] and green [78] QLEDs, respectively.

Simultaneously, QLEDs made by solution processing of the functional layers (excluding the electrodes) have been proposed in order to reduce the fabrication cost. These solution-processed QLEDs are normally made by spin coating, replacing, for instance, evaporated organic molecules with solution-processed polymers. A red solution-processed QLED with forward structure [79] was early reported with record EQE above 20% and brightness of 42 000 cd m⁻². Subsequently, higher peak brightness of 356 000, 614 000 and 62 600 cd m⁻² were demonstrated for red, green and blue solution-processed QLEDs with forward structure [80]. More surprisingly, by effective thermal management at high current density (3885 mA cm⁻²/EQE ~10%), a record ultrahigh brightness of 1.6 × 10⁶ cd m⁻² was recently achieved with green forward QLEDs made by solution process [81]. Simultaneous moderate brightness (≥10⁴ cd m⁻²) and efficiency (EQE ≥10%) of all red, green and blue solution-processed QLEDs in latest reports make them promising for future lighting application [80, 82]. It is worth noting that a record white solution-processed QLED with R-G-B QD tandem structure and comparable efficiency to that of state-of-the-art WOLEDs was also reported [83]. This last work set a record EQE of 28% and 20.7% for solution-processed inverted white and red QLEDs, respectively. The current record brightness (146 000 cd m⁻²) for red solution-processed QLEDs with inverted structure was reported by our group [73].

As for the lifetime, the requirement for display application was recently achieved by red solution-processed QLEDs with forward structure, exhibiting T₅₀ operation lifetime of more than 2.2 × 10⁴ h at display luminance of 100 cd m⁻² [84]. The best T₅₀ operation lifetime at initial luminance of 100 cd m⁻² for green and blue QLEDs to date are 1.7 × 10⁴ and 7 × 10⁴ h, reported by Shen et al [80]. Clearly, the blue QLED still evidences severe degradation with a lifetime lying far below the display requirement for commercialization (5 × 10⁴ h).

On the other hand, regardless of the great advance in performance of Cd-based QLEDs, researchers are currently working on new Cd-free QLEDs due to the RoHS restriction demanding cadmium content below 100 ppm. InP-based QDs seem to be the favorite candidate for substitution of Cd-based QDs, with Samsung Electronics leading the performance of new InP based QLEDs. The latest reported device [85] was a red forward QLED with InP/ZnSe/ZnS core/shell/shell QDs as emissive material, maximum EQE of 21.4%, peak brightness of 1 × 10⁵ cd m⁻² and T₅₀ lifetime of 1 × 10⁴ h at 100 cd m⁻². Such performance is almost comparable to that of the state-of-the-art Cd-based QLEDs. Nevertheless, research and further optimization of Cd-based QLEDs is still ongoing, as proper core shelling of the QDs and encapsulation of the devices can prevent leakage of toxic Cd⁺², and Cd content in the devices can also be reduced below the limit of 100 ppm.

In addition to the on-glass rigid QLEDs previously mentioned, flexible devices are being developed since the first flexible QLED was reported in 2009 [86]. These flexible devices were red forward QLEDs made on ITO-precoated poly(ethylene terephthalate)(PET) substrates, and exhibited a maximum luminance and CE of 7070 cd m⁻² and 2.57 cd A⁻¹, respectively. A great advance has been achieved in terms of the efficiency,
considering that the current record flexible QLED exhibits an EQE of 24.1% and CE of 19.5 cd A⁻¹ [87].

This was a red inverted flexible QLED using solution-processed silver nanowires (Ag NWs) embedded in polyimide (PI) as the flexible transparent conductive electrode (TCE), which also acted as a light extraction medium.

Other emerging materials with great potential and outstanding optical, excitonic and charge transport properties for use in solution-processed electroluminescence devices are perovskite nanocrystals (NCs). However, practical application of perovskite materials has been hindered by their intrinsic structural instability in ambient conditions. A lot of effort has been devoted and steady improvement in the stability has been achieved with the development of novel strategies. Among the strategies implemented are: swelling-deswelling microencapsulation in polymer matrices [88, 89], impregnation in solid organic salt matrices via coprecipitation [90], polymer-ligated [91] or polymer-ligated/SiO₂-shelled NCs via amphiphilic star-like block copolymers as nanoreactors [92], etc. These last two techniques were developed for synthesis and preservation of individual QDs. Compared to traditional QDs, perovskite NCs emitting green color have shown better optical properties, with narrow emission spectrum (FWHM as narrow as 18 nm) and high photoluminescence quantum yield (PL-QY up to 90 %). Currently, the remaining instability issues have limited their direct application as self-emissive materials, and they are preferred as down-converters for assembly of white-emitting LEDs. Importantly, the red-emitting perovskite QD electroluminescence devices, which are highly relevant for the present photomedical application, need further optimization since the current devices can reach an EQE as high as 21.3% (at 653 nm) but still have very low brightness (in an order of 10² cd m⁻²) and extremely short lifetime [93, 94].

Steady and substantial increase on brightness, efficiency and lifetime of QLEDs in the last years has encouraged further optimization for potential application of self-emissive QLEDs in lighting, projection displays, transparent displays, outdoor digital signage and vehicle headlamps. However, the development of new QLEDs with mechanical flexibility, lightweight, large-area emission uniformity, long-term stability, solution-process compatibility and low cost for mass production, is promising earlier commercialization of QLEDs through other emerging applications such as wearable displays and photomedical light sources.

7. Design strategies and materials for flexible QLEDs/OLEDs

Practical application of PDT and PBM demands wearable and ergonomic QLEDs, and transition from rigid on-glass to flexible devices seems simple but it can be challenging. Though flexible QLEDs/OLEDs can be made keeping the original multilayer structure, by changing the nature of the substrate, electrode and encapsulation material, the efficiency, operational lifetime and shelf-life of the devices can drastically drop. Overall, the properties required for the flexible substrate, electrode and encapsulation material will depend on the specific application of the QLEDs. Therefore, it is of utmost importance for the QLED fabricant and provider to have a comprehensive knowledge of the application requisites and available technologies that can properly satisfy those requisites. Several reviews have already detailed the advance and current status of the materials and technologies for fabrication of flexible QLEDs/OLEDs [4, 5, 95–98], with flexible QLEDs offering a relatively mature technology for the highly demanding display industry. Herein, we summarize the materials and technologies that are currently available, emphasizing in those that can satisfy the requisites for application and early commercialization of FQLEDs in the field of photomedicine, which is less demanding in terms of lifetime compared to the display industry.

In order to guarantee acceptable or similar performance to that of on-glass devices, the new flexible substrate must have relatively high transparency in the emission range of the QLEDs, low oxygen and moisture permeability, solvent resistance, smooth surface, mechanical bending capability and thermal stability. In principle, applying small changes to the structure of the devices should simplify the fabrication process and reduce potential detriment, for instance, replacing conventional rigid glass with flexible thin glass. Thin glass has high barrier properties, thermal stability and optical transmittance comparable to conventional glass, but restricted flexibility and weight. Then, application of thin glass based QLEDs in photomedicine would be limited to non-contact treatment of external body parts and would be inappropriate for oral cavity treatment applications, due to the high brittleness of thin glass posing a risk of injury to patients. Metal foil has also been used as the material of flexible substrates, presenting high thermal stability and low moisture/gas permeation. However, the rough surface and characteristic conductivity of metals complicate the device fabrication, which requires additional steps for planarization and insulation. Most importantly, the opacity of the metal foil narrows its use to top-emitting devices, excluding direct application in bottom-emitting or transparent devices. Although several new materials have been proposed to fabricate flexible substrates (fabric clothe, glass-fabric [99], silk [100] and biological material [101, 102] based substrates), plastics are the most widely used for flexible electronic devices to the present, with the two most common polymers being: poly(ethylene terephthalate) (PET) and poly(ethylene naphthalate) (PEN).
In contrast to transparent amorphous polymers, semicrystalline PET and PEN polymers exhibit both desirable mechanical and solvent resistance properties. High glass transition temperature ($T_g$) polyimide (PI) shows excellent thermal properties and colorless polyimide (CPI) is already available, however, the main factors still preventing its wide application are: limited commercially available products resulting in high cost, and synthetic difficulties [103, 104]. For now, commercially available heat stabilized (HS) PET and PEN constitute the main transparent flexible substrates that simultaneously provide solvent resistance, discrete tolerance to temperature and transparency, with HS PEN having higher thermal stability [105]. The substitution of the phenyl ring of PET by the naphthalene double ring of PEN has a significant effect on the $T_g$, which increases from 78 °C for PET to 120 °C for PEN [106, 107]. Additionally, the heat stabilization process can increase the upper operating temperature up to 150 °C and 200 °C for PET and PEN, respectively. The surface quality of these plastic substrates can also be improved with planarizing coating, which covers all surface defects creating a smooth surface with anti-scratch properties, additionally acting as a barrier to oligomer migration. In terms of water absorption, the prevailing humidity of the processing environment is critical, since uncontrolled moisture pickup of the polymer substrates can influence the dimensional reproducibility and promote degradation of moisture-sensitive materials in the device. For instance, both PET and PEN absorb about 1500 ppm water at a relative humidity (RH) of 60% at 20 °C after reaching the equilibrium level, typically after 12 h depending on thickness [107]. Appropriate pre-heating of the plastic substrates and processing environment with low moisture level are of high priority next. Finally, planarized HS PEN is considered a high-performance option commercially available that can couple well with low-temperature processing of organic/inorganic materials.

As for the flexible transparent conductive electrodes (TCEs), modified ITO and new electrode materials are being proposed for replacement of the most common ITO on plastic, which suffers from poor mechanical robustness. For instance, mesh pattern [108] and island-shape [109] based ITO anodes have been developed in order to improve the flexibility and avoid cracking after bending, while preserving the characteristic high transmittance and conductivity of ITO. The new materials proposed for flexible electrodes are conductive polymers, thin metal films, dielectric/thin metal/dielectric (DMD) multilayers, metal nanowires, graphene and carbon nanotubes (CNTs). To mention some of them, PEDOT:PSS is considered a promising conducting polymer because of its low cost, high transmittance, excellent flexibility, and high work function, while having disadvantages such as intrinsic acidity and poor conductivity. Ultrathin metal films (UTMF) were fundamentally thought to be an ideal alternative having high electric conductivity and good mechanical robustness, however, their light transmittance and conductivity highly dependent on film thickness demand the transformation of UTMFs into more complex films. DMD multilayers have also been proposed to combine the properties of thin metal and metallic oxide materials, i.e. high conductivity and flexibility of the thin metal film, and optical coupling and carrier injection of the outer and inner dielectric layers, respectively. The Ag NWs seem to be the most prominent solution-processed metal nanowires, with relatively low sheet resistance and high visible light transmittance (>85%). Ag NWs are also considered a highly competitive candidate for many flexible device applications. For instance, Ag NWs have been successfully fabricated on PET by roll-to-roll process for fabrication of large-area flexible OLEDs [110], the schematic illustration of the R2R fabrication process is shown in figure 7(b). OLEDs made on the embedded AgNWs electrodes showed 30%-40% better performance than those on commercial ITO/glass. Furthermore, as mentioned in previous section, the current record EQE in FQLEDs was achieved by using a flexible PI/Ag NWs film as the TCE (see figure 7(a)) [87]. Overall, comparing the properties of available TCE materials one can highlight the high transmittance and low bending radius of current Ag NWs, Ag stacked film (DMD), conducting PEDOT:PSS, graphene and CNTs, and on the other hand, the smoothness, moderate cost, good stability of current ITO on plastic, which has achieved a sheet resistance as low as ~6 Ω/sq. Ultimately, the development of ‘cold’ or room temperature deposition of ITO coating has overcome the plastic substrate limitations, also competing with the performance of high-heat deposited ITO (>190 °C). While the research in new TCEs advances, ITO on plastic (either PEN and PET) can be a good alternative for fabrication and application of QLEDs in the photomedicine field, since one-time use flexible QLED for external treatment requires low-cost materials and does not demand very low bending radius (as discussed in the following section).

The final step in manufacture of FQLEDs is the encapsulation. Organic materials in either hybrid or all solution-processed QLEDs are usually oxygen/moisture sensitive, thus proper flexible encapsulation is of crucial importance in order to extend the lifetime of the devices under ambient conditions. Thin film encapsulation (TFE) is a well-known approach first developed for flexible OLEDs, which consists in a hybrid organic-inorganic alternating multilayer barrier (see figure 7(c)). Inorganic metal oxides (commonly ZnO, MgO, Al$_2$O$_3$) or other inorganic materials (e.g. SiN) act as thin barrier layers, while the inserted organic films temper the defect growth and increase the effective diffusion length (e.g. polyacrylate, polyurea, cycloaliphatic epoxy hybrid) [96]. Al$_2$O$_3$ deposited by atomic layer deposition (ALD) has been reported to have excellent barrier properties for polymeric substrates [98]. In general, the TFE technology uses chemical
vapor deposition (CVD) or ALD for in situ grow of nanoscale films immediately after the OLED fabrication, so water vapor and oxygen transmission rates (WVTR and OTR, respectively) in the order of $10^{-6} \text{ g m}^{-2} \text{ d}^{-1}$ can be reached [4]. Nevertheless, complex composite encapsulation using organic-inorganic alternating barrier and ALD has a low production throughput and fabrication process of TFEs needs to be simplified for practical application. Alternatively, flexible lamination or solution-processed encapsulants could simplify the encapsulation process, offering good flexibility and mechanical stability while making the whole process compatible with cost effective R2R processing.

For instance, the flexible lamination method has been used to encapsulate OLEDs using a laminar structure consisting of a thin metal foil and a rubbery polymer layer (e.g. PDMS) [112]. In all measurements the flexible lamination of OLEDs was comparable to conventional glass encapsulation. Such approach has been proposed for simplicity, low price, scalability and suitability to the R2R processing. On the other hand, a highly durable flexible QLED was recently demonstrated by encapsulation with a solution-based amorphous fluoropolymer (CYTOP) [111]. The CYTOP-encapsulated flexible QLED emitted strong luminescence after being immersed in water for ~20 min (see figure 7(d)), even when subjected to continuous tensile stress with a 5 mm bending radius. CYTOP was also previously used in combination with a Al2O3/MgO laminated structure made by ALD for encapsulation of OLEDs [113]. The optimized inorganic/organic bi-layer resulted in superior WVTR in the order of $10^{-6} \text{ g m}^{-2} \text{ d}^{-1}$ (at 60 °C and 100% RH), attributed to the hydrophobic surface of the capping polymer. Ultimately, an integrated barrier layer between the plastic substrate and the TCE, and top encapsulation by solution-processed polymer and/or barrier lamination could demonstrate sufficient barrier performance for practical application of FQLEDs in the photomedical field.

Finally, in order to avoid overheating of the devices caused by Joule-heat generation, thermal management is also needed. Excess heat generated during continuous operation might cause failure of the device, discomfort and even superficial burns on patients. Depending on the irradiation period and respective light source, the energy dose applied can cause local temperature increase leading to tissue damages [22, 114]. Accordingly, heat sinks layered on the flexible device are normally used for heat dissipation [59, 67]. Flexible graphite sheets have a high thermal conductivity in the planar direction (up to ~1950 W m⁻¹ K⁻¹, several times as high as copper and aluminum), and are suitable as heat sinks for FQLEDs.
8. Perspective on near future introduction of QLEDs in the photomedicine market

The industry and the academy are pushing forward to take the maximum advantage of the unique capabilities of QLEDs as individual devices and in integrated electronic systems, particularly in the field of flexible/wearable electronics. According to the targeted application, FQLEDs can be made white-emitting, transparent, stretchable/foldable, transferable and so on, thus providing special features for a vast range of applications, including ‘at home’ and mobile electronics. As discussed in the course of this review, the FQLEDs have special features which make them ideal light sources for PDT and PBM phototherapies, and were demonstrated to have comparable or better performance than that of mainstream light sources. Low-cost and lightweight FQLEDs also promise wider adoption of PDT and PBM, opening up the opportunity for more convenient at-home treatment. This eliminates the need for costly treatment and unrealistic multiple visits to the hospital. Most importantly, these devices could be quickly introduced and commercialized as practical light sources for phototherapy, considering the fundamental, urgent demands of this field. The advantages and characteristics of QLEDs in relation to other types of light source were already presented in table 1 and previously discussed. In addition, the authors propose in figure 8 a set of basic requisites for near future application of FQLEDs in PDT and PBM. As depicted, a suitable and effective QLED should be a disposable and bendable light source with operating lifetime $\geq 6$ h (average in air), shelf-life $\geq 1$ month and minimum bending radius $\sim 6.5$–$10$ mm. Simultaneously, the figure excludes some features such as transferability, transparency, stretchability and foldability, which could be usable but are not restrictive for external treatment of the body’s skin and/or oral cavity. The rationale of these requisites and how QLEDs can meet them is briefly discussed.

First, the need for a low-cost disposable QLED is underscored by several factors, one of which is the high cost of laser or LED based phototherapy preventing the adoption of PBM and PDT by small clinics and low-resource populations. Other reasons to make them disposable are the characteristics of skin-contact and oral cavity treatments, and the concerns that arise from inappropriate reuse of the device (e.g. overtreatment or undertreatment and possible cross contamination from repeat use). FQLEDs can be made one-time-use devices due to the low cost of solution-processed materials and R2R processing. A maximum operating lifetime of $\sim 6$ h has been estimated according to the range of total fluence (F) and power density (PD) normally used in in-vitro and in-vivo studies. Setting a maximum power density of $10$ mW cm$^{-2}$ (for low irradiance phototherapy) and a maximum irradiation time of $6$ h will fix a maximum available fluence of

\[ F \leq \frac{6 \text{ h} \times 10 \text{ mW cm}^{-2}}{\text{PD}} \]
216 J cm$^{-2}$ ($F = PD^*t$) for each light source (assuming constant power density). Thus, even if the lifetime of deep-red QLEDs is below the high requirement of the display and lighting markets, these parameters do not restrict their use in phototherapy. Though disposable light sources could be sold under request instead of in-stock modality, a minimum shelf life of 1 month has been set. It was found that FQLEDs (without encapsulation) can last for 1 month or more in inert atmosphere ($O_2$: 5 ppm/$H_2O$: <0.1 ppm) without signal of deterioration (dark spots or luminance detriment) [65]. Regarding the minimum bending radius, the average radius of curvature found for the palate in adults is $r \sim 10$ mm (sample of 24 individuals) [118], and the average radius found for the little finger in children between 3 and 10 years is $r \sim 6.5$ mm (sample of 160 individuals) [119]. The earliest work in FQLEDs [86], reported a critical bending radius of ~5 mm for a PET/ITO based QLED in the bent state (device structure on the concave side), which was correlated to reduced current density of the device at the same driving voltage. The authors ascribed the failure mechanism to the electrode degradation rather than the QD and organic/inorganic layers, and attributed the critical radius to the onset of the cracking phenomenon in the ITO films [120]. Accordingly, it has been found for ITO/PET and ITO/PEN substrates fixed on a cylindrical surface, that the tensile stress degradation occurs for $r < 14$ mm while the compressive stress degradation occurs for $r < 8$ mm, based on degradation of the conductivity [105]. Finally, a flexible QLED for external application of PDT and PBM needs to be bendable rather than foldable or stretchable, and to be conformable for one time fit on a curved surface.

9. Conclusions and outlook

This paper provides a review on the use of QLEDs and OLEDs in the field of photomedicine, specifically for PDT and PBM. The research works discussed here in chronological order demonstrated the efficacy of both light sources in PDT and PBM through in-vitro and in-vivo studies, resulting in performance comparable to that of either LED arrays or lasers. QLEDs have been tested as a light source for destruction of cancer cells with PDT, to increase cell metabolism for wound repair with PBM and to kill bacteria with antimicrobial PDT, showing satisfactory results in all the in vitro studies to date. By matching the peak emission wavelength with the peak wavelength of the absorption spectra of photosensitizers, QLEDs with narrow emission bandwidth can take full advantage of photons and be more effective for specific treatment, reducing heating and the exposure times. Considering the additional advantages of FQLEDs such as high-power density at deep-red wavelengths and emission wavelength tunability, we envision a bright future for QLEDs in the photomedicine and healthcare fields. We also believe that the mature Cd-based QLEDs with record efficiency and brightness will pave the way for application of emerging Cd-free QLEDs in the photomedical field, as the research in synthesis of new materials continues making progress. Finally, we have proposed a set of basic requirements for near future introduction of FQLEDs in the photomedicine market, only considering external PDT or PBM treatment of the body’s skin and oral cavity. Although the application of QLEDs in phototherapy can be extended to internal treatment of organs with the development of new devices exhibiting multiple form factors (e.g. cylindrical-shaped to be used as a probe), its external application will cover a wide spectrum of medical treatments such as: treatment of skin cancer, oral cancer, inflammation, diabetic wound healing, superficial bacterial infections and beyond.

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Conflict of interest

The authors declare the following competing financial interest(s): QLEDCures, LLC is a for-profit start-up company focusing on developing quantum dot light-emitting diodes for photomedical applications.
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