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Review Article

Recent advances in electrochemiluminescence devices for point-of-care testing

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A dynamic progress of methodologies has increased demand for high performance detection technologies for point-of-care testing (POCT). Electrochemiluminescence (ECL) is now established as an important, highly sensitive detection strategy for the development of POCT devices. In this short review, we summarize the recent advances of portable ECL devices, such as portable power sources, bipolar ECL devices, wireless ECL devices, ECL detectors, and microfluidic chips. Moreover, we address the remaining challenges and future perspectives to integrate ECL sensing devices into point-of-care solutions.

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Introduction

Due to the urgent need of fast diagnosis at or near patients, point-of-care testing (POCT) was proposed and have attracted immense attention in the past few years [1–5]. It aims to provide rapid analysis and show healthcare trends using portable, low-cost and user-friendly devices [4]. POCT devices are highly desirable in global market especially in the developing countries for hospital/nonhospital settings, and for patients at home. Many sensors for POCT have been designed based on different analytical methods including electrochemical and optical methods [5,6], and some of them have been successfully commercialized [1,7]. The successful implementation and application of these sensors still has several challenges and largely depends on the development of analytical and engineering techniques.

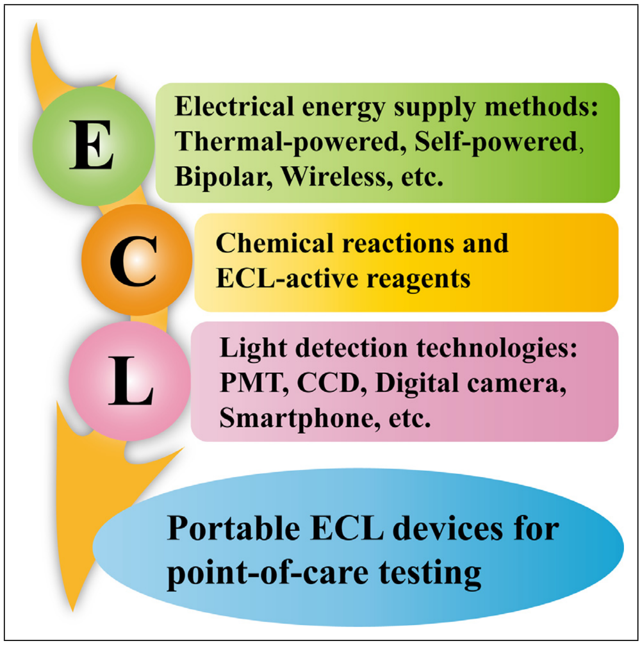
Electrochemiluminescence (ECL), also known as electrogenerated chemiluminescence, is a powerful analytical technique and has been extensively studied [8–27]. As the combination of chemiluminescence and electrochemistry, ECL possesses several advantages, such as simplicity, rapidity, high sensitivity and easy to control. Due to its excellent features, it has been widely used in many fields including bioanalysis, immunoassays, clinical diagnostics, food and environmental monitoring, biowarfare agent detection, etc. [28–30]. It receives increasing attention for POCT devices. Figure 1 shows the key components of a point-of-care device including the methodologies used to drive ECL reactions, the luminophores and detectors. This review summarizes the recent development of power supply methods, ECL detectors, and ECL microchips.

Electrical energy supply devices

Wired electrical energy supply devices

In traditional ECL detection methods, the luminescence is initiated and controlled by an electrochemical workstation. Due to high cost of electrochemical workstation, great efforts have been made to develop alternative power sources for ECL POCT. Portable and low-cost rechargeable battery is one example [31–33]. The advantages including high efficiency, output voltage stability, large capacity and low self-discharge rate, make rechargeable batteries appropriate for the fabrication of portable devices for POCT and on-site test [34•]. An inexpensive light-rechargeable supercapacitor was also used to supply voltage to screen-printed carbon electrodes for ECL light generation by Rusling and co-workers [35••]. Moreover, a mobile phone that can serve the basic functions of a potentiostat in controlling an applied potential was also demonstrated by Hogan and co-workers to initiate ECL emission [36••]. The voltage was initiated from the headphone jack of the device, and modulated by an audio output. Later, they further devised a novel, universal, standards-based approach exploiting the USB On-The-Go (USB-OTG) specification [37•]. In this approach, current can be drawn from any USB-OTG certified mini-USB port and modulated via the audio jack using a tone-detection circuit. A self-powered system was developed to further simplify and miniaturize the design of ECL sensors. A portable thermal-powered ECL visual sensor composed of a tiny power supply and a facile prepared electrode array was successfully developed by Chen's group (Figure 2a) [38]. The unique power supply is valuable for the miniaturization of ECL devices for field operation and

Figure 1.



The elements of ECL sensing process and the recent developments of ECL sensing devices access to POCT.

POCT. A self-powered 3D microfluidic ECL biosensing platform based on the origami technique was developed by Zhang *et al.* and used to detect glucose to demonstrate the sensing function of the design [39•]. By assembling the energy part and the sensing part together in a 3D paper chip, this proposed microfluidic origami ECL device exhibits broad application prospect in point-of-care diagnostics.

Bipolar electrochemistry devices

In contrast to conventional three-electrode ECL, bipolar electrochemistry-based ECL methods only needs one conductor which serves as both cathode and anode without any direct electrical connection [40••]. Bipolar ECL systems (BPE) are usually simple, low-cost, high-throughput, convenient to operate, easy to be miniaturized and thus ideally suited for application in POCT. Recently, bipolar electrochemistry has attracted much attention and has been widely used in constructing ECL sensors for chemical and biological analysis [41–44]. A number of attempts have been made to develop signal amplification approaches to improve the sensitivity and broaden its analytical applications [45–48]. Also, ECL sensing platforms based on multichannel bipolar systems have been proposed to demonstrate its potential in multianalysis [44,49,50]. Wang and co-workers constructed a novel microfluidic-based bipolar system with two-directional driving electrodes and dual-channel mode [51••]. As shown in Figure 2b, this novel BPE system achieved 100% current efficiency, and completely eliminated the background ECL signals from the driving electrodes. Conventional bipolar ECL is a two-dimensional process where light emission is strictly confined to the geometric surface area of the electrode. To overcome this intrinsic limitation, the bulk generation of ECL in a three-dimensional configuration using BPE as the driving force was demonstrated by Sojic *et al.* [52••] As shown in Figure 2c, a suspension of multi-walled carbon nanotubes where each one acts as an individual ECL nano-emitter was polarized in a bipolar electrochemical manner and ECL light was generated simultaneously from the entire solution. The higher sensitivity of this approach provides attractive potential in visual detection.

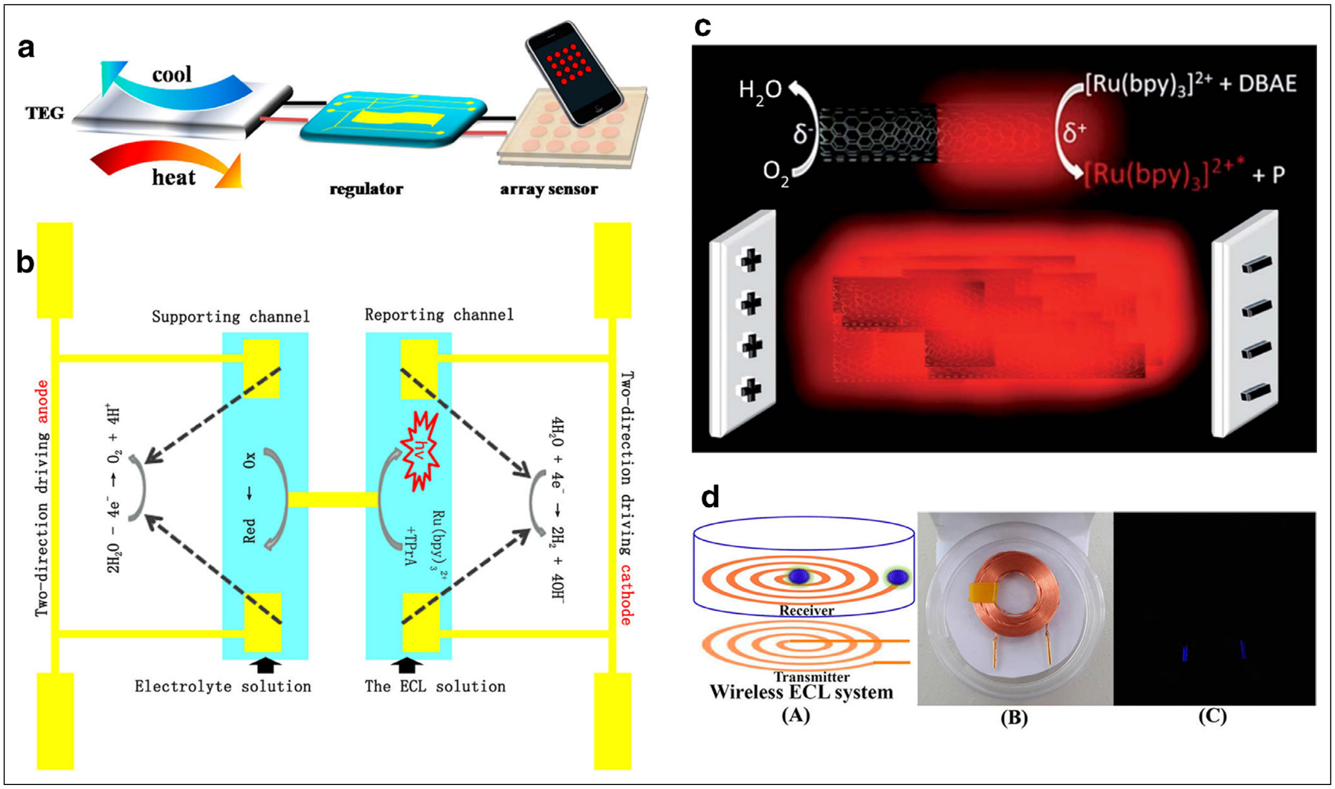
Wireless energy transmission devices

BPE-ECL can avoid the direct contact of electrochemical instruments with sensing electrodes, but they still require a direct contact of electrochemical instruments with driving electrodes in solutions. Besides, signal-on sensing electrodes in BPE-ECL sensors usually suffer from the background noise from driving electrodes. Thus, new ECL methods are still required to overcome these serious drawbacks. In 2014, our group proposed a wireless ECL minidevice based on the wireless energy transmission technique [53••]. Wireless energy transmission (wireless power transmission) is the transmission of electrical energy from a power source to an electrical load without using conductors [54]. As shown in Figure 2d, it consists of a disposable transmitter and a coiled energy receptor that used as the electrode. It can avoid the direct electrical contact of electrochemical instruments with any electrodes. It is promising for the development of portable ECL devices for various applications including POCT and field analysis. Later, a mini-diode that can rectify alternating current into direct current was embedded into a wireless ECL electrode microarray chip and thus strikingly enhanced the ECL intensity [55••]. This enables the visual detection using ordinary cameras or smartphones as facile and inexpensive detectors. We believe that this technique has great potential in construction of ECL minidevices integrating power supplier, and signal detector for POCT.

Light detection technologies

Signal collection is one of the most important parts in ECL sensing systems. It is often accomplished using a photomultiplier tube (PMT) because of its higher sensitivity. The demand for portable, cost-effective and user-friendly ECL detectors for POCT devices with acceptable sensitivity has given rise to use of alternative light sensors, such as charge-coupled devices (CCD), complementary metal oxide semiconductors (CMOS) devices, and silicon and organic photodiodes [56]. The use of a digital camera as an ECL detector was also reported to reduce the cost of the measurement [33,38,57••–59]. Smartphones, thanks to their high imaging and computing capabilities, open-source operation systems, increasingly play

Figure 2.



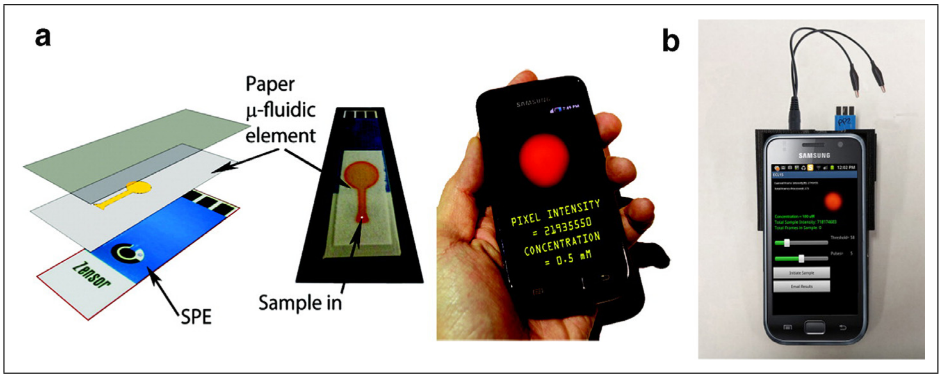
(a) Design of the thermo-powered high-throughput visual ECL sensor. Reprinted with permission from [38]. Copyright 2013 American Chemical Society. (b) Fundamental principle of the dual-channel bipolar ECL sensor. Reprinted with permission from [51••]. Copyright 2013 American Chemical Society. (c) Principle of bulk ECL produced by a suspension of multi-walled carbon nanotubes. They are polarized by the electric field generated between the feeder electrodes in a bipolar electrochemical manner. Reproduced from Ref. [52••] with permission from the Royal Society of Chemistry. (d) Schematic description of the wireless ECL system (A), the photo (B) and ECL image (C) of the wireless ECL minidevice using two short gold wires connected with small lacquered copper coils. Reprinted with permission from [53••]. Copyright 2014 American Chemical Society.

a pivotal role in recreational activities and healthcare delivery [7,60]. Possessing various advanced features, smartphone has emerged as a promising digital platform for the development of various bioanalytical devices for rapid, real-time, and point-of-care monitoring, which can significantly simplify design and reduce cost of the detection systems [56,60–64]. The portability and ubiquitous availability of smartphone offer great convenience for the development of portable ECL devices. The integration of ECL sensing elements into “all-in-one device” is one attractive direction. It is forecasted that the development of portable ECL sensors will greatly depend on the advance of light detection and analysis technologies. Many existing techniques may pave the way for this goal, such as wireless power technology, three-dimensional printing technology, Wireless Fidelity and Bluetooth transmission protocols.

The integrated portable ECL devices

The integration of ECL sensing processes including sample collection, power supply and signal detection into one minidevice is an exciting research area and will play an important role in POCT. Microfluidic platforms can be easily integrated with various analytical techniques to fabricate miniaturized systems. Their various useful capabilities, such as low cost, short assay time, low sample and reagents consumption, and the possibility for automation and integration of several analytical steps into one device, enable them to be widely used in the diagnostic and life science fields [65]. Different materials have been reported for preparing the microfluidics ranging from silicon and glass to soft materials, such as polymer (e.g., poly(dimethylsiloxane), PDMS) and paper [63]. Since Whitesides and co-workers proposed the first patterned paper as a microfluidic platform for bioassays [66], the paper-based devices have attracted rapidly increasing interest. It holds great potential for applications in POCT due to low-cost, portability, flexibility, and the porous structure of paper enables it to easily immobilize sensing materials with reduced sample volumes [67]. The combination of paper microfluidics with ECL was first demonstrated by Hogan and co-workers in the year

Figure 3.



(a) Schematic diagram of a paper-based microfluidic ECL sensor. Using inkjet-printed paper fluidic substrates and screen-printed electrodes, this ECL sensor can be read with mobile phone cameras. Reprinted with permission from [57••]. Copyright 2011 American Chemical Society. (b) A mobile phone used for ECL sensing. The audio jack supplies the potential to the paper microfluidic sensor, while the resultant ECL emission is detected by the camera in video mode. Both the excitation and detection processes can be controlled by a software application which can also transmit the results via e-mail. The black plastic sleeve surrounding the top of the phone holds the sensor adjacent to the camera and blocks ambient light [36••]. Copyright 2013, reprinted with permission from Elsevier.

of 2011 [57••]. By utilizing inkjet-printed paper fluidic substrates and screen-printed electrodes, the authors constructed low-cost and disposable ECL sensors which can be read-out with conventional photodetectors or mobile phone cameras (Figure 3a). Since then, several paper-based ECL sensors have been constructed [67,68]. The integration of disposable paper-based platform with bipolar electrode was first demonstrated by Chen's group for the sensitive ECL determination of prostate-specific antigen [40••]. Later, many paper-based ECL sensors utilizing bipolar electrodes have been proposed for the analysis of biomolecules [33,69] and DNAs [70]. Besides, an electrophoretic separation technique was successfully coupled with microfluidic paper-based analytical device with an on-column wireless ECL detector for the first time by Ge *et al.* [71]. Yu's group carried out extensive works on paper-based ECL origami devices for sensitive detection of DNAs [72], proteins [73–77], cancer cells [78–80], etc. As shown in Figure 3b, the integration of power resource and signal detector into smartphone was developed by Hogan *et al.* The power was initiated from the headphone jack of the device, and modulated by an audio output. The light emitted from the reaction was easily detected using the in-built phone camera. It significantly reduced the analysis cost due to generation, detection and analysis of the ECL signal in a single step.

Conclusions and future perspectives

ECL methods have been widely used in constructing sensors for bioanalysis, immunoassays, clinical diagnostics, food and environmental monitoring, and an increasing attention has been made to develop ECL sensors for POCT due to its higher sensitivity, easy to control, real-time analysis and high throughput readout. Recent developments in bipolar electrochemistry, microfluidic chips, wireless power and data transmission, and light detection technologies have unprecedentedly improved the performance of ECL sensors toward POCT. There is no doubt that the significant advances and major breakthroughs in POCT in the next few years will greatly enhance the development of these emerging technologies. Research efforts toward integrating a variety of processes (including sample collection, separation and detection) into a miniaturized analytical system will continue. The smart combination of different techniques and elements to fabricate integrated ECL sensors, and ensuring high specificity, sensitivity and reproducibility of the sensors in POCT are still challenges. Finally, these devices will play much important roles in pharmaceutical assay, food safety, environmental monitoring, homeland security, and other point-of-care applications.

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