

Prospects for the commercialization of chemiluminescence-based point-of-care and on-site testing devices

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Abstract Chemiluminescent reactions have found application in a number of commercial point-of-care and on-site testing devices. Notable examples include allergy tests (e.g., MASTpette, OPTIGEN® systems), flu tests (e.g., ZstatFlu®-II), cartridge-based immunoassay systems (FastPack® IP System, PATHFAST®), forensic tests for bloodstains, portable analyzers for biochip array assays (Evidence MultiStat), water quality tests (Eclox), air pollutants (e.g., oxides of nitrogen), and handheld devices for detecting explosives (e.g., E3500 Chemilux®). Many other point-of-care or on-site testing devices with a chemiluminescent end point have been devised on the basis of a variety of formats (e.g., cuvette, cassette, dipstick, test strip, microchip), but most have not progressed beyond a proof-of-principle or prototype stage.

Keywords Chemiluminescence · Point of care · Photographic film · Microchip · Cartridge · Luminometer · Allergy testing · Explosives

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Introduction

Point-of-care testing covers a wide range of medically important tests that can be performed in locations that are convenient for the patient and/or the health care provider. These locations may include the home, the physician's office, a clinic, or a patient's bedside. Blood glucose testing and pregnancy testing are two prominent examples of this type of testing. Point-of-care testing may be qualitative (e.g., pregnancy test reporting pregnant/not pregnant result), semiquantitative (e.g., urine dipstick result compared against a color chart), or quantitative (e.g., blood glucose measured using a glucose meter) [1].

The size of point-of-care devices ranges from handheld devices to small benchtop instruments that are portable and easily moved between locations as needed. Current point-of-care testing technologies mostly rely on electrochemical end points (e.g., glucose test strip) or on colorimetric end points (e.g., urine dipstick) that can be assessed qualitatively, semiquantitatively, or quantitatively [1].

Disposable assay devices in the form of dipsticks, cassettes, and cartridges are an established format in point-of-care testing. In some cases, all of the reagents necessary for the assay are contained in the device, and the user assesses the test result by observing the development of a colored line or by viewing a message or icon displayed on a liquid crystal display screen built into the disposable device. This level of an all-in-one device sophistication has not been reached for chemiluminescence (light emitted during a chemical reaction) assays. However, the combination of chemiluminescence and instant photographic film does contain the potential for creating self-contained test devices [2].

A related area of nonmedical testing is on-site testing. This includes food testing, testing for environmental toxins, forensic testing for bloodstains, and testing for biowarfare agents and explosives. Chemiluminescence has played a major role

in both point-of-care testing and on-site testing (subsequently and collectively termed “point-of-use” testing), and this review assesses the current state of research and development and the prospects in these areas of application.

A range of analytical formats (e.g., reaction vessel, detection reaction, readout) have been used to make possible reliable point-of-use testing. We have chosen to consider the applications of chemiluminescence in point-of-use testing on the basis of the type for reaction vessel used (microwell, cuvette, cartridge, dipstick, lab-on-paper, membrane, microchip).

Microwell-based assays

Point-of-use chemiluminescence assays can be performed in strips of microwells, and the light emission is detected using photographic film, especially high-speed instant film (e.g., Polaroid type 612 film, ASA 20,000). This has provided a simple qualitative means to detect the light emission from an analytical chemiluminescent reaction such as an immunoassay [3]. Special camera luminometers have been designed for this purpose [4]. These consist of a Polaroid film back that is placed underneath a reaction vessel that is separated from the film by a shutter. Removal of the shutter exposes the film, and the degree of exposure provides a semiquantitative indication of the intensity of the light emission. A further refinement is to interpose a graded neutral density filter between the film and the reaction vessel so as to further distinguish between different intensities of light emission [3]. The conventional pipetting, incubation, washing, and signal generation steps in an enzyme-linked immunosorbent assay (ELISA) are performed in the microwell strip, and then the light emission (in the form of a glow from the enhanced chemiluminescent peroxidase label detection reaction) is detected using a sheet of instant film contained in the camera luminometer.

The combination of chemiluminescence-based ELISAs in microwells and photographic film for detection has been exploited in point-of-use environmental applications, such as screening water samples for herbicides (e.g., chlortoluron) [5] and organophosphorus compounds [6] because of the rapidity, simplicity, and portability of this technology.

Cuvette-, vial-, and flow-cell-based assays

An important application of point-of-use testing is detecting intentional or accidental contamination of water for civilian or military applications at the point of sampling. Chemiluminescence has played an important role in this type of testing because the chemiluminescence assay is rapid and convenient. Known as the enhanced chemiluminescence and oxyradical (Eclox) assay, it is performed in a cuvette into which the water sample and enhanced chemiluminescence

reagents (peroxidase, luminol, oxidant, and enhancer) are added. The cuvette is then placed into a handheld luminometer, and the light emission is analyzed for 4 min. Light emission is compared against a standard, and any inhibition of light emission is indicative of contamination [7].

The ZstatFlu®-II test provides another example of a chemiluminescence-based point-of-use device based on a reaction vial (termed a “chemical implementation device”) comprising a polypropylene top chamber and a polystyrene bottom chamber that screw together [8–10]. The test involves an initial step of extracting the specimen (e.g., a nasal aspirate) followed by squeezing the extract through a 10- μ m filter into the bottom chamber of the chemical implementation device, which contains the chemiluminescent influenza-specific viral neuraminidase substrate (1,2-dioxetane-4,7-dimethoxy-*N*-acetylneuraminic acid) and light enhancers. The upper chamber is then screwed onto the top of the bottom chamber, and the assembly is then placed in an imaging device and incubated for 15 min at 25 °C. In the final step, the lid of the imaging device (a modified Polaroid type 600 camera) is closed, and this causes the 40 % sodium hydroxide in the upper part of the device to be released through a frangible flap into the lower part of the device and the subsequent chemiluminescence from the released dioxetane. Imaging on high-speed Polaroid film (ASA 7,000–8,000) proceeds for 5 min, after which a plus-shaped image appears on the film for positive specimens.

Multiple portable devices utilize chemiluminescence for the detection of ambient air pollutants nitric oxide (NO) and NO₂. The basic principle for using chemiluminescence for NO detection was first presented in 1970 [11]. The air being monitored for NO is mixed in a flow cell reaction chamber with a reactant gas (ozone, O₃); this forms an excited state species, NO₂^{*}, that decomposes to NO₂ with the release of light. There are many devices for NO detection that combine ozone generation with a luminescence detector. The instruments can be tabletop instruments (Teledyne 200E, Horiba PG-250/300) and often combine chemiluminescence for NO detection with other methods to detect additional gases such as SO₂, CO, O₂, and CH₄.

Cartridge-based assays

An early point-of-use application for chemiluminescence was the multiple allergen simultaneous tests (MAST) system for allergen detection. This used a combination of a cartridge (a pipette-like device), chemiluminescence, and photographic film [12]. It was an immunoassay for a panel of up to 36 different specific anti-allergen IgE antibodies in serum that was conducted in a pipette device that contains a series of cellulose threads, each thread coated with a specific capture allergen. After the completion of the various filling, incubation, and washing steps, the pipette device was filled with a luminol-

based substrate for the bound peroxidase label and light emission was imaged directly onto photographic film.

The original photographic detection-based allergy test system devised and developed by MAST Immunoseystems has been updated and the new version is now marketed by Hitachi Chemical Diagnostics as the CLA® allergen-specific IgE assay [13]. In this system, a camera luminometer for photographic detection is replaced by a small portable benchtop luminometer that measures light emission from the individual threads in the pipette device (CLA® Pette) (Fig. 1a).

A redesigned version of the system, the OPTIGEN® allergen-specific IgE assay, replaces the threads with wells and includes optical components [13] (Fig. 1b). The disposable OPTIGEN device is based on a reaction pipette that comprises three injected molded parts: (1) a “pette body” with

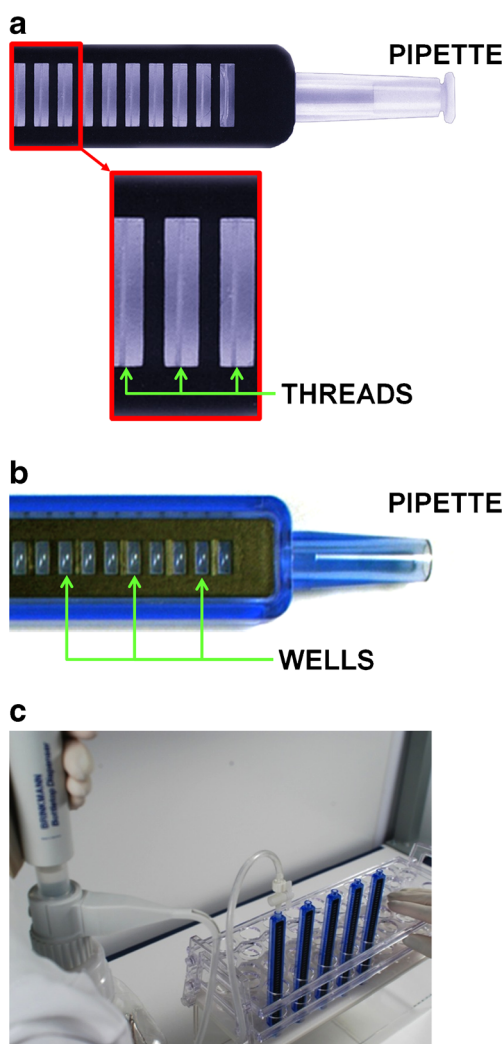


Fig. 1 **a** CLA® Pette for simultaneous measurement of the severity of a patient's allergic reaction to up to 36 different allergens using a single 1.5-mL serum sample. Close-up of allergen-coated threads in the CLA® Pette (*inset*). **b** Close-up of reaction wells of the OPTIGEN® Pette device **c** Filling of OPTIGEN® Pette (for generation of 20–36 specific IgE results from a single 230-μL serum sample). (Reproduced with permission from Hitachi Chemical Diagnostics)

a serum channel for fluid flow, (2) a coverslip with wells on the channel side for the binding of allergens and small lenses on the outer side for light collimation, and (3) a partition that separates the individual wells to isolate the light emission. The device is filled with sample using a suction device (Fig. 1c), and on completion of the assay, light emission from individual wells is measured in a small benchtop luminometer. The portability of the luminometer makes this system well suited to operation in a point-of-care setting such as a clinic as opposed to a central laboratory.

Other cartridge-based immunoassay systems include the PATHFAST® immunoanalyzer (results in 16 min) and the Qualigen FastPack® IP System (results in 10 min). For both systems, all the required reagents for analyzing serum or plasma specimens for analytes are contained in a single cartridge (pack) (Fig. 2). After a sample from a patient has been applied into either system's cartridge, the cartridge is inserted into the respective analyzer. The analyzers automate the mixing, sample and reagent movement, and reading of light emission from the cartridge. The PATHFAST® immunoanalyzer has cardiac assays, including cardiac troponin I (cTnI), myoglobin, creatine kinase MB and N-terminal

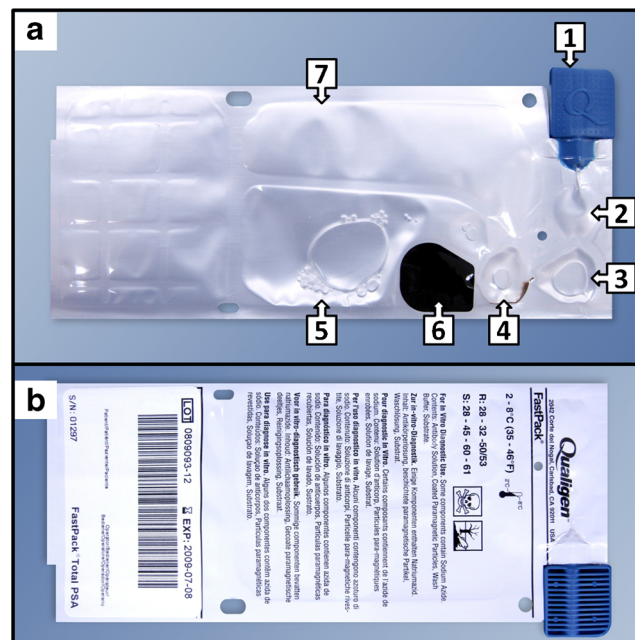


Fig. 2 FastPack® pouch for total prostate-specific antigen (PSA). The front of the pouch has a transparent film which contains multiple reaction chambers (**a**). A sample is applied into the injection port (1) and is collected in the sample chamber (2). The sample is mixed in a chamber containing both capture antibodies and reporter antibodies labeled with chemiluminescent enzyme reporters (3). In the reaction chamber (4), paramagnetic particles bind the capture antibodies. A wash solution is applied from a storage reservoir (5), and once washing is complete, the antibody–analyte sandwich is exposed to the substrate (6). The chemiluminescent emission is measured by a detector on the separate nondisposable unit. All residual solutions from the process are deposited in the waste chamber (7). The back of the pouch has the label and barcode affixed (**b**). (Photo courtesy of Qualigen)

of the prohormone brain natriuretic peptide assays. The cTnI assay has a sandwich-assay format with a cTnI capture antibody on a magnetic particle, the analyte, and a second cTnI antibody conjugated to alkaline phosphatase. The PATHFAST® immunoanalyzer uses a chemiluminescent substrate specific for alkaline phosphatase activity (CDP-Star) in combination with a polymeric enhancer (Sapphire-II) [14]. The FastPack® IP System assay also has a sandwich-assay format. For prostate-specific antigen (PSA) assay with the FastPack® IP System, the cartridge contains a monoclonal anti-PSA antibody labeled with alkaline phosphatase, biotinylated monoclonal anti-PSA prebound to streptavidin-coated paramagnetic particles, wash solution, and a chemiluminescent substrate (a mixture of indoxyl 3-phosphate and lucigenin).

The lateral flow assay cartridge format has become very popular for point-of-care immunoassays with colorimetric end points, such as pregnancy tests. This type of assay format has been developed with a chemiluminescent end point for on-site detection of the explosive trinitrotoluene (detection limit 0.2 µg/mL) and for fumonisins (from *Fusarium* moulds) in maize flour (detection limit 2.5 µg/L). On-site, this was made possible by means of a portable battery-operated thermoelectrically cooled CCD camera [15, 16].

Other chemiluminescence-based lateral flow tests have been described (e.g., for detection of *Trypanosoma* messenger RNA) but the detection step used equipment (CCD imager, microplate reader) that was unsuitable for implementation at the point of care [17]. The combination of lateral flow assay systems and chemiluminescence detection has been described in the patent literature (e.g., detection with or without quantitation of an analyte in a sample containing whole cells) [18].

Another important cartridge-based handheld point-of-testing chemiluminescence-based system is the E3500 Chemilux® trace explosives detector (Scintrex Trace) (Fig. 3). This handheld device detects the presence of traces of particulates and vapors of explosives (homemade, military, and commercial explosives) noninvasively in luggage, mail,

cars, trucks, clothing, electronic articles, backpacks, documents, and containers. Within the device, explosives in sampled air are converted to NO₂, and this reacts with a luminol solution in a disposable cartridge to produce chemiluminescence (luminol Chemilux® technology, US patent 6,984,524B). Other types of portable devices have been commercialized and include a gas chromatography step prior to the chemiluminescent reaction (e.g., Scintrex Trace 4500 series) [19]. Other compact systems have been described in which an infrared laser illuminates an interrogation area on the surface of an object being scanned. The illumination causes selective desorption of molecules of the contraband substance (explosives, narcotics) and a collection system collects the desorbed molecules. Explosives are converted to NO₂, which is detected via chemiluminescence using the luminol reaction [20].

Dipstick-based assays

Dipsticks have a long history as simple dip-and-read-type tests, and the commonest end point for a dipstick has been a colorimetric end point (e.g., urine test strips, litmus paper) [21]. A chemiluminescence-based dipstick competitive immunoassay for multiresidue analysis of *s*-triazine pesticides in water based on a linear array of six immobilized antibodies (cross-reactive) against a series of pesticides has been described [22]. Horseradish peroxidase labeled antigen bound to the spots on the membrane was detected using an enhanced chemiluminescent luminol reaction and light emission was detected using a portable luminometer. This was a proof-of-principle-type study and it also used an artificial neural network to discriminate between the presence of three different structurally related pesticides (atrazine, terbutylazine, and ametryn).

Several other dipstick immunoassays with a chemiluminescent end point have been described, e.g., for urine hemoglobin [23], dichlorodiphenyltrichloroethane (DDT) [24], atrazine (limit of detection 0.1 ng/mL) [25], and vitamin B₁₂ in energy drinks (limit of detection 1 ng/mL) [26], and although they have the potential for point-of-use applications, they have not been commercialized.

The combination of a dipstick or a test strip and a chemiluminescent end point has also been described or claimed in the patent literature. Examples include a dipstick kit for rapidly determining infection or food contamination [27], a method for detecting circulating antibody types using a dipstick with discrete test areas [28], a strip for determining the presence of an endotoxin or endotoxin-like material in a sample [29], a test strip for assaying prothrombin [30], a test strip for detecting target-specific DNA:RNA hybrids [31], and a strip for detecting pathogens [32].

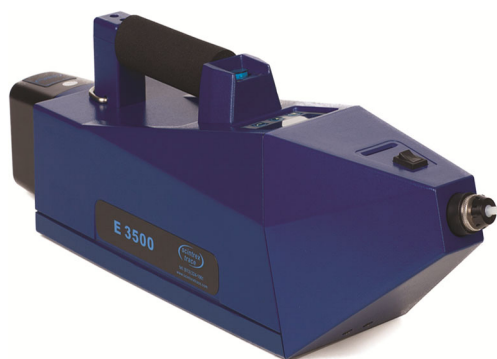


Fig. 3 E3500 Chemilux® trace explosives detector. (Photo courtesy of Autoclear)

Lab-on-paper-based assays

Low-cost microfluidic paper-based analytical devices (μ PADs) have been devised for a range of assays, and these are usually designed to have a colorimetric end point [33]. This type of device has been adapted to a chemiluminescent end point for ELISAs for various cancer markers (a-fetoprotein, carcinoembryonic antigen 125) [34]. The μ PAD was fabricated by wax screen printing and capture antibodies were immobilized onto a chitosan-modified area of the μ PAD. Light emission from the pads was detected using a luminometer.

Microchip-based assays

In recent years different type of “chips” have been designed for a wide range of analytical procedures [35]. The different types include microfluidic chips and chips with different analytical reagents (antigens, antibodies, nucleic acid probes) arrayed on the surface of the chip (microarrays). Some of these chips utilize chemiluminescence as the output signal. The small size of microfluidic chips makes them well suited for point-of-use applications, but in most cases the assays have been limited to laboratory-based assays.

The Evidence MultiStat in combination with Biochip Array Technology (Randox) provides an example of a commercial point-of-use microarray chip-based chemiluminescence assay. Biochip Array Technology (Randox) is based on a 9 mm×9 mm disposable chip formed from a sheet of silanized aluminum oxide [36, 37]. The surface of each chip has an array of test spots that can evaluate up to 49 analytes. The detection system is chemiluminescent-substrate-specific for a horseradish peroxidase label. Because the biochip is small, the assay system has the potential to become more portable as the analyzers become smaller.

Tablets and spray-on reagents

This final category does not involve a device. Instead, it uses reagents in tablet form, a format that is used in point-of-care urine glucose tests (e.g., Clinitest® alkaline copper sulfate reagent tablets) [38]. This format is also used today in a point-of-testing forensic application based on chemiluminescence. A luminol-based reagent kit is available in tablet form (e.g., BLUESTAR® FORENSIC). A luminol-containing tablet and a hydrogen peroxide–urea-containing tablet are made up into a working solution that is then sprayed onto an area suspected of containing bloodstains. Heme present in the bloodstain catalyzes the characteristic blue luminol chemiluminescence, which can be observed or photographed [39].

Commercialization

Some of the major steps involved in taking an idea to a commercial product are as follows [40]:

- (a) Basic principles observed and reported/patented
- (b) Technology concept and/or application formulated
- (c) Proof-of-principle studies in a laboratory environment
- (d) Prototype demonstration in a relevant operational environment (e.g., point of care)
- (e) Production prototype testing in a relevant operational environment
- (f) Final system completed and qualified through test and demonstration in an operational environment (beta site testing)
- (g) Regulatory approval (e.g., FDA)
- (h) Launch of product

Crucial steps in this process include the transition from proof-of-principle studies to a commercial prototype and subsequent field studies to confirm the operating features, and finally full commercialization. Although there are several successful commercial chemiluminescence-based point-of-use assays and assay systems, the majority of these types of assays have only progressed to a proof-of-principle stage in the commercialization pathway, and various analytical challenges still remain [41].

A number of factors underlie this limited application of chemiluminescence in point-of-use testing. In some instances, the market size for intended application has simply been too small to attract commercial investment. In other instances, the application has not presented a viable alternative to the current technology for existing applications. Point-of-use immunoassays provide a good illustration of this limitation. Most of the proof-of-principle studies for point-of-use chemiluminescence assays have required a separate instrument to measure light emission. This contrasts with the simpler direct visual readout of colorimetric-based immunoassays (e.g., lateral flow tests for detecting pregnancy based on the appearance of a colored line). Currently configured chemiluminescence immunoassays cannot be read visually because the low-level light emission is not detectable by the naked eye, so they cannot compete with a direct visually read colorimetric immunoassay. Likewise, they cannot compete with the new generation of digital immunoassays that incorporate a disposable microspectrophotometer [42]. Although luminometers have been miniaturized, there are no commercially available disposable luminometers analogous to the disposable microspectrophotometers. The closest technical solution would be a photographic-film-based single-use camera [43], but these are usually loaded with low-speed (low-sensitivity) film that would be likely unsuitable as a detector.

A handheld camera may also have potential in the context of point-of-use chemiluminescence tests. A Nikon D700 SLR camera has been compared with X-ray film in the detection of serial dilutions of horseradish peroxidase labeled antibody spotted onto nitrocellulose membranes and developed with commercial enhanced chemiluminescence reagents [44]. The optimized digital images from the SLR camera were more sensitive than X-ray film. Considering some recent smartphones, such as the Nokia Lumia 1020 (41-megapixel sensor) [45], are equipped with hardware and software optimized for low-light and high-resolution images, perhaps smartphones will make possible point-of-use chemiluminescence assays, in much the same way as phones are being used in combination with dipstick-based tests [46].

Conclusions

Chemiluminescent reactions have found successful applications in a number of commercial point-of-care and on-site testing devices. Some notable examples include allergy tests (e.g., MASTpette, OPTIGEN® systems), flu tests (e.g., ZstatFlu®-II), cartridge-based immunoassay systems (FastPack® IP System, PATHFAST®), forensic tests for bloodstains, portable analyzers for biochip array assays (Evidence MultiStat), water quality tests (Eclox), and air pollutants, and handheld devices for detecting explosives (e.g., E3500 Chemilux®). Commercialization of any technology is difficult, and the pathway to success is complicated by competing products and the ability to meet unmet needs. Many other point-of-care or on-site testing devices with a chemiluminescent end point and based on a variety of formats (e.g., cuvette, cassette, dipstick, test strip, microchip) have been devised, but most have not progressed beyond a proof-of-principle or prototype stage.

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