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Designs, formats and applications of lateral flow assay: A literature review

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Abstract This manuscript provides a brief overview of latest research involving the use of lateral flow assay for qualitative and quantitative analysis in different areas. The excellent features and versatility of detection formats make these strips an ideal choice for point of care applications. We outline and critically discuss detection formats, molecular recognition probes, labels, and detection systems used in lateral flow assay. Applications in different fields along with selected examples from the literature have been included to show analytical performance of these devices. At the end, we summarize accomplishments, weaknesses and future challenges in the area of lateral flow strips.

1. Introduction

Point of care (POC) testing has become the most famous way of diagnosis in clinical analysis, food safety and environment. Compared to centralized labs, POC provides prompt results in shorter times. Lateral flow assay (LFA) based POC devices are among very rapidly growing strategies for qualitative and quantitative analysis. LFA is performed over a strip, different parts of which are assembled on a plastic backing. These parts are sample application pad, conjugate pad, nitrocellulose membrane and adsorption pad. Nitrocellulose membrane is further divided into test and control lines. Pre-immobilized reagents at different parts of the strip become active upon flow of liquid sample. LFA combines unique advantages of biorecognition probes and chromatography. LFA based strips have different detection formats. Drawbacks associated with conventional clinical technique, enzyme linked immunosorbent assay (ELISA), were flabbergasted by LFA. Rapidity and one step analysis, low operational cost, simple instrumentation, user friendly format, less or no interferences due to chromatographic separation, high specificity, better sensitivity, long term stability under different set of environmental conditions and portability of the device are unique advantages related to LFA strips [1] (See Table 1). Rather than changing different physical parts, mathematical models are being used to optimize and improve quantitation ability of LFA [2–5].

Lateral flow assay basically combines a number of variants such as formats, biorecognition molecules, labels, detection systems and applications. Several review articles have been published which highlight different aspects of lateral flow

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Table 1 Advantages and pitfalls of LFA.

Advantages	Pitfalls
• Ease of device preparation • Low cost • Stability over a wide range of environmental conditions and very long shelf life. • Simple and user friendly operation • Requirement of small sample volume • Most of the time, allows sample application without pretreatment • Versatility of formats, biorecognition molecules, labels and detection systems. • Less time of analysis • Comparable or better sensitivity and specificity than other well established methods • High potential of commercialization • Easy integration with electronics • Wide range of applications • No or very little energy consumption	• Mostly qualitative or semi-quantitative • Reproducibility varies from lot to lot • Most of the devices can detect more than one or two analytes simultaneously • Suffers from low biomolecules affinity toward analytes and tendency of cross-reactivity • Sometimes, pretreatment of sample is required which is time consuming • Once sample is applied to the strip, capillary action cannot be decreased or speeded up. • Analysis time is also dependent on nature of sample itself i.e. viscosity, surface tension.

assay. A recently published review emphasizes on principles of immunochromatography, its advantages and special use of lateral flow immunoassay in determination of toxic contaminants in agricultural and food products. Different methodologies for developing immunochromatographic systems have been considered in detail [6]. Labels used in LFA play an important role in determining sensitivity of analysis and a variety of labels are being employed in LFA. Description of labels along with advantages and pitfalls is given in a review [7]. A brief review of the LFA based test strips for detection of mycotoxins in food and feed is given by Rudolf and Alexandra [8]. LFA based strips can be an alternate and cheapest diagnostic tools in clinical areas particularly in the developing world and thus have been discussed in a review article of microfluidic diagnostic devices [9]. Another review article focuses on applications of lateral flow assay for detection of biological infectious agents and chemical contaminants. Bacteria, viruses, toxins, veterinary drugs and pesticides are considered in detail [10]. Paper based biosensors come in different configurations and formats and they employ nanomaterials for detection of proteins, cells and nucleic acids in diagnostic applications. LFA represent a special type of paper based biosensors and they have been discussed as a major component in reviews of nanomaterial based paper biosensors [11,12].

In this review, we intend to overview recent advances in different variants of LFA. We have summarized different formats, biorecognition molecules, labels, detection systems and applications in some specific areas.

2. Formats

Different formats are adopted in LFA. Strips used for LFA contain four main components. Brief description of each is given before describing format types.

Sample application pad: It is made of cellulose and/or glass fiber and sample is applied on this pad to start assay. Its function is to transport the sample to other components of lateral flow test strip (LFTS). Sample pad should be capable of transportation of the sample in a smooth, continuous and homogenous manner. Sample application pads are sometimes designed to pretreat the sample before its transportation. This pretreatment may include separation of sample components, removal of interferences, adjustment of pH, etc.

Conjugate pad: It is the place where labeled biorecognition molecules are dispensed. Material of conjugate pad should immediately release labeled conjugate upon contact with moving liquid sample. Labeled conjugate should stay stable over entire life span of lateral flow strip. Any variations in dispensing, drying or release of conjugate can change results of assay significantly. Poor preparation of labeled conjugate can adversely affect sensitivity of assay. Glass fiber, cellulose, polyesters and some other materials are used to make conjugate pad for LFA. Nature of conjugate pad material has an effect on release of labeled conjugate and sensitivity of assay.

Nitrocellulose membrane: It is highly critical in determining sensitivity of LFA. Nitrocellulose membranes are available in different grades. Test and control lines are drawn over this piece of membrane. So an ideal membrane should provide support and good binding to capture probes (antibodies, aptamers etc.). Nonspecific adsorption over test and control lines may affect results of assay significantly, thus a good membrane will be characterized by lesser non-specific adsorption in the regions of test and control lines. Wicking rate of nitrocellulose membrane can influence assay sensitivity. These membranes are easy to use, inexpensive, and offer high affinity for proteins and other biomolecules. Proper dispensing of bioreagents, drying and blocking play a role in improving sensitivity of assay.

Adsorbent pad: It works as sink at the end of the strip. It also helps in maintaining flow rate of the liquid over the membrane and stops back flow of the sample. Adsorbent capacity to hold liquid can play an important role in results of assay.

All these components are fixed or mounted over a backing card. Materials for backing card are highly flexible because they have nothing to do with LFA except providing a platform for proper assembling of all the components. Thus backing card serves as a support and it makes easy to handle the strip.

Major steps in LFA are (i) preparation of antibody against target analyte (ii) preparation of label (iii) labeling of biorecognition molecules (iv) assembling of all components onto a

backing card after dispensing of reagents at their proper pads (v) application of sample and obtaining results.

2.1. Sandwich format

In a typical format, label (Enzymes or nanoparticles or fluorescence dyes) coated antibody or aptamer is immobilized at conjugate pad. This is a temporary adsorption which can be flushed away by flow of any buffer solution. A primary antibody or aptamer against target analyte is immobilized over test line. A secondary antibody or probe against labeled conjugate antibody/aptamer is immobilized at control zone.

Sample containing the analyte is applied to the sample application pad and it subsequently migrates to the other parts of strip. At conjugate pad, target analyte is captured by the immobilized labeled antibody or aptamer conjugate and results in the formation of labeled antibody conjugate/analyte complex. This complex now reaches at nitrocellulose membrane and moves under capillary action. At test line, label antibody conjugate/analyte complex is captured by another antibody which is primary to the analyte. Analyte becomes sandwiched between labeled and primary antibodies forming labeled antibody conjugate/analyte/primary antibody complex. Excess labeled antibody conjugate will be captured at control zone by secondary antibody. Buffer or excess solution goes to absorption pad. Intensity of color at test line corresponds to the amount of target analyte and is measured with an optical strip reader or visually inspected. Appearance of color at control line ensures that a strip is functioning properly. Fig.1 shows schematic of general sandwich format of LFA. In some of sandwich assays, control line was not included (See Fig. 3a).

2.2. Competitive format

Such format suits best for low molecular weight compounds which cannot bind two antibodies simultaneously. Absence of color at test line is an indication for the presence of analyte while appearance of color both at test and control lines indicates a negative result. Competitive format has two layouts. In the first layout, solution containing target analyte is applied onto the sample application pad and prefixed labeled biomolecule (antibody/aptamer) conjugate gets hydrated and starts flowing with moving liquid. Test line contains pre-immobilized antigen (same analyte to be detected) which binds specifically to label conjugate. Control line contains pre-immobilized secondary antibody which has the ability to bind with labeled antibody conjugate. When liquid sample reaches at the test line, pre-immobilized antigen will bind to the labeled conjugate in case target analyte in sample solution is absent or present in such a low quantity that some sites of labeled antibody conjugate were vacant. Antigen in the sample solution and the one which is immobilized at test line of strip compete to bind with labeled conjugate [13]. In another layout, labeled analyte conjugate is dispensed at conjugate pad while a primary antibody to analyte is dispensed at test line. After application of analyte solution a competition takes place between analyte and labeled analyte to bind with primary antibody at test line (See Figs. 2 and 3b).

Recently, a unique change was introduced in conventional design of LFA by introducing a new line (antigen line) in between test and control lines for detection of C-reactive protein (CRP) in serum samples. This format involves somehow a competition between analyte in solution and analyte pre-dispensed on a new line. New line was formed by dispensing CRP antibody solution followed by CRP solution. In case of very low concentration of CRP in sample, most of the labeled conjugate molecules will remain unreacted and migrate to antigen line and CRP present at antigen line will capture these labeled conjugates and it will result in an intense color at antigen line and rest of labeled conjugate will move to control line and will produce relatively a light color. In case of very high concentrations, most of CRP molecules will be captured at test line and will be sandwiched in between labeled conjugate and prefixed antibody at test zone, this complex will move and be captured by control line antibody. In this case very few labeled conjugate molecules will be retained at antigen line. The lesser the color at antigen line, the higher the concentration of analyte. This format can be tried for other clinical and non-clinical analytes [14].

2.3. Multiplex detection format

Multiplex detection format is used for detection of more than one target species and assay is performed over the strip containing test lines equal to number of target species to be analyzed. It is highly desirable to analyze multiple analytes simultaneously under same set of conditions [15]. Multiplex detection format is very useful in clinical diagnosis where multiple analytes which are inter-dependent in deciding about the stage of a disease are to be detected [16]. Lateral flow strips for this purpose can be built in various ways i.e. by increasing length and test lines on conventional strip, making other structures like stars or T-shapes. Shape of strip for LFA will be dictated by number of target analytes [17]. Miniaturized versions of LFA based on microarrays for multiplex detection of DNA sequences have been reported to have several advantages such as less consumption of test reagents, requirement of lesser sample volume and better sensitivity [18]. A very recent example of multiplex detection format of LFA was demonstrated by Ye Xu et al. where they used a series of test lines immobilized with capture probes to detect four common human papillomavirus (HPV) types simultaneously [19] (See Fig. 3c). Multiplex detection format resulted in LODs in the range of 0.05–3.0 ppb for a series of mycotoxins in cereal samples and results were in good agreement with LC-MS/MS [20].

3. Biorecognition molecules

3.1. Antibodies

Antibodies are employed as biorecognition molecules on the test and control lines of lateral flow strip and they bind to target analyte through immunochemical interactions. Resulting assay is known as lateral flow immunochromatographic assay (LFIA). Antibodies are available against common contaminants but they can also be synthesized against specific target analytes. Mice or other animals are immunized with target and secreted antibodies are subcloned and purified according to application. Antibodies are being utilized in clinical analysis since five decades for diagnostic needs. An antibody which specifically binds to a certain target analyte is known as primary antibody but the one which is used to bind a target containing

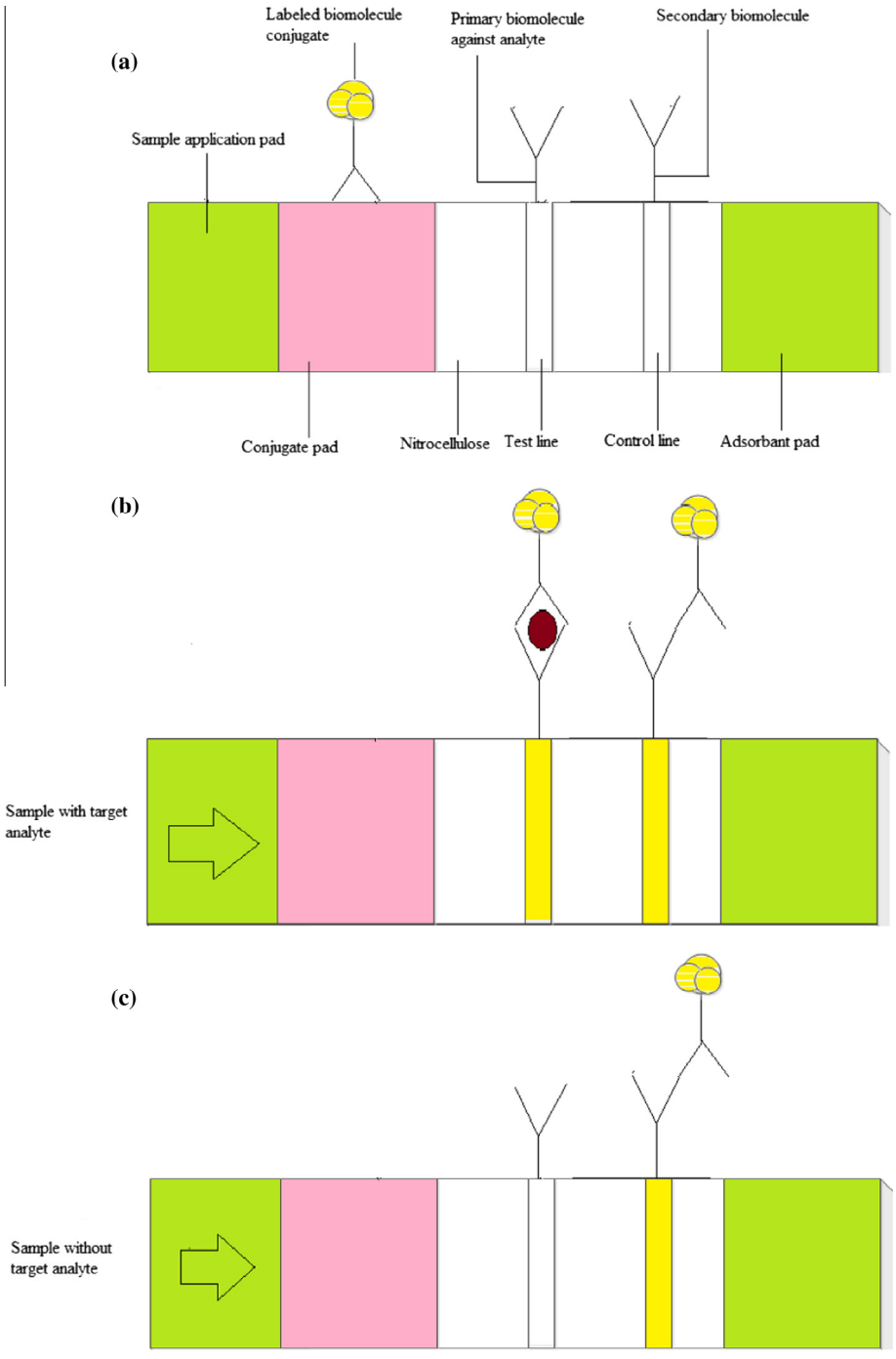

Fig. 1 Schematic of sandwich format of LFA (a) Labeled lateral flow strip (b) When sample with target analyte is applied on sample application pad, it flows over the strip under capillary action and color appears at test and control lines. (c) When sample without target analyte is applied on sample application pad, it flows and a color appears only on test line.

antibody or another antibody is known as secondary antibody. Process of synthesizing an antibody against toxic analytes is challenging because of toxicity of injected analyte into animal body which may not be bearable by animal. Antibodies are generally produced from rat or mice and then applied to detect analytes from human samples. Production and application in different matrix raise serious questions on reliability of analysis. Process of their generation is strenuous and also temperature sensitive [21]. Affinity of any antibody toward corresponding antigen is a concentration dependent factor because of immune response between them and a reasonable response is observed in the range of 10^7 to 10^{10} M^{-1}. Concentration of the target analyte is critical in deciding applicability of antibodies as biorecognition molecules. Limit of detections as low as nanomolar to picomolar range are achievable by using current theoretical methods and changing physical parameters (amount of reagents on various zones of strip, signal enhancement through modifications on label, pre-incubation of sample

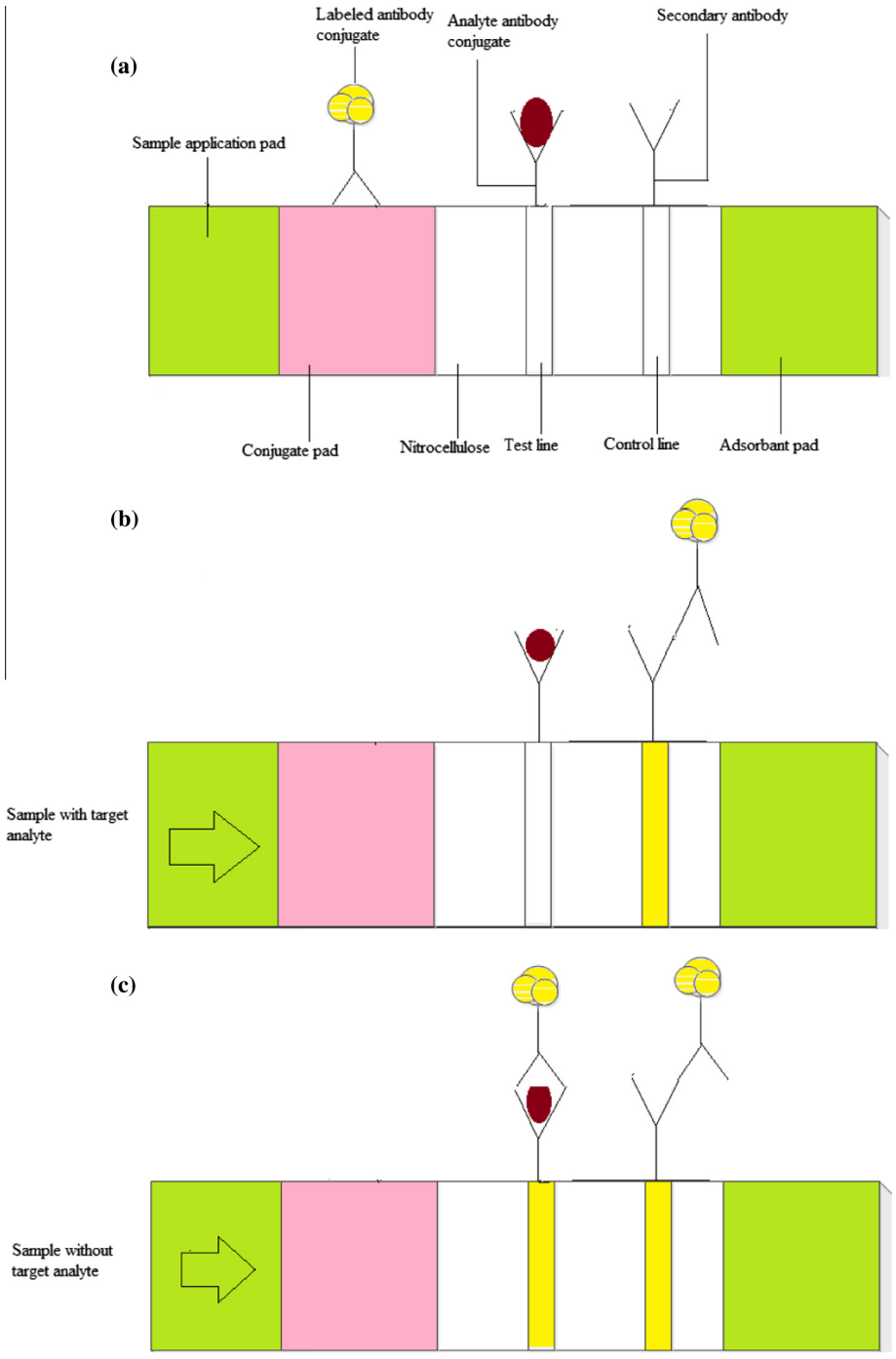

Fig. 2 Schematic of competitive format of LFA (a) Labeled lateral flow strip (b) When a sample with target analyte is applied on sample application pad, it flows through the strip and a color appears on at test line. (c) when a sample without target analyte is applied on sample application pad, it flows on the strip and color appears on both test and control lines.

with labeled antibodies) of analysis for a variety of target analytes [22,23].

3.2. Aptamers

Aptamers are the artificial nucleic acids and their discovery was reported by two groups in 1990. Aptamers are generated by an in vitro process known as SELEX (systematic evolution of ligands by exponential enrichment) [24,25]. Aptamers have very high association constants and can bind selectively with a variety of target analytes Organic molecules having molecular weights in the range of 100–10,000 Da are outstanding targets for aptamers. Because of their unique affinity toward target molecules, very closely related interferences can be differentiated [26]. They are preferred over antibodies due to many features which include easy production process, simple labeling process, amplification after selection, straightforward structure modifications, unmatched stability, reproducibility and versatility of

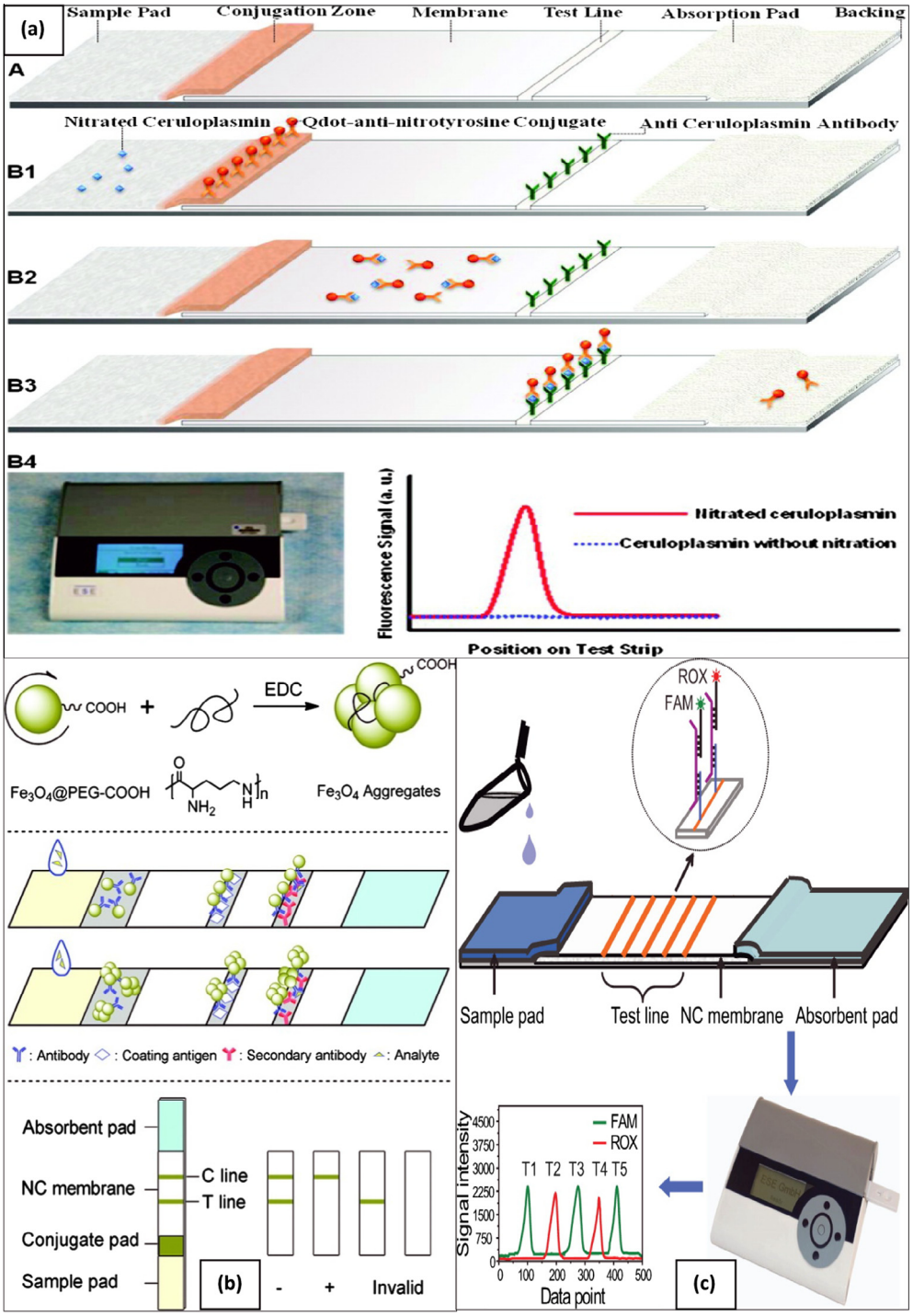

Fig. 3 (a) Step wise description of sandwich format of LFA for detection of nitrated ceruloplasmin using quantum dots as a label and fluorescence strip reader as detector. Reproduced from [1] with permission from ACS. (b) A competitive format of LFA for detection of paraoxon methyl using Fe3O4 aggregates as a label. Reproduced from [13] with permission from ACS. (c) Multiplex detection format of LFA for simultaneous detection of human papillomavirus types. Reproduced from [19] with permission from ACS.

applications [21]. Their current applications focused on areas of selective chromatography, cell imaging, target capturing, in vivo therapy, molecular sensing, protein based imaging, cancer cell biology, as enzymes in many biological applications, cellular physiology, and drug delivery [27–30]. Specifically in the areas of biosensing, aptamers are used in electrochemical, florescence, colorimetric, and mass based detection systems [28].

3.3. Molecular beacons

Molecular beacons were first time reported in 1996 [31]. Molecular beacons are a special DNA hairpin structure with fluorophore at one end and quencher at the other end. Fluorophore cannot produce fluorescence in the absence of analyte because

of closely located quencher. But when complimentary DNA sequence is present as a target analyte, stem and loop are opened as a result of a force and fluorescence signal is observed. Molecular beacons can bind with high specificity and selectivity to nucleic acid sequences, toxins, proteins and other target molecules. Molecular beacons are composed of 15–30 base pairs in loop which are complimentary to target analyte and 4–6 base pairs at double stranded stem [32,33]. Molecular beacons are being used in messenger RNA detection, intercellular imaging, protein and small molecule analysis, biosensors, biochip development, single nucleotide polymorphism and gene expression studies [32].

Simple DNA probes are also employed in LFA for detection of DNA sequences related to different diseases, and genetic problems [34]. Formation of DNA hybridized complexes is kinetically different from the formation of antibody-antigen complexes which are most commonly employed in LFTS [35].

4. Labels

List of materials used as a label in LFA is very vast which includes gold nanoparticles, colored latex beads, magnetic particles, carbon nanoparticles, selenium nanoparticles, silver nanoparticles, quantum dots, up converting phosphors, organic fluorophores, textile dyes, enzymes, liposomes and others. Any material that is used as a label should be detectable at very low concentrations and it should retain its properties upon conjugation with biorecognition molecules. This conjugation is also expected not to change features of biorecognition probes. Ease in conjugation with biomolecules and stability over longer period of time are desirable features for a good label. Concentrations of labels down to 10^{-9} M are optically detectable [36]. After the completion of assay, some labels generate direct signal (as color from gold colloidal) while others require additional steps to produce analytical signal (as enzymes produce detectable product upon reaction with suitable substrate). Hence the labels which give direct signal are preferable in LFA because of less time consumption and reduced procedure. Here we discuss some of the above mentioned labels in brief.

4.1. Gold nanoparticles

Colloidal gold nanoparticles are the most commonly used labels in LFA. Colloidal gold is inert and gives very perfect spherical particles. These particles have very high affinity toward biomolecules and can be easily functionalized. Optical properties of gold nanoparticles are dependent on size and shape. Size of particles can be tuned by use of suitable chemical additives. Their unique features include environment friendly preparation, high affinity toward proteins and biomolecules, enhanced stability, exceptionally higher values for charge transfer and good optical signaling [37]. Optical properties of gold nanoparticle enhance sensitivity of analysis in LFA [38]. Sensitivity is a function of molar absorption coefficient and accumulation of gold nanoparticles on target molecule [13]. Optical signal of gold nanoparticles in colorimetric LFA can be amplified by deposition of silver, gold nanoparticles and enzymes [39–41].

4.2. Magnetic particles and aggregates

Use of magnetic particles as colored labels in LFA has been reported by number of researchers [42–45]. Colored magnetic particles produce color at the test line which is measured by an optical strip reader but magnetic signals coming from magnetic particles can also be used as detection signals and recorded by a magnetic assay reader. It has been reported that magnetic signals are stable for longer time compared to optical signals and they enhance sensitivity of LFA by 10 to 1000 folds [46]. Fe_3O_4 particles with small size and spherical geometry resulted in high sensitivity for detection of Vibrio parahaemolyticus [47]. Major shortcoming of iron oxide nanoparticles is their drab absorption spectrum which covers whole visible region. Poly ethylene glycol modified magnetic iron oxide particles were changed into different sized aggregates by cross-linking with poly-L-lysine. These aggregates showed better sensitivity for detection of pesticide paraoxon methyl than individual iron oxide nanoparticles [13].

4.3. Fluorescent and luminescent materials

Fluorescent molecules are widely used in LFA as labels and the amount of fluorescence is used to quantitate the concentration of analyte in the sample. Detection of proteins was accomplished by using organic fluorophores such as rhodamine as labels in LFA [48,49]. Problem of photobleaching is linked with organic fluorophores which results in reduced sensitivity [1]. They also suffer from chemical and metabolic degradation. High photostability and brightness are required in case of LFAs. Fluorescent microsphere showed better sensitivity than gold colloidal for detection of *Escherichia coli* O157:H7 [50].

Current developments in nanomaterial have headed to manufacture of quantum dots which display very unique electrical and optical properties. These semiconducting particles are not only water soluble but can also be easily combined with biomolecules because of closeness in dimensions. Owing to their unique optical properties, quantum dots have come up as a substitute to organic fluorescent dyes. Like gold nanoparticles QDs show size dependent optical properties and a broad spectrum of wavelengths can be monitored. Single light source is sufficient to excite quantum dots of all different sizes. QDs have high photo stability and absorption coefficients [51]. They can retain their fluorescent properties within the cells and bodies of organisms and less suspected to metabolic degradation because of inorganic nature [52]. Formation of QD-biomolecule complexes is difficult which resulted in limitation of their applications compared to gold nanoparticles [53]. Moreover, their toxicity is another issue [54]. In a very recent work, multicolor quantum dots were used to demonstrate the concept of "Traffic Light" immunochromatographic strip by using multiplex detection format for simultaneous detection of three antibiotics in complex matrix. Antibodies against three different antibiotics were labeled with quantum dots having emission peaks in red, yellow and green spectral regions respectively [55].

Upconverting phosphors (UCP) are among the labels which got very much attention in LFA. UPA labels are characterized by their excitation in infra-red region and emission in high energy visible region. Compared to other fluorescent materials, they have a unique advantage of not showing any

auto fluorescence. Because of their excitation in IR regions, they do not photo degrade biomolecules. A major advantage lies in their production from easily available bulk materials. UCP particles were found to show size dependent sensitivity and specificity for detection of antibodies using LFA in sera of neurocysticercosis patients and healthy controls [56]. Although difference in batch to batch preparation of UCP reporters can affect sensitivity of analysis in LFA, it was observed that they can enhance sensitivity of analytical signal by 10 to 100 folds compared to gold nanoparticles or colored latex beads, when analysis is carried out under same set of biological conditions [57]. Preparation and labeling of UCP reporters is not a simple task and multiple steps are needed to perform assay [19]. UCP phosphors are used as a label in sandwich format of LFA for detection of nucleic acids [58], respiratory syncytial virus [59] and many other pathogens [60]. UCP-LFA showed a very good correlation with ELISA for detection of biomarkers related to mycobacterial diseases.

Use of fluorescent europium (III) nanoparticles in LFA showed several folds better sensitivity for detection of free prostate specific-antigen than gold nanoparticles [61]. Lanthanide chelate-loaded silica nanoparticles were used as a label for detection of Pantoea stewartii subsp. stewartii in maize and detection limit was 100 folds better than gold colloidal [62]. Other fluorescent labels used in LFA include silica nanoparticles [63], and microspheres [64].

4.4. Enzymes

Enzymes are also employed as labels in LFA [65]. But they increase one step in LFA which is application of suitable substrate after complete assay. This substrate will produce color at test and control lines as a result of enzymatic reaction. Horseradish peroxidase labeled antibody conjugates were used for detection of Rabit IgG (R-IgG) [66]. Enzymes were also used as labels in LFA to produce chemiluminescence as a result of reaction with suitable substrate for on field detection of explosives [67]. In case of enzymes, selection of suitable enzyme substrate combination is one necessary requirement in order to get a colored product for strip reader or electroactive product for electrochemical detection. In other words, sensitivity of detection is dependent on enzyme substrate combination. Enhanced LFA sensitivity was observed when enzyme loaded gold nanoparticles were used as a label [68].

4.5. Colloidal carbon

Colloidal carbon is comparatively inexpensive label and its production can be easily scaled up. Because of their black color, carbon NPs can be easily detected with high sensitivity. Colloidal carbon can be functionalized with a large variety of biomolecules for detection of low and high molecular weight analytes. Colloidal carbon was used as a label in LFA for visual detection of pesticide methiocarb in surface water [69]. A work was designed to make a comparison between gold nanoparticles, latex bead, silver enhanced gold, and carbon black nanoparticles as a label for biomolecules for detection of biotin-streptavidin interactions. Carbon black nanoparticles showed very low detection limits compared to other labels [70]. The sensitivity of LFA employing colloidal carbon is reported to be comparable with ELISA [60]. Presence of irregular shaped large particles and non-specific adsorption of proteins and biomolecules are major problems with colloidal carbon. Detail of strengths and weaknesses of amorphous carbon nanoparticle based labels can be found in a recent review [71].

5. Detection systems

In case of gold nanoparticles or other color producing labels, qualitative or semi-quantitative analysis can be done by visual inspection of colors at test and control lines. The major advantage of visual inspection is rapid qualitative answer in "Yes" or "NO". Such quick replies about presence of an analyte in clinical analysis have very high importance. Such tests help doctors to make an immediate decision near the patients in hospitals in situations where test results from central labs cannot be waited for because of huge time consumption. But for quantification, optical strip readers are employed for measurement of the intensity of colors produced at test and control lines of strip. This is achieved by inserting the strips into a strip reader and intensities are recorded simultaneously by imaging softwares [72,73]. Optical images of the strips can also be recorded with a camera and then processed by using a suitable software [13]. Procedure includes proper placement of strip under the camera and a controlled amount of light is thrown on the areas to be observed. Such systems use monochromatic light and wavelength of light can be adjusted to get a good contrast among test and control lines and background. In order to provide good quantitative and reproducible results, detection system should be sensitive to different intensities of colors. Optical standards can be used to calibrate an optical reader device. Automated systems have advantages over manual imaging and processing in terms of time consumption, interpretation of results and adjustment of variables.

In case of fluorescent labels, a fluorescence strip reader is used to record fluorescence intensity of test and control lines. Fluorescence brightness of test line increased with an increase in nitrated ceruloplasmin concentration in human cerum when it was detected with a fluorescence strip reader [1]. A photoelectric sensor was also used for detection in LFA where colloidal gold is exposed to light emitting diode and resulting photoelectrons are recorded [74]. Chemiluminescence which results from reaction of enzyme and substrate is measured as a response to amount of target analyte [75]. Magnetic strip readers [46] and electrochemical detectors [76] are also reported as detection systems in LFTS but they are not very common. Selection of detector is mainly determined by the label employed in analysis.

6. Applications

6.1. Clinical analysis

A major part of LFA applications lies in clinical analysis. It includes detection of a variety of clinical analytes in plasma, serum, urine, cells, tissues and other biological samples. Table 2 shows applications of LFA for detection of clinical and non-clinical analytes.

Table 2 Overview of LFA applications in different areas.

Application area	Analyte	Label	Sample type	Detection Limit	Time of detection	Ref.
Clinical Analysis	Thrombin	Gold Nanoparticles	Plasma	2.5 nM	–	[73]
	Ramos cells	Gold Nanoparticles	Blood	800 Ramos cells	15 min	[82]
	Cardiac Troponin I	Superparamagnetic nanobeads		0.01 ng/mL	< 15 min	[79]
	Alpha fetoproteins	Quantum dots	Serum	1 ng/mL	10 min	[123]
	Troponin I	Dual gold nanoparticle	Serum	0.01 ng/mL	10 min	[124]
	C-jun	Gold nanoparticles	Standard	0.2 footprint unit	10 min	[125]
	Influenza antigen	Fluorescently doped silica particles	Allantoic fluid	250 ng/mL	30 min	[63]
	miRNA	Gold nanoparticles	Cell lysate	60 pM	20 min	[77]
	HBs antigens	SiO_2 modified magnetic nanoparticles	Serum	0.1 pg/mL		[126]
Toxins and Pathogens	Clenbuterol	Fluorescent Nanosilica	Urine	0.037 ng/L	–	[104]
	Clenbuterol	Gold Nanoparticles	Urine	0.1 ng/mL	10 min	[127]
	1-Aminohydantoin	Gold Nanoparticles	Meat	1.4 ng/mL	1 min	[128]
	Aflatoxin B(1)	Gold nanoparticles	Pig feed	5 μg/kg	10 min	[129]
	T-2 toxins	Gold nanoparticles	Wheat and oat	100 μg/kg	4 min	[130]
	Escherichia coli mRNA	Liposome	Drinking water	5fmol	15–20 min	[131]
	Salmonella enteritidis	Gold nanoparticles		10 CFU		[97]
Pesticides	Carbofuran	Gold nanoparticles	Water	32 μg/L	8–10 min	[108]
	Triazophos	Gold nanoparticles	Water	4 μg/L	8–10 min	[108]
	Atrazine	Gold nanoparticles	Water	1.0 ppb	5 min	[132]
	Paraxon methyl	Magnetic Fe_3o_4 aggregate		1.7 ng/mL		[13]
	Carbaryl	Gold nanoparticles	Agricultural products	100 μg/L		[41]
	Endosulfan	Gold nanoparticles	Agricultural products	10 μg/L		[41]
	Carbaryl	HRP	Agricultural products	10 μg/L		[41]
	Endosulfan	HRP	Agricultural products	1 μg/L		[41]
	Trichloropyridinol	HRP	Plasma	0.1 ng/mL		[133]
	Triazophos residues	Gold nanoparticles	Standard	4 ng/mL	10 min	[134]
	Chlorpyrifos-methyl	Gold nanoparticles	Water	50 ng/mL	10 min	[135]
	Dichlorodiphenyltrichloroethane	Gold nanoparticles	Food	27 ng/mL		[136]
	Thiabendazole		Standard	0.08 ng/mL	10 min	[137]
	Methiocarb	Carbon nanoparticles	Surface water	0.5 ng/mL	10 min	[69]
Metal Ions	Hg^{2+}	Gold nanoparticles	Water	0.1 nM	–	[114]
	Cr^{3+}	Gold nanoparticles	Water and serum	5 ng/mL	5 min	[138]
	Hg^{2+}	Gold nanoparticles	Water	6 nM	5 min	[139]
	Cd^{2+}	Gold nanoparticles	Drinking and tap water	0.4 ppb		[116]
	Cu^{2+}	Gold nanoparticles	Water	10 nM		[140]
Pharmaceuticals and drugs	Enrofloxacin	Gold nanoparticles	Chicken muscles	0.138 μg/kg	5–10 min	[141]
	Sulfonamides	Gold nanoparticles	Eggs and Chicken Muscles	10 ng/mL	15 min	[142]
	Morphine	Gold nanoparticles	Urine	2.5 ng/mL		[143]
	Chloramphenicol	Gold nanoparticles	Milk	10 ng/mL	10 min	[144]
	Ofloxacin	Gold nanoparticles	Swine urine	10 ng/mL	< 10 min	[145]
	Ofloxacin	Gold nanoparticles	Milk, chicken and pork meat	30 ng/mL	10 min	[146]

6.1.1. RNA/DNA detection

MicroRNA was detected in cell lysate using a DNA-AuNP based LFA within a time of 20 min [77]. DNA was quantified in plasma by using dry reagent nucleic acid biosensor employing blue dye doped latex beads as a label. Detection was based on hybridization between DNA conjugate and specific target DNA sequence in plasma [35].

LFA was developed to identify nucleic acids by using recognition properties of molecular beacons and optical properties of gold nanoparticles and very low detection limits were achieved [78]. Modified hairpin oligonucleotide with double target binding DNA sequence and gold nanoparticles was employed in LFA for detection of single base mismatches in DNA by visual observation. Incorporation of double target DNA binding sequences into loop of hairpin oligonucleotide has led an increase in the tendency of this probe to discriminate between perfect and single base mismatches in DNA [72].

6.1.2. Proteins and cells

Proteins serve as biomarkers for the uncovering of some diseases and their analysis has key prominence in clinical diagnosis. Radioimmunoassay, protein chips, fluorescence, and other methods are used to detect low levels of proteins in biological matrices. Disadvantages of these methods include disposal of radioactive substances, tiresome sample preparation steps, lavish instrumentation, necessity of skilled analyzers, washing and incubation procedures.

Concentration of thrombin protein in plasma samples was determined with high specificity using unique properties of aptamers and gold nanoparticles in LFA [73]. Cardiac marker cardiac troponin I is a protein, its concentration in bloodstream is very important in determining and diagnosing acute myocardial infarction (AMI). In healthy people, concentration of cardiac troponin I is 20.4 pg/mL but as the AMI starts, the level of this protein marker rises with time and after few hours it reaches to its peak value 195.9 ng/mL. As central clinical laboratories consume much time in detection, rapid and sensitive methods are desired. Xu et al. developed a sensitive method for detection of cardiac troponin I using superparamagnetic nanobeads as a label for LFA. Limit of detection was 0.01 ng/mL and analysis time was less than 15 min [79]. 173 specimens were obtained from the patients appeared with symptoms of AMI and screened for cardiac troponin I and myoglobin by using electrochemiluminescence immunoassay, commercially available lateral flow strips and lateral flow strips modified with nanoparticles. All methods showed same quantitative results but nanoparticle modified strips were found more sensitive [80].

Recently, LFA was used for detection of human pluripotent stem cells employing gold nanoparticles as a label and it was capable of detecting down to 10,000 cells by visual inspection and 7000 cells by a strip reader [81]. LFA based strip was prepared by combining molecular recognition properties of aptamers and optical properties of gold for detection of cancer cells. Ramos cells were chosen as model analyte for this study. Visual limit of detection was down to 4000 Ramos cells while a strip reader was able to detect minimum 800 Ramos cells [82].

6.1.3. Other clinical analytes

Diagnosis which involves tests on blood serum is termed as serodiagnosis. It involves diagnosis of disease by detection of antibody or antigen. LFA was used to detect Leptospira-specific immunoglobulin M (IgM) antibodies in human blood serum and reported results were in good agreement with routinely used ELISA [83]. Human Brucellosis was diagnosed by LFA detection of brucella specific IgM antibodies in sera [84]. Antibodies to phenolic glycolipid-I (PGL-I) of Mycobacterium leprae were detected using LFA for classification of leprosy patients and results showed good agreement with ELISA [85]. Prostate specific antigen which is thought to be a reliable marker for early diagnosis of prostate cancer was determined in human serum using gold nanoparticles as reporter and electrochemical detection system [76].

A commercial lateral flow strip was used to detect fixed concentrations of laboratory grown vaccinia and monkeypox viruses. It showed good reproducibility and 9 out of 11 clinical samples were correctly identified [86]. Low or high level concentrations of thyroid stimulating hormone (TSH) are linked with hypothyroidism and hyperthyroidism in human. Cell phone based detection system was used with LFA to measure the levels of TSH in serum [87]. Rotavirus was detected in bovine fecal samples using LFA, commercial latex agglutination test (LAT) and electron microscopy. Compared to electron microscopy, sensitivities of LFA and LAT were 70% and 80% respectively but both tests showed 100% specificity [88].

6.2. Foodborne pathogens and toxins

Quality of food is affected during each stage from its transportation to processing [89,90]. Scientific community is focusing on the nutritional qualities of food and their possible associations on the human health [91,92]. Rapid and convenient POC methods are desired for detection of foodborne pathogens and toxins. Food products require extensive labeling of major and minor constituents. Currently conventional culture based methods are being used in food industry. Although they have reasonable sensitivity and selectivity, tedious assay procedure and extended analysis time are their major disadvantages [93]. LFA technology has come up with many advantages like reliability and short assay times. 72% of pathogen detection studies mainly focus on Food industry and Water & Environment. Moreover 60% of the detection methods deal with Salmonella and *E. coli* [94].

Botulinum neurotoxins (BoNT) are the most dangerous neurotoxins. They are produced by the Clostridium botulinum, which is spore forming obligate anaerobe naturally, occurs in the soil. BoNts are divided into seven types. These toxins act to inhibit acetylcholine release and result in paralysis and death. Highly sensitive LFA was designed to detect and differentiate between BoNT/A and B which are known to be toxic and responsible for 80% of illnesses caused by milk and apple juice [95]. Corn, feedstuff and wheat were screened for simultaneous detection of mycotoxins zearalenone and fumonisin B1 by using a colloidal gold lateral flow strip. The results were in good agreement with ELISA and LC-MS [96].

Recently gold nanoparticle and aptamer based LFA was used for detection of *Salmonella enteritidis* and it was capable of detecting as low as 10^1 colony forming units (CFU) [97]. Newly developed antibodies coupled with AuNPs were employed in LFA for detection of Vibrio cholera [98]. A

nucleic acid lateral flow assay was developed for quantification of Salmonella. A DNA probe which was highly specific to 16s ribosomal RNA and DNA of salmonella was conjugated with gold nanoparticles to detect target. Signal was enhanced by silver deposition [99]. Staphylococcus aureus was detected in the respiratory samples obtained from very severe asthmatic patients using LFA and detection limit of 106 cfu/mL was achieved. Test showed high specificity toward target pathogen [100]. Staphylococci are gram positive bacteria and recently they are showing much resistance against existing antibiotics. Staphylococci are known to cause many diseases either directly or through their products. These products are food poisoning toxins like SEB. Many diseases arise from digestion of these toxins through contaminated foods. Some countries consider SEB as a biological aerosol weapon for contamination of food and water resources. LFA showed ability to detect 1 ng/mL of SEB and with highly reproducible results. The practical use of this strip was checked by spiking SEB in real serum, urine, cow milk powder [101]. LFA has very high specificity for influenza virus and thus can be used as a useful tool for detecting this virus [102].

Clenbuterol is a compound which is fed to animals as a bronchial and it increases growth rate, protein accretion and decreases fat deposition. As this compound has very enhanced half-life, upon entrance into human body, it distributes within meat and induces cardiovascular and central nervous system diseases [103]. LFA was used to detect this analyte in the urine using fluorescent nanosilica and visual detection limit for qualitative analysis was found 0.1 ng/mL and limit of detection for quantitative analysis was down to 0.037 ng/mL [104]. Presence of ultra-small amounts of crustacean protein in processed foods can lead to allergic reaction. A strip with very low visual detection limit was devised to detect crustacean protein in processed food [105].

6.3. Pesticides

Pesticides represent a wide class of chemicals including organic compounds which are volatile, semi-volatile or non-volatile in their nature. Some inorganic compounds and organometallics are also used as pesticides but such instances are infrequent [106]. Pesticides have extensive applications in the agriculture division to grow crops and different food material [107]. Through food chain, these pesticides find their way to human body and wild animals.

Two LFA strips for simultaneous detection of carbofuran and triazophos in water samples were developed based on an immunogold conjugate. Unlike other strips, they contained two test lines and one control line. Total analysis time was 10 min [108].

Organophosphorus pesticides can be detected by using an indirect method. Their exposure results in an increase of the total amount of phosphorylated cholinesterase which can be a biomarker to detect and quantify these pesticides. Immunochromatographic strip coupled with disposable screen printed electrode was used to quantify this enzyme in in vitro red blood cells and it can detect low to 0.02 nM within a small period of time [109]. A typical format of LFA was used for detection of paraoxon methyl using Fe3O4 aggregates as a label and fluorescence strip reader as a detector [13].

6.4. Toxic pollutants

Bisphenol A (BPA) has wide applications in industry for preparation of epoxy resin, polycarbonate bottles, and also as a flame retardant. It has been stated that Bisphenol A belongs to endocrine disrupting compounds and placed in watch list for further review. Several reports have indicated involvement of Bisphenol A in reducing fertility and sperm quality in fishes [110]. A simple and rapid method based on LFA was designed for the detection of BPA in water and results showed better sensitivity compared to GCMS and LCMS. Moreover, this method has advantages of short analysis time, one step and on spot detection [111]. A lateral flow strip method based on colloidal gold tag as a label was used to analyze TNT in real samples and it was able to detect down to 1 mg/mL [112]. Ractopamine which was used as feed additive in livestock can be toxic to humans, LFA was successfully developed for its quantification in swine urine [113].

6.5. Heavy metals

Heavy metal pollution is the biggest concern to safety of human environment. Various environmental and health agencies have regulated maximum allowable limits of metals in water, air and food stuff. Analytical techniques used for detection of heavy metals are atomic absorption spectroscopy (AAS), inductively couple plasma mass spectrometry (ICP-MS), and inductively coupled plasma optical emission spectroscopy (ICP-OEC). These techniques cannot be utilized as POC because of large sized instruments, need for expert personnel, and complex sample preparation.

A simple, sensitive and rapid visual detection of Hg^{2+} ions in aqueous solution was achieved by using gold nanoparticles as reporter in LFA for coordination events of Hg^{2+} between thymine rich hairpin oligonucleotide and digoxin labeled DNA probes which was complementary to a part of hairpin oligonucleotide [114]. An immunochromatographic assay (ICA) was used to detect and quantify chromium ions in water and serum samples using gold nanoparticles as tracers in a competitive format. Very low limit of detections was got by visual and quantitative inspection and the strip was stable for 12 weeks at 37 C without substantial loss of performance [115]. Cd-EDTA-BSA-AuNP based LFA was used to detect Cd^{2+} ions in tap and drinking waters and it resulted in 0.1 ppb detection limit which was so far better than any paper based metal sensors [116].

7. Microfluidic devices for POC diagnosis

Concept of POC testing has led to development of a variety of microfluidic devices. They can be divided based on their working principles i.e. capillary driven (include LFA strips), pressure driven, centrifugal, electrokinetic and acoustic. These devices have been reviewed in detail with an emphasis on working principle, market requirement, strengths and limitations [117,118]. A recent article extensively reviews applications of microfluidic devices for biomarker analysis [119]. After polydimethylsiloxane, paper based microfluidics has got attention in recent years. Paper is a very cheap, abundant, lightweight, thin and flexible material and its main component is cellulose fiber which has already shown potential for

diagnostics in LFA. Paper based POC devices have unique advantages of easy patterning, movement of fluid by capillary action, requirement of less volume of sample and ease in disposing paper after testing. But they have disadvantage of varying sensitivity and selectivity. Several review articles covering both development and use of paper based devices can be found in the literature [120–122]. LFA strips are creating remarkable market share and despite their limitations, they are most successfully commercially developed POC devices. Although some of other microfluidic devices have been commercialized, main focus remained up to demonstrations. Huge initial investment and providing solution to all problems that might occur are main hurdles in bringing these devices to consumers [118].

8. Major challenges, expectations and commercialization potential of LFA devices

Ideal POC based devices are characterized by low cost, operational robustness, no need for long storage or transportation of samples and readily available results. Although LFA is the most suitable technology for POC applications, its use is limited when highly quantitative and reproducible results are demanded. Such challenges can be dealt by developing existing LFA systems and overcoming their weaknesses. There is a continuous stress on all existing analytical technologies because of growing demands for sensitivity and on field applications. LFA technology has major advantage on other POC applications that it costs very less and presents a very wide range of applications. Improvement in materials and detection methods can be helpful in improving sensitivity and reproducibility of existing LFA methods. Materials that were employed in LFA in beginning were not prepared specifically for this assay, hence each one has some inhomogeneity in combination. Searching materials which can serve multipurpose job can be useful in achieving goals of good sensitivity and high reproducibility i.e. same material for sample application pad, conjugate pad and membrane. New materials having well distributed pore size can increase affinity for biomolecules and help in controlling flow of samples.

One major goal in clinical analysis is to use biological samples for analysis without any sample preparation or pretreatment. Many liquid samples such as blood can be directly employed to LFA or other microfluidic devices but a labor extensive sample preparation may be required in case of highly viscous, solid and complex biological samples. Selection of method for sample pretreatment is decided according to nature of matrix. Microfluidic devices are being designed in a way that they can perform a process necessary before analysis such as mixing, separation, pumping, phase extraction, physical adsorption, cell selection, covalent linking and nucleic acid separation [36].

Despite its widespread applications in LFA, nitrocellulose does not represent an ideal membrane and it presents drawbacks such as difference in reproducibility within same set of experiments, environment dependent variations, less shelf life and breakable structure. Labels show a different behavior in releasing from conjugate pad and sensitivity of signal is lost when labeled conjugate materials are partially released. A good combination of label, biorecognition molecule and detection system is critical in enhancing sensitivity of LFA.

Before commercialization of any POC device, several aspects of the product are carefully examined. Every lab tested prototype cannot be brought to market without a detailed optimization of assay steps, device material and results read out. Suitability of assay, development of device design, study of consumables and application areas serve as drivers in commercialization of any device. Growing rate of commercial applications of lateral flow assay based devices is very high. It can be safely said that LFA devices are among first commercialized microfluidic based POC products. These devices are being used for qualitative and quantitative analysis for a variety of analytes. All the products including labels, biorecognition molecules, strip readers and a kit of whole set up are being provided by many companies. DCN (Diagnostic consulting networks) is providing lateral flow assay strips for applications in medical, veterinary, and consumer diagnostics, food and beverage testing, environmental and agriculture testing. Market size and opportunities in future have been described in terms of generated revenues and growing demand. Clinical and veterinary applications of LFA were reported in 2010 to comprise 89% and 8% of market size respectively and generating largest revenues and same trend is expected in 2015 (http://www.dcndx.com/company). List of the companies providing tools or whole kits for LFA is very long and a few of them can be found in a recent review [6].

9. Conclusion

In last few years, more research focused on the use of LFA for detection of clinical and non-clinical analytes. LFA has advantages of simple test procedure; requirement of low sample volume, fast analysis, no need for expert personnel and low cost of operation. Integration of the nanotechnology into LFTS biosensors has resulted in enhanced signal to noise ratio, reduced analysis time and simultaneous analysis of multiple analytes. Colloidal gold conjugation with biomolecules has provided an excellent platform for detection of a variety of target analytes.

No doubt, the LFA strips have a broad range of applications in clinical and non-clinical analysis but several flaws have been indicated by researchers which include poor reproducibility and less sensitivity toward high analyte concentrations. Most of LFAs give qualitative or semi-quantitative results which can be observed by naked eyes. Conventional LFA are normally qualitative and give answers in yes or no.

A good LFA biosensor can be recognized by such figures of merit: biocompatibility, high specificity, high sensitivity, rapidity of analysis, reproducibility/precision of results, wide working range of analysis, accuracy of analysis, high throughput, compactness, low cost, simplicity of operation, portability, flexibility in configuration, possibility of miniaturization, potential of mass production and on-site detection.

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