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Nanoparticle-based lateral flow biosensors

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ABSTRACT

Lateral flow biosensors (LFBs) are paper-based devices which permit the performance of low-cost and fast diagnostics with good robustness, specificity, sensitivity and low limits of detection. The use of nanoparticles (NPs) as labels play an important role in the design and fabrication of a lateral flow strip (LFS). The choice of NPs and the corresponding detection method directly affect the performance of these devices. This review discusses aspects related to the application of different nanomaterials (e.g. gold nanoparticles, carbon nanotubes, quantum dots, up-converting phosphor technologies, and latex beads, between others) in LFBs. Moreover, different detection methods (colorimetric, fluorescent, electrochemical, magnetic, etc.) and signal enhancement strategies (affording secondary reactions or modifying the architecture of the LFS) as well as the use of devices such as smartphones to mediate the response of LFSs will be analyzed.

Contents

Abbreviations: AEC, 3-amino-9-ethylcarbazole; AuNPs, gold nanoparticles; CL, control line; CNPs, carbon nanoparticles; CNTs, carbon nanotubes; GMR, giant magnetoresistive sensor; HRP, horseradish peroxidase; IAs, immunochromatographic assays; LBs, latex beads; LFBs, lateral flow biosensors; LFS, lateral flow strip; MAR, magnetic assay readers; MNPs, magnetite nanoparticles; OVA, ovalbumin; TL, test line; TMB, 3,3′,5,5′-tetramethylbenzidine; QDs, quantum dots; QR, quick response code; SERS, surface-enhanced Raman scattering; UPTs, up-converting phosphor technologies

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1. Introduction

Nowadays biosensors are very helpful tools in our everyday life, being used for the detection of allergens in food, toxicants in water, in chronic diseases control, pregnancy tests and other diagnostic applications. Certainly, it can be ensured that biosensors are going to enter even deeper in our life in the future, so it is a research field looking for new and improved easy-to-be-used device technologies.

Since the appearance of the first biosensor (Clark et al., 1953), the technology has evolved, but it is still not crowned with the expected devices that would work as easily as a glucose biosensor or a pregnancy test, present in any pharmacy all over the world. Low cost and efficient devices for the detection of other analytes such as DNA, proteins or even whole cells in real scenarios are still in the way.

One of the possible paths that the researchers could take to reach to this future is the development of paper-based biosensors, following the same principle as the immunochromatographic assays (IAs) (Lou et al., 1993; Cho and Paek, 2001; Lönnberg and Carlsson, 2001; Ho and Wauchope, 2002; Shyu et al., 2002): the separation of analytes which flow across a porous medium taking into account the specific interactions that occur between antigen and antibody, enzyme and substrate, or receptor and ligand. Paper is a simple, cheap, abundant and an easy-to-manufacture material that fulfils cost/efficient requirements in biosensing technology (Costa et al., 2014). It is noteworthy that it is in developing countries where this type of biosensors are more requested due to the lack of resources to use conventional laboratory tools which are more expensive and require trained operators, huge amount of equipment and installations, so the development of paper-based devices could be of vital importance in these regions.

Paper, this mere material made from cellulose (the most abundant polymer on Earth) or nitrocellulose, offers many others advantages in the development of biosensors. Various biochemical reactions with interest for biosensing applications can easily be carried out within this matrix. In addition, simple microfluidics including platform architectures tuning can be applied thanks to the controlled porosity and capillary forces of the nitrocellulose network in addition to simple modification or integration processes. Moreover paper-based platforms are compatible with either naked eye detection or simple optical or electrical readers.

1.1. Lateral flow biosensors (LFBs)

The aim of this review is to discuss and analyze the current advances concerning the class of paper-based biosensors, called lateral flow biosensors (LFBs), which are the modern version of paper IAs (Parolo and Merkoçi, 2013). These devices may fit all the requirements expected from a biosensor: low limit of detection, high sensitivity, good selectivity, low quantity of sample volume required, no washing steps are necessary, robustness, low cost, quick assay performance in just one step and a user-friendly format. Nevertheless LFBs also have some weaknesses, such as the fact that the response obtained with naked-eye is just qualitative, not quantitative, although with the help of certain reading devices it can be converted into semiquantitative. Another drawback is that the sample must be always in liquid state, with enough viscosity to flow across the porous of the nitrocellulose. These pores, in some cases, could be obstructed by different matrix compounds and provoke unspecific adsorptions in the membrane; it is in those cases when a sample pretreatment or predilution will be required. Because of the limitation of the detection area, the surface where receptors (e.g. antibodies, enzymes, proteins, etc.) are placed, at higher concentrations of analyte, can be oversaturated, giving false blank response; it is another factor to consider making the predilution of the sample before the analysis.

LFBs can be used to detect a large range of biomarkers that may include not only proteins but also nucleic acids and even whole cells, among other biocompounds. Furthermore, LFBs are not limited only to biomolecules detection; several publications have appeared in the last years about the detection of pollutants such as metallic ions, pesticides, etc. The range of LFBs applications is including detection of hazardous substances (Shyu et al., 2002), heavy metals in drinking waters (Mazumdar et al., 2010; Torabi and Lu, 2011; Kuang et al., 2013; López-Marzo et al., 2013a, 2013b), allergens and pathogens in food (Wang et al., 2007; Shukla et al., 2011; Preechakasedkit et al., 2012; Leem et al., 2014; Berlina et al., 2013; Anfossi et al., 2012, 2013), pesticides (Zhou et al., 2004; Kim et al., 2011; Wang et al., 2014a), drugs screening (Inoue et al., 2007), etc.

There exist different commercial LFBs (Cazacu et al., 2004; Held et al., 2013), being pregnancy and fertility tests the most known examples beside tests for HIV (Pesce et al., 2006), drugs of abuse, Malaria (Cordray and Richards-Kortum, 2012; He et al., 2014; Kersting et al., 2014), etc. Behind LFBs there is a well-known technology (Qian and Bau, 2003, 2004; Assadollahi et al., 2009; Lee et al., 2012; Linares et al., 2012) with several publications reporting different modifications of the standard designs/structure, either in terms of the materials used as transducers for the signal generation (Linares et al., 2012), in the methodology employed to translate the signal or in improving the device with different enhancement strategies.

With the recent development and explorations of nanomaterials in the field of sensors and biosensors LFBs have been taking advantages for their use as alternative materials to improve their performance requested in real sample applications. Application of nanomaterials in DNA, protein, cell and various inorganic/organic compounds in various biosensing technologies is now being extended to LFB field bringing interesting results to this technology (Walcarius et al., 2013; Merkoçi, 2010; De la Escosura-Muñiz et al., 2010, Parolo et al., 2013a; Perfezou et al., 2012; Aragay et al., 2011, 2012).

1.2. How lateral flow strips (LFS) work?

LFBs are manufactured in strip form, a convenient format for the user, normally with a width between 4 and 6 mm and a length no more than 6–7 cm. A standard lateral flow strip (LFS) consists of four main sections made of different materials, as shown in Fig. 1: sample pad, made of cellulose, where the sample is dropped; conjugate pad, made of glass fiber, impregnated with the bioconjugates solution (the label particle and a receptor for the analyte); detection pad, a nitrocellulose sheet (Lee et al., 2012; Ahmad et al., 2009) where test line (TL) and control line (CL) are printed; and absorption pad, also made of cellulose. Other