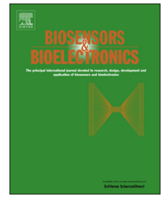
Biosensors and Bioelectronics 79 (2016) 98–107

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios



Sensitive biomolecule detection in lateral flow assay with a portable temperature–humidity control device

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ARTICLE INFO

Article history:
Received 31 July 2015
Received in revised form
30 November 2015
Accepted 4 December 2015
Available online 7 December 2015

Keywords:
LFA
POC
Nucleic acid hybridization
Antigen–antibody interaction
Temperature
RH
Portable temperature–humidity control device

ABSTRACT

Lateral flow assays (LFAs) have currently attracted broad interest for point-of-care (POC) diagnostics, but their application has been restricted by poor quantification and limited sensitivity. While the former has been currently solved to some extent by the development of handheld or smartphone-based readers, the latter has not been addressed fully, particularly the potential influences of environmental conditions (e.g., temperature and relative humidity (RH)), which have not yet received serious attention. The present study reports the use of a portable temperature–humidity control device to provide an optimum environmental requirement for sensitivity improvement in LFAs, followed by quantification by using a smartphone. We found that a RH beyond 60% with temperatures of 55–60 °C and 37–40 °C produced optimum nucleic acid hybridization and antigen–antibody interaction in LFAs, respectively representing a 10-fold and 3-fold signal enhancement over ambient conditions (25 °C, 60% RH). We envision that in the future the portable device could be coupled with a fully integrated paper-based sample-to-answer biosensor for sensitive detection of various target analytes in POC settings.

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1. Introduction

With the rapidly increasing incidence of infectious diseases (e.g., Ebola, dengue, malaria, human immunodeficiency virus (HIV) and influenza) owing to globalization, limited access to medical services in developing countries has become a major challenge (Laursen, 2012; McNerney and Daley, 2011). To address this issue effectively, a robust system is required to bring accurate diagnostic assays to the point of care (POC). This could greatly simplify the existing laboratory-based assays (i.e., quantitative real-time polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA)) as well as reducing the cost and time demands they bring about, especially in resource-limited settings, where most diseases exist (Burke and Gorodetsky, 2012; Han et al., 2014; Sackmann et al., 2014). Today, the use of a paper-based platform represents a promise of a simple, portable, cost-effective, and user-friendly POC diagnostic tool, which holds a great potential as an alternative to the conventional laboratory techniques (Choi et al., 2015; Song et al., 2012). Recent studies have focused on the use of lateral flow assay (LFA) for accurate POC diagnostics (Blažková et al., 2009; Hu et al., 2013; Wang et al., 2013). These assays normally involve hybridization of a single stranded-target analyte (RNA or DNA) with a complementary probe to form a double-stranded nucleic acid, or binding between antigen (Ag) and antibody (Ab) to form an Ag-Ab complex, which produces a colorimetric, fluorescent or chemiluminescent signal (Cate et al., 2014; Martinez, 2011). However, to date, the main limitations of LFA are the difficulties in quantification and lack of sensitivity (Feng et al., 2015; Hu et al., 2014).

Several efforts have been made to address these limitations. To achieve quantification, researchers have developed a variety of handheld or smartphone-based readers to quantify the LFA results (Mudanyali et al., 2012). As for the sensitivity improvement, various techniques have been developed through probe-based signal enhancement (Hu et al., 2013), enzyme-based signal enhancement (He et al., 2011), thermal contrast (Qin et al., 2012), or fluidic

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http://dx.doi.org/10.1016/j.bios.2015.12.005
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control (Parolo et al., 2013; Rivas et al., 2014). However, the sensitivity of LFA might be significantly affected by the environmental conditions, which have been overlooked in most studies. Accumulating evidence has shown that environmental factors (e.g., temperature and relative humidity (RH)) may have a significant influence on biomolecular reactions (Barry and DeMille, 2012; De Roy et al., 2013; Wu et al., 2014), including nucleic acid hybridization (Zhang et al., 2012) and Ag–Ab interaction (Reverberi and Reverberi, 2007). Further, RH may also influence the assay readout by affecting the fluid wicking rate in the paper, which may in turn affect the sensitivity of paper-based assays (Giokas et al., 2014; Lutz et al., 2013; Renault et al., 2013; Rivas et al., 2014). As LFAs are intended for field application, they may be affected by user's environmental conditions (e.g., extremely hot or cold, and dry or wet environments) more than in a typical controlled laboratory. For instance, the temperature and RH of well-known dengue endemic area, Malaysia, is in the range of 25–37 °C and 70–90% RH, respectively, which may not produce an optimum assay outcome. Therefore, effective monitoring and control of environmental factors plays an important role in maintaining optimum conditions for biomolecular reactions, and in turn enhancing the analytical sensitivity of the current LFA. Several studies have investigated the stability of LFA in different environmental conditions (Chien et al., 2006; Johnson et al., 2005). However, the optimum environmental requirement for sensitivity enhancement in LFA for nucleic acid or antigen/antibody detection has not been explored yet.

The present study reports the use of a portable temperature–humidity control device to provide an optimum environmental requirement for sensitivity improvement in LFAs, followed by quantification of multiple types of targets (DNA or protein) by using a smartphone. Interestingly, in DNA detection, temperatures between 55–60 °C (representing the annealing temperature in PCR) provides the maximal DNA hybridization signal, without significantly affecting the shape of the paper (e.g., deformation), whereas an RH beyond 60% could effectively facilitate the fluid to completely wick through the paper to produce the desired signal. With optimum experimental conditions (55 °C, > 60% RH) our lateral flow test strip was able to improve the sensitivity of almost 10-fold compared to that achieved at ambient conditions (25 °C, 60% RH), using dengue viral DNA and HIV DNA as model analytes. We have also successfully shown the optimum Ab–Ag interaction at 37–40 °C by using this simple test strip. Given that precise temperature and humidity control is technically challenging outside the laboratory, we developed a portable temperature–humidity control device to achieve optimum LFA performance in a POC setting (Fig. 1). We envision that in the future, the integration of a fully integrated paper-based sample-to-answer biosensor into this portable device offers great potential for sensitive detection of various target analytes in resource-poor settings.

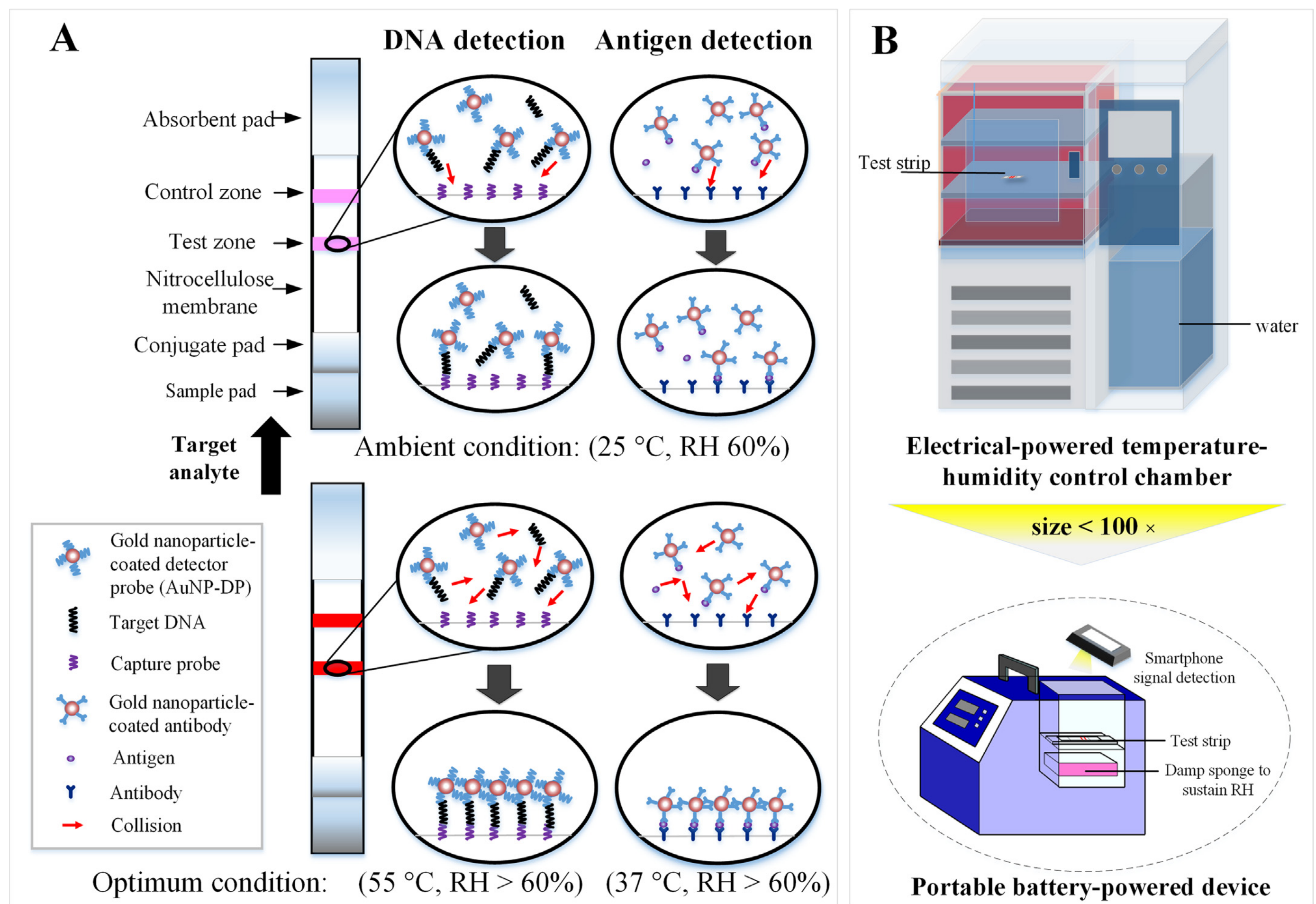

Fig. 1. Schematic of sensitive biomolecule detection in lateral flow assay at optimum temperature and humidity. To rapidly and accurately detect the target analytes by LFA at optimum conditions (55 °C for nucleic acid detection or 37 °C for antigen detection, > 60% RH) in the remote settings, a small and portable temperature–humidity control device was developed, coupled with a smartphone signal detection, to substitute the large and complex commercial temperature–humidity control device. The optimum temperature of 55 °C and 37 °C enhanced the binding of the DNA–DNA and antigen–antibody, respectively, producing the enhanced LFA signal than that of 25 °C. RH: relative humidity.

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