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Review

Application of microfluidic “lab-on-a-chip” for the detection of mycotoxins in foods☆

Lujia Guo [a, 1], Jinsong Feng [a, 1], Zecong Fang [b], Jie Xu [c], Xiaonan Lu [a, *]

[a] Food, Nutrition and Health Program, Faculty of Land and Food Systems, The University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada
[b] Department of Mechanical Engineering, Washington State University, Vancouver, 98686, United States
[c] Department of Mechanical & Industrial Engineering, University of Illinois at Chicago, Chicago, IL 60607, United States

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ABSTRACT

Background: Various foods are susceptible to contamination and adulteration with mycotoxins, presenting serious health risks to humans. Microfluidic “lab-on-a-chip” devices could integrate and miniaturize versatile functions from sample preparation to detection, showing great potential in rapid, accurate, and high-throughput detection of mycotoxins.
Scope and approach: This review focuses on the application of microfluidic “lab-on-a-chip” platforms to detect mycotoxins in foods. Fabrication processes and major components of microfluidic devices, as well as separation and detection methods integrated with “lab-on-a-chip” systems are summarized and discussed. Finally, challenges and future research directions in the development of microfluidic devices to detect mycotoxins are highlighted.
Key findings and conclusions: Microfluidic “lab-on-a-chip” devices have a great potential for accurate and high-throughput detection of mycotoxins in agricultural and food products.

1. Introduction

Mycotoxins are secondary metabolites of fungi and the major fungal genera producing them include *Aspergillus* spp., *Fusarium* spp. and *Penicillium* spp. These molds produce various types of mycotoxins, such as aflatoxins (AFs), deoxynivalenol (DON), zearalenone (ZEA), fumonisin B_1 (FB_1), ochratoxin A (OTA) and citrinin (CIT), almost all of which are toxic to humans (Arévalo, Granero, Fernández, Raba, & Zón, 2011; Zheng, Richard, & Binder, 2006). Representative mycotoxins widely identified in different food matrices are listed in Table S1 (Richard, 2007; Stoloff, 1976; van Egmond, Schothorst, & Jonker, 2007). Mycotoxin contamination can occur throughout the entire food chain, from processing to transportation and storage (O'Brien & Dietrich, 2005). Besides, mycotoxin in feed could also lesion in animal origin food, exposing potential high risks to consumers (Zain, 2011). For example, AFs are the major mycotoxins which account for almost 93% of mycotoxin contamination in foodstuffs and beverage, resulting in carcinogenic cases in consumers (Petroczi, Nepusz, Taylor, & Naughton, 2011). Studies on AFs showed the LD_{50} for ducklings, rats and sheep were 0.4, 1, and 500 mg/kg, respectively (Hussein & Brasel, 2001). OTA is toxic as nephrotoxic. Besides, due to possible occurrence of Balkan Endemic Nephropathy (a renal tumor), it is considered as carcinogen (Frenette et al., 2008; Pfohl-Leszkowicz, Petkova-Bocharova, Chernozemsky, & Castegnaro, 2002). In addition, ZEA has been associated with human cervical cancer (Shim, Dzantiev, Eremin, & Chung, 2009). Due to the potential carcinogenic, teratogenic, and mutagenic effects of mycotoxins as well as their wide existence in agricultural and food products, rapid, high-throughput and portable methods for sensitive detection are needed.

Conventional methods for the detection of mycotoxins in the environment and agricultural products are primarily chromatographic-based techniques, including thin-layer chromatography (TLC), high performance liquid chromatography (HPLC), gas chromatography coupled with mass spectrometry (GC–MS) (Lehotay & Hajšlová, 2002; Sforza, Dall'Asta, & Marchelli, 2006). However, all these methods require extensive sample preparation procedures and they are time consuming and need highly trained personnel. In addition, large amount of hazardous regents and solvents are often required during analysis. Commercially available methods for the detection of mycotoxins are mainly

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* Corresponding author.
E-mail address: xiaonan.lu@ubc.ca (X. Lu).
[1] Equal contribution as co-first author.

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immunological-based techniques, which are on the basis of specific interaction between monoclonal and/or polyclonal antibodies and the toxins. These techniques can be further divided into immunoaffinity column (IAC)-based analysis and enzyme-linked immunosorbent assay (ELISA) (Magan & Olsen, 2004). Compared with chromatographic-based methods, immuno-based methods have higher selectivity, but the high expense for antibody screening and poor limit of detection inhibit the application of immuno-based methods. Due to the wide distribution of mycotoxins and analytical complexity of food matrices, a rapid, in-field, high-throughput, and lab-independent method to record mycotoxin contamination is highly demanded. Further, the developed methods should be highly sensitive to meet the legislative LOD of mycotoxins in foods (van Egmond et al., 2007). Table S2 summarizes the regulations for some typical mycotoxins that are presented in European Community (Egmond & Jonker, 2004). Taken together, a great effort has been devoted to ultra-fast and ultra-accurate determination of extremely low levels of mycotoxins in foods, and microfluidics devices have emerged as a promising alternative as modern analytical platform.

2. Microfluidic device: major principles and components

The idea of microfluidic analytical platform derives from the concept of Total Analysis System (TAS), which aims to shrink and integrate all necessary steps for chemical analysis of a sample onto a single device. The whole system mainly include types of driving apparatus (*e.g.*, pumps and reactors) and processes patterns (*e.g.*, sample preparation, filtration, dilution, reaction, and detection) (Connelly et al., 2012). While microfluidic analytical platform, also known as Micro Total Analysis Systems (μTAS), further expands its application, making the whole setup of a laboratory onto a single chip in micro-meter level (Dittrich, Tachikawa, & Manz, 2006; Kovarik et al., 2013). As its name indicates, microfluidics deals with controlling fluids of tiny amount (typically in nanoliters) in microscale channels (Squires & Quake, 2005). The characteristic channel size of microfluidics analytical devices ranges from 10 μm to 200 μm and in some cases down to 1 μm (Bayraktar & Pidugu, 2006). Fluid flow in these microchannels behaves quite differently from those in macroscale channels. For example, surface forces are dominating over volume forces at the microscale. As one of the most important forces affecting flow behaviors at the macroscale, the gravitational force in the fluid flow is usually negligible on a microfluidic platform (Mark, Haeberle, Roth, von Stetten, & Zengerle, 2010). Moreover, strong viscous forces usually limit the flow to laminar regime, making molecular transport a challenging task in many microfluidics sensing experiments (Squires & Quake, 2005). Since chemical and biological analysis usually involves multiple steps of fluid manipulation (*e.g.*, dilution, mixing, separation, aliquoting etc.), for these applications, microfluidics originated in these fields since 1980s. Indeed, the development of early microfluidics was mainly driven by molecular analysis and molecular biology (Whitesides, 2006). Motivated by rapid development of biomedical and cell biology in the recent years, microfluidics has witnessed extraordinary advancements in the past decade. Many microfluidics branches have been established to utilize unique behaviors of fluidic flow in microscale, such as droplet-based microfluidics (Seemann, Brinkmann, Pfohl, & Herminghaus, 2012; Teh, Lin, Huang, & Lee, 2008; Xu & Attinger, 2008; Zhang, Betz, Qadeer, Attinger, & Chen, 2011), bubble-based microfluidics (Ahmed et al., 2013; Ahmed, Mao, Shi, Juluri, & Huang, 2009; Chen & Lee, 2014; Hashmi et al., 2012; Xu et al., 2013), paper-based microfluidics (Martinez, Phillips, Whitesides, & Carrilho, 2009), and inertial microfluidics (Di Carlo, 2009).

Compared to traditional fluidic platform, microfluidic analytical platforms provide tremendous advantages, such as low sample and reagent consumption, low fabrication costs, flexible design with more functions, fast analysis and response time, high throughput screening, precise process control (*i.e.* hydrodynamic parameter and temperature), and easy to carry which facilitate in-field detection (Atalay et al., 2011; Sackmann, Fulton, & Beebe, 2014). As mycotoxins often disperse from a small area to a wholefood systems and usually require on-site and in-field detection, these advantages of microfluidics devices fully cater the requirement for mycotoxins detection.

2.1. Basic physics of microfluidics

The development of microfluidics depends on abroad of disciplines, expanding from fluid mechanics, thermodynamics, electrostatics, chemistry, to material science (Bayraktar & Pidugu, 2006; Squires & Quake, 2005; Stone, Stroock, & Ajdari, 2004). In the recent years, the interplay among microflow, microstructures (Chen et al., 2011; Chen, Lam, & Fu, 2012; Lam, Sun, Chen, & Fu, 2012) and nanomaterials (Mao & Koser, 2006; Zhang & Wang, 2013) have been extensively explored for “lab on a chip” (LOC) applications. Understanding of microfluidics physics facilitates the design of chips to realize different functions. Several dimensionless numbers are used to parameterize competitions among a variety of forces. (1) Reynolds number is the most important dimensionless number in microfluidics, which determines the ratio between inertial and viscous forces. Since characteristic length of microfluidics devices is at microscale, Reynolds number is usually very small, making inertial forces irrelevant. (2) Peclet number relates to convective and diffusive transport. If Peclet number is smaller than unity, diffusion would dominate over convection and tracers in fluid would flow side-by-side, making fluid transport and target detection very slow and inefficient (Squires, Messinger, & Manalis, 2008). (3) Capillary number relates to viscous and interfacial forces and concerns multiphase flow in a microfluidics device. Surface tension plays an important role in the dynamics of interfaces between different fluids, creating all types of interesting phenomena in droplet-based or bubble-based microfluidics (Squires & Quake, 2005). (4) Weber number is associated with inertial and interfacial forces, another critical parameter concerning multiphase microfluidics. For example, drops or bubbles will undergo substantial deformation if the flow rate is high enough to induce high Weber number in a microfluidics device (Xu, Vaillant, & Attinger, 2010).

Microfluidic devices are mainly composed of actuators and sensors. Due to different functions, actuators can be categorized as microvalves, micropumps, and micromixers, while sensors are mainly molecular and cellular detectors (Beebe, Mensing, & Walker, 2002). Microvalves are used for flow control in the microfluidics systems for purposes, such as separation and timing. Basically, there are two kinds of microvalves, naming as active and passive microvavels. More specifically, according to different actuation force, microvalves also can be classified as mechanical, pneumatical, electrokinetical, magnetical, or capillary microvalves (Oh & Ahn, 2006; Pan, McDonald, Kai, & Ziaie, 2005). One type of flow control using active microvalves are driven by active pressure, and in order to achieve this, the chip structures will be more complicated compared to passive microvalves, which open to forward pressure and derive flow. A representative micromechanical flap microvalve used to control biochemical reactions of two compounds is shown in Fig. S1. When the pressure outside the flap micro-valve was higher than that inside channel, the valve would be forced to open and then chemical reactions happen (Au, Lai, Utela, & Folch, 2011; Voldman, Voldman, Gray, & Schmidt, 2000). Although a variety of microvalves have been developed in the

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