Review on Lab on Chip fabrication and its application in food safety sensing

Author contributions

This review was written by the author and the author read and approved the final manuscript.

ABSTRACT

Lab on chip (LOC) is a miniaturized and automatic platform when combined with microfluidic techniques giving an improved analysis in several applications. Applying this LOC concept in biosensors gives easier and more rapid detection for several analyses, especially in food safety sensing. The processing method and fabrication of lab-on-chip material and some important application in food safety is reviewed in this paper.

Keywords: LOC, microfluidics, rapid detection, analyses, biosensors, food safety

1.INTRODUCTION

Lab on Chip (LOC) is a device that integrates various laboratory functions onto a small chip of only millimeters to a few square centimeters to enable automation and high-throughput screening (1). It is possible to handle minimalamounts of fluids even less than Pico liters. Being a subset of microelectromechanical systems (MEMS) devices, LOCs can also be called "micro total analysis systems" (μTAS). Lab on Chip is a concept that has brought tremendous application and advancement in many fields, especially in food safety sensing.

In recent years food safety issues have been a hot topic globally due to the excessive content of additives, metals, microbial contamination, and pesticide residues in food. These terrible food safety issues demand strict monitoring of entire food processing, production, and distribution from farm to table. In this scenario sensing food safety issues using biosensors gives a very trustable platform. For more precise and accurate sensing it is beneficial to integrate biosensor designs with microfluidic flow channels to improve the overall performance of the sensing system. The main advantage of applying microfluidics in biosensors is that it fastens the recognition by the ease of transport of sample analyte to the biorecognition site. Furthermore, carefully constructed channels can improve convective transport to sensor surfaces by integrating flow concentrating or helical flows, for example (2,3). To further improve the food safety sensing along with microfluidics, it can adapt the LOC concept which comprises the entire sample preparation procedure, so incorporating this along with the microfluidic flow channel can simplify the sensing platform. Miniaturization of the sensing platform by applying the LOC concept also gives ease of usage.

This paper mainly focuses on the processing, types, and materials used for LOC fabrication and application of LOC in food safety sensing.

2.1 Microfluidic- based LOC Systems

Micro fluidization is a great way to make Nanoemulsions, submicron emulsions, Nano suspensions, liposomes, and encapsulated materials while also promoting particle De agglomeration and cell disintegration. In the 1990s, Manz et al.,(4) pioneered microfluidic chip technology, also known as the micro-total analysis system (TAS) technique. Microfluidic chips are etched and processed on their substrates using micro-processing technology before being enclosed into inlet, intermediate, and outlet packing chips. The three most prevalent microfluidic chip channel shapes utilized in various application scenarios are as follows.

1. T-shaped sensors can produce perfect laminar flow, and signal aggregation in the downstream area can detect weak signals, enhancing the limit of detection (LOD);
2. Pathogen chemotaxis and susceptibility are detected by Y-shaped sensors, permitting hierarchical separation;
3. Serpentine structures, such as the Christmas tree structure, in which many liquid strands carrying substances of differing concentrations shunt and confluence in a split laminar flow, generating a progressive concentration gradient perpendicular to the flow direction, which is suitable for gradient detection.

The advancement in biosensors to lab on chip devices is possible through implementing microfluidics integrated sensing platforms. Microfluidics is an upcoming and novel research area that gives an innovative stream to work with fluid analysis. It has wide range of application including the field of food quality control testing and food safety. Applying microfluidic devices in biosensor can control and minimize the fluid volume in the analysis and also it reduces the cost.

In addition to that, paper- based μ- D (microfluidic device) makes a very cost- effective analysis with fewer steps to handle. It can reduce the laborious work and minimize the complexity of other traditional techniques (5,6). Other than paper some other types of microfluidic-based devices are PDMS, glass, thermopolymers, and silicon, - based LOC.

2.1.1 Lab-on-a-chip combines microfluidics and biosensors

Biosensors are faster, more precise, and sensitive than traditional detection methods. Microfluidic systems are frequently used for biosensors to achieve miniaturization due to its unique benefit. On a single tiny chip, microfluidics enables the integration of sample pre-processing, signal identification, and signal transmission (including amplification and output). It also enables the use of many biosensors to achieve high detection throughput. For lab-on-a-chip technology, the integration of microfluidics and biosensors combines the benefits of both, and is thus characterized by precision, sensitivity, speed, stability, mobility, and high throughput(7).

Biological microfluidic chips are also being transformed by the advancement of numerous technologies, which is allowing them to improve their detection performance and expand their application scenarios. Nanomaterials are frequently utilized in microfluidic chips for surface immobilization and signal enhancement of collected elements. Smartphones feature powerful central processing units (CPUs), executive connection functions, a large pixel count, a high-sensitivity camera, and a built-in light source. As a result, the use of cellphones

for visual detection is becoming a more common POCT application. When optical microfluidic biosensors are integrated with a smartphone, efficient automatic detection can be achieved. Complex and highly integrated microfluidic-bio sensing chips, on the other hand, are expensive to manufacture, whereas paper chips are cheap for one-time field detection. To accomplish more accurate inspection, 3D printing can generate more complex structures and more precise microfluidic devices.

2.1.2 Chip Materials and Fabrication Technologies

The main platform of LOC fabrication is photolithography. Earlier construction of LOC mainly relies on semiconductor fabrication in which silicon is the major material. The potential of this was apparent but not feasible with silicon technology, there comes the demand for new materials and processes that will enable faster prototyping at lower manufacturing costs and also yield advanced properties, such as specific bio or chemical compatibility and optical characteristics.

Other than silicon, the new materials which are suitable for LOC fabrication are ceramics and glass. Another advantage is that it is possible to suitably employ new techniques such as metal etching, deposition and bonding, soft lithography with polydimethylsiloxane (PDMS) processing, thick-film and stereo lithography on these new materials. Also fast replication methods via electroplating, injection molding, and embossing is also possible. Implementing nanotechnology in the LOC field boosted it beyond the lithography –based microsystem giving a way to precision engineering.

2.1.3 Processing Method of Chip

(i) Micro-Molding

Polydimethylsiloxane (PDMS) has become the most popular material for making Lab on chip processing. Along with PDMS, it is common SU-8 photoresist as a mold to mold PDMS (8,9).The SU-8 photoresist is spun-coated on a silicon chip and photo etched and it is free to adjust thickness of chip freely with in a range of more than 10 to 200 microns. The spun coating speed can be controlled according to different types of SU-8 photoreceptors. A 10:1 combination of PDMS and hardener was used. Then it's carefully poured onto the SU-8 microstructure, avoiding air bubbles and heating. After an oxygen plasma treatment, the

hardened PDMS is carefully removed from the SU-8 mold and glued to the glass substrate. It is possible to re-use the SU-8 mold.

(ii) Laser Ablation

The process of laser ablation specifically refers to ablating and machining a micro flow channel on the surface of polymer material by using a carbon dioxide laser with a wavelength of 10.6 μm (10). Machining the micro flow channel using laser ablation is fast, simple and only one time is needed to complete the whole process. Most of the polymers and glasses can be able to use the above mentioned method. The main drawback of machining the micro flow on the surface is that the machining done on the inner wall of the polymer will not be uniform and more number of bubble will be in turn to be treated by chemical methods(11).The protrusions formed on both sides of the flow channel during casting and re-solidification of molten material on the polymer surface are not suitable for subsequent bonding. The method is limited in processing accuracy and is only fit for flow channels of which width and depth are more than 80μm. When comes to the case of low-costmicrofluidic lab on a chip, the technology is still focused on a single polymer material. There is still a high scope for advancement in the field of low-cost chip with the insight of biodegradable plastics, conductive plastics, paper, and other materials.

(iii) 2D/3D Printing

2D printing is a method used in processing a microfluidic chip or a microfluidic chip pour back mold commonly used in experimental time and in offices, like laser printers(12), inkjet printers (13), wax printers (14), screen printing(15), etc. Recently 3D printing emerged as a technique to directly print a microfluidic chip or a pour-back mold by using a 3D printer. Low-cost chips likepaper microfluidic chips are 2D printed microfluidic chips in which hydrophobic ink is impregnated on hydrophilic paper materials to form microchannel and the pattern accuracy depends on printer accuracy or screen mesh commonly in a range of 80 and 400 μm. Other than that in PDMS-based microstructures, SU-8 can be directly deposited on a glass or polymer substrate like using inkjet printing or screen printing to form microfluidic chips (16), In the case of electrode printing conducive ink containing silver nanoparticles used (17).

Stereolithography and fused deposition modeling (FDM) are the main methods of 3D printing used to process microfluidic chips(18). A fused deposition modeling 3D printer is used to produce relatively low-cost 3D microfluidic chips. FDM may also be used for direct printing on materials such as PC, PLA (polylactic acid), ABS (acrylonitrile butadiene styrene), and

other materials to create 3D microfluidic chips (19). In addition, FDM is also utilized to print the mold for the PDMS reverse mold (20). Commercial FDM have an accuracy in a range of 10-500µm, which restricts its application on most microfluidic chips ,other than this it is difficult to select transparent consumables needed for microfluidic chips is limited and processing speed of chip is also slow compared with the other.

(iv)Injection Molding

PMMA (polymethyl methacrylate), COC (cycloolefin) and PDMS (polydimethylsiloxane) are the mostly used injection materials in injection molding(21). Injection molding is the method adopted in plastic processing for years. Advancement in microinjection technology gave a way for researchers to think about applying this in microfluidic chip fabrication. Mold processing has to be done firstly in case of injection molding which is costlier and time consuming. To overcome this drawback, Hansen et al.,(22) introduced the use of su-8 photoresist on the surface of nickel as an injection mold, which improved its reusability around 300 times. In addition to that it increased the processing speed which enable processing of 3D microfluidic chips, repeatability and give a way for processing of large scale micrfluidic chips. Some of the disadvantages are reduced flexibility, need to reopen the mold when the chip structure differ and higher cost of mold.

2.1.4 Chip Bonding Technology

It is necessary to cover microfluidic chips with a layer of material (cover sheet) above the flow channel after the microstructure processing is completed, is called as bonding of the microfluidic chip. Bonding is required for all other materials except paper chips which use open flow channels. In bonding both the cover sheet and substrate material can be same material with uniform thickness, in case of special purposes bonding between different materials of varied thickness can be done. Apart from bonding between silicon and glass chips which requires ultra clean room with precision instruments, recently scientists have developed various low cost chip bonding methods such as thermal compression bonding, adhesive bonding, plasma surface treatment and laser welding,

2.1.4.1 Thermal Compression Bonding

In PMMA (polymethyl methacrylate), PC (poly carbonate), PS (poly styrene), Glass, and other thermoplastic materials, thermal compression bonding is used as an ideal method for bonding microfluidic chips. Thermal compression bonding is the method in which two layers

of materials are joined and aligned with heating and pressurization, in which heating temperature is set slightly higher than the glass transition (Tg) of thermoplastics and pressure adjusted accordingly. Many studies have been conducted by the researchers in the field of microfluidic chip bonding especially with hot embossing method, and have observed the bonding strength of PMMA/PMMA (23), PMMA/PS and Glass materials (24)at varied temperatures and pressures. From the observation, they realized that failure of thermo compression bonding for thermoplastic materials is due the collapse of microstructure during the bonding process, because of excessive temperature or pressure. In addition researchers also observed that it is important to control the temperature and pressure settings, while on the other hand, it can also use oxygen plasma or ultraviolet light to pretreat the surface of polymer materials, Molecular weight of the bonding surface also should be reduced in order to reduce the glass transition temperature of the surface (25).

3 Types of LOC

3.1Polydimethylsiloxane LOC

Polydimethylsiloxane (PDMS) is a material mainly used in microfluidic circuitry. PDMS surface is hydrophobic in nature and hence it is focused mainly on making macromolecule based sensor. Shin etal., 2017 (26) conducted a study on polydimethylsiloxane (PDMS) microchip coupled with a microfluidics system and found that it is easy, cheap, biocompatible, and less laborious and can be used for direct analysis technique. All these strategies are favorable to various microfluidic technologies based on physical process such as amphiphilic polymers/copolymers and chemical process like self- assembled monolayer surface modification(27). Nanoscale modification of PDMS based microfluidic devices (μ- D) are unique surface properties like surface charge, attachments of protein, DNA- binding chemistry, and DNA intercalation, which make system- specific applications an LOC concern (28).

3.2 Glass and Thermopolymers LOC

Modified three-dimensional microfluidic devices fabricated with photostructurable glass is an upcoming field in manufacturing LOC. Sugioka et al., illustrated details about fabrication of 3D hollow microstructures with photostructurable glass by femtostructured laser detection as a prototype havinghigh selectivity at 40–50 times. This would be very useful for LOC systems in the future for making quick and robust prototypes(29). Srinivasan et al., 2004 (30)conducted a study on droplet- based glass digital μ- D for clinical testing on human

whole blood serum, urine, saliva, tear, sweat, and plasma as human physiological fluids achieved successful bioassays on real sample analysis.

Other than glass thermoresistancepolymer-based materials such as fibers, elastomers, polyesters, and nylon are being used in μ- D basedprocesses (31). Polymers are low-cost and simple in the fabrication process by electrochemical gas activation along with electrolysis processes. This prototyping is by using a cheap polymer-based μ- D tool by simple stencil printing (32).Recently by applying thermoresistance polymer conjugated with an ITO heater and probe, were able to control cell attachment and cell growth in 10–20 hours instead of 5–6 days. Based on recent studies, it can be concluded that a polymeric chip with μ- Dbased LOC device will apply for controlling living cells and microbes on large scales.

3.3 Silicon and Paper- based LOC

Silicon and paper–based LOC is cheap, fast and straightforward compared to other materials. In the beginning, silicon was one of the most successful platforms for μ- Ds. Silicon based μ- Ds are mainly used as a portable diagnostic tool in sensitive for detection of pathogenic agents to maintain the environmental conditions(33). Gradually silicon based devices are being replaced by paper based μ- D devices due to the few demerits of simple paper, compared to silicon- based devices that need ultraviolet light, conventional optical methods, valves, and pumps, which made this problematic as per POC concerns (34). Then the paper based μ- D device became a new trend to improve over conventional silicon based devices. Later on researchers started making prototypes of paper- based μ- D devices with wax for affordable and portable assays. Paper devices are best suited for direct analysis. It only needs an inkjet printer or wax pen for making a microfluidics chamber, and it takes 5–10 minutes without any usage of UV lamp, any chemical reagent, or more laborious steps(35). Carrilho et al., 2009(36) reported that a wax- printed chamber and detection prototype took less than five minutes which can fabricate soon with target analyte as real sample analysis at the cost of ~$0.60 for whatman filter paper. Other than this, it was found that the advantage of using filter paper and wax printing is to make the difference between hydrophobic and hydrophilic barriers. This prototype will be a successful method for large- scale preparation of μ- D. And it is also possible for miniaturization of heavy instruments for greater applications in near future.

4 Essential requirements of LOC

(i)Automation in liquid handling(mixing, transport, and separation if necessary). This is one of the important experimenting areas in lab-on-a-chip technology. Y- or T-junction

channels have been used to accomplish liquid mixing, coupled with several different designs of passive/pulse/serpentine mixer designs(37), more active mechanisms of microfluidic mixing have been suggested and tested, especially using micro valves and micro pumps fabricated on chip (38). This seemed promising and provided improved performance than the passive/pulse/serpentine microfluidic mixers. Liquid transport is made by applying electro osmotic flow or by external pressure syringe pumping

(ii) Reduced sample pre-treatment. In a diagnostic laboratory lab on chip has the advantage of easy sample pretreatment, since the necessary equipment is readily available in those environments. In field situations, pre-treatment could become very difficult. For instance, most pathogenic contaminations are detected on the surface of food, hence food samples are routinely cleaned with buffer. For rigorous sample pre-treatment and higher performance, several centrifugations, re-suspension of pellets with a vortex mixer and/or a sonicator, and cell lysis/nucleic acid extraction for PCR are required. Small and basic equipment, such as a battery-powered mini-centrifuge or a syringe with filter, can simplify these intricate procedures into one or two steps, allowing non-experts to utilize the sensor with minimal processing time.

There have been number of attempts to ease of the sample pretreatment procedure and to incorporate these processes into lab-on-a-chip. Centrifugation and membrane filtration are the mostly investigated, as they are very important in dealing with food samples. One of the most common examples of lab-on-a-chip centrifuging is lab-on-a-CD (39). Microchannel are made directly on the surface of a CD (compact disc), from its center to the outside, and the sample/reagent liquid is loaded to the inlet wells. The fabricated CD is then loaded into the CD player and rotated, creating a centrifugal force that makes the liquid to flow through the microchannel. Another example is the microfabrication of porous structure within microchannel, *i.e.*, on-chip fabrication of membrane filter(40).

(iii) Fast. When we conduct an ELISA, PCR (including cell lysis and gene extraction) or a normal cell culture and colony counting, it takes few hours in a laboratory environment. In this case we do not consider sample delivery time in to consideration. Real time detection indicates that the detection should be made simultaneously with sampling, commonly less than 10-minute detection as real-time sensing using LOC. But in some assays, it may extent up to up to 4–8 hours or a single day. In most cases it is hard for general public to accept these 4-8 hours detection as real time detection in case of food analysis.

(iv) Total integrated system. The entire system should be installed into a single device, for the ease of use and equipment delivery. Most of the biosensor systems require separate equipment for pre-treatment and/or detection. Commonly, all commercial biosensor systems (including lab-on-a-chips) require an external computer. A true fully-integrated system should not need any extra equipment. Minimally, it should have its own user interface) and an integrated liquid crystal display (LCD) panel for system operation and displaying test results. It is more acceptable, the system have a data storage unit and/or data transmission system. The latter can be accomplished by using wireless protocols, such as Wi-Fi or cellular phone network (3 G or 4 G LTE). It is an advantage that it is possible to use cellular phones for such data storage and transmission purposes, and in addition, smart phones can also be used for data processing or even as an optical detection system using its flash and camera.

(v) Battery-powered. It is not easy to avail AC outlets in field situations. Therefore, it is necessary for the system to be operated fully with battery power consuming very low power, which may prevent the use of electro osmotic flow (EOF; very common in lab-on-a-chip but requires relatively high voltage and power). So it is better to rely on battery-powered lab-on-a-chips as such kind of demonstrations are in developing stage.

(vi) Independent of refrigeration. If reagents such as antibodies, nucleic acids, or enzymes, are required in an assay, it is a necessity to refrigerate. In field applications, however, these reagents have to be packed in an ice box or lyophilized (freeze-dried) as powder for a possible storage in room temperature. This long-term storage study of reagents is relatively less in biosensor and lab-on-a-chip studies.

(vii) High sensitivity TheLimit of detection for common ELISA tests can be as low as tens of picogram proteins per mL of sample. Detection limits for common PCR can theoretically be at the level of single cell per 10–100 μL of sample, equivalent to 10–100 CFU per mL of sample. Almost the same levels of detection limits are expected for lab-on-a-chips, but the actual limits have been a few or a few tens of nanogram proteins per mL of sample or a few hundred or million cells per mL of sample (10^2–10^6 CFU/mL) (41,42).

4.1 Advantages of Lab-on-Chips

LOC technology is very useful and applicable in various fields. Some of the notable advantages are:

- Very less amount of fluid volume consumption (less amount samples, less reagents)
- Faster analysis and rapid responses due to its smaller size
- Improved process control due to rapid responses

- Higher degree of compact ability and integrity of multiple assemblies will improve the functionality at reduced volumes.

4.2 Disadvantages of Lab-on-Chips

Some of the drawbacks of the LOC platform due to geometry of its smaller size give rise to some phenomena such as:

- The influence of some chemical and physical effects on small scale like capillary forces, surface roughness, and the interference of construction materials on the reaction processes will make the behavior of integrated systems on chip complicated
- Low to signal to noise ratio are frequently reported
- Though the geometric accuracy and precision in micro fabrication is quite high, but it has not reached level of precision engineering
- As LOC remains as a novel technology, it is yet to be developed.

4.3 Application in Food safety sensing

Lab on chip technology has got enormous application in food safety detection. Some of the main applications in food safety detection are as follows.

4.3.1 Detection of Pesticide Residue

Pesticides are to improve the crop yield and to defend it from attacking pests. The residues of the pesticides prevailing in crops can be harmful for human health, such as respiratory disorder, sleep distraction. It is reported that in china 15% of the population develop cancer by consuming food containing pesticide residue (43). Currently, rapid determination method involves enzyme inhibition method, spectral detection method and chromatographic detection method depending upon its principle(44,45). Rapid detection method can overcome the disadvantages of traditional method which is high cost, low degree of automation and time consumption.

For detecting the presence of dichlorvos residues in cucumber, tomato and cabbage Wei et al. (46)used a luminol–H_2O_2chemiluminescence system with the limit of detection (LOD) as 3.6 ng/mL, which is more sensitive than gas chromatography. Another study by Liu et al. (47)was based on a molecularly-imprinted polymer (MIP) based paper chip with Chemiluminescence (CL) for detecting dichlorvos (DDV). It is observed that the reaction between DDV, luminol and H_2O_2 can produce CL emission directly(48).Yang et al.(49)Demonstrated a multilayer paper chip which works on the principle of enzyme

inhibition and internal heating. A heating layer was made in the paper-based chip to enable that the reaction process with the enzyme at the optimal temperature. This method can directly estimate whether the pesticide is beyond the standard depending on the reaction color. The LOD of trichlorfon under optimal conditions was 0.0406 mg/L which is comparatively better than the conventional instrumental methods.

4.3.2 Detection of Pathogenic Bacteria

Food poisoning is a major threat to food safety which is mainly caused by pathogenic bacteria. Hence it is very necessary to develop methodologies which can able rapid determination and quantification of pathogenic microbe especially pathogenic bacteria in foods. Escherichia coli, Salmonella and Listeria monocytogenes and E. coli O157: H7 are most prevalent bacteria causing food borne illness which even cause hemorrhagic colitis and hemorrhagic uremic syndrome.Jokerstetal.,(50)conducted an experiment on a paper-based microfluidic chip technique for detecting the presence of E. coli O157: H7, L. monocytogenes and Salmonella in ready-to-eat meat products, specific enzymes secreted by bacteria will react with substrates this will give changes in the color intensity. The LOD obtained in this method was 106, 108 and 104 CFU/mL for E. coli, L. monocytogenes and Salmonella respectively. Thedeveloped paper chip can detect the pathogenic bacteria even in a very low concentration of 101 CFU/mL in ready-to-eat meat with in 12 h or less which is very faster than the detection range of the standard method.

Sun et al.(51)Firstly developed an eight-chamber lab-on-a-chip (LOC) system combined with magnetic bead-based sample preparation and LAMP for the quick and computable detection of Salmonella species in food. The developed system was able to analyze eight samples of eutrophic pork containing Salmonella in 40 min, and the LOD of each detection was sensitive and of 50 cells. In some other study Kim et al. (52)developed a detection method based on quantum dot nanoparticles for detecting Salmonella cells. The LOD of this developed sensor in borate buffer and food extract was 10 (3) CFU/mL Salmonella. Fronczek et al.(53)Introduced a detection method in fresh poultry packaging to determine the presence of Salmonella typhimurium based on a hand-held optical immunoassay.

4.3.3 Detection of Heavy Metals

The presence of heavy metals in food can be hazardous to human health insuch a way that these metals can react with different enzymes andproteins present in the human body which

may interfere with its activity and if they exceed a certain concentration in the human body can even cause chronic poisoning and health effects. So it is very essential to develop faster methods to detect the presence of heavy metals in food(54).

Fan Chunhui et al. (55)developed a 11-mercaptoundecanoic acid (MUA) modified gold nanoparticles (AuNPs) probe for detection of Pb2+. When Pb2+ is present in the analyte it forms aggregate through chelating mechanism and the color of the solution changes from red to purple, which is due to the influence of plasma coupling. The LOD was observed as 10µm in this case. In another study Salvoet al.,(56)used an on an epitaxial graphene sensor coupled to a 3D printing microfluidic chip to detect low trace of Pb2+. LOD for this technique was 95 nM which is very lower than the World Health Organization recommended limit. A three dimensional (3D) origami ion imprinted polymer with ion imprinting technology was developed by Qi Ji et al.,(57)for multiplex detection of Cu2+ and Hg_2^+ ions. In this study CdTe quantum dots (QDs) were employed on to glass fiber paper. When the photoluminescence energy from QDs strike on ion imprinted surface forms QD complexes and as a result, there will be change in fluorescence. This chip is having good sensitivity and selectivity having LOD of 0.035 µg/L and 0.056 µg/L for Cu2+ and Hg2+ ions respectively. This method is successful in analyzing actual water samples.

4.3.4 Detection of Food Additives

Enhancing food appearance using food additives is a very common thing now a day. Using these pigments in more than approved specified limit can cause potential threat to human health, it may even turn as teratogenic and carcinogenic (58).Hence detection and analysis of food additives in a faster manner is an important area to be taken care.

Based on the Janovsky reaction theory, Liu et al.(59)proposed a microfluidic paper-based analysis device (PAD) and a portable benzoic acid concentration detection system. Due to the reaction of benzoic acid sample with KNO3 and H2SO4, 3, 5-dinitrobenzoic acid was produced and it is dropped in the reaction part of the chip and this chip is transferred to a portable detection system and heated to trigger the Janovsky reaction. Complementary Metal Oxide Semiconductor (CMOS) was used to determine the color change and then the color image was transmitted to the smartphone via connector and based on the RGB color intensity of the image benzoic acid sample was analyzed with help of a self-made application program. 21 kinds of commercial food sample containing benzoic acid can be detected by this method.

A “green” biocompatible fiber-based paper disk on a screen-printed carbon electrode for detection ofglucose was made by Lawrence etal.,(60). The method was amperometric using immobilization of glucose oxidase enzyme which has better hydrophilicity and able to maintain catalytic reaction of glucose oxidase.

4.3.5 Food allergens

A food allergy is an abnormal immune-mediated response to certain foods. Food allergies have become a critical food safety and public health issue due to the dangers of allergic reactions and the legal regulations imposed on the food industry. Eight types of food are responsible for the majority of allergic reactions: peanuts, tree nuts, milk, eggs, wheat, soy, fish, and shellfish (61). Monitoring of food allergens is critically important to both the food industry and to susceptible individuals. There is no cure for food allergies and the only way for sensitive individuals to protect themselves against an allergenic reaction is strict avoidance of food containing the offending components. The increase in allergen regulations and awareness highlights the need for accurate, on-site, sensitive, and rapid assays to detect potential allergens in food.

Clinical diagnosis of patients suffering from food allergies is usually performed by immunochemical methods such as RAST (radio-allergosorbent) or EAST (enzyme allergosorbent) assays which are based on the use of IgE isolated from the serum of individuals who are allergic to certain foods(62). One limitation of using IgE for clinical diagnosis of food allergies is that serum samples are required from allergic individuals, which creates a potential biological hazard risk. In addition, standardization and false positives are the other two challenges in developing microfluidics as a tool for rapid allergen detection(62). Thus, in this review, we focus on the direct detection and measurement of allergens in food samples.

Electrochemical microfluidic chip is a powerful tool to perform food analysis which benefits from the advantages of electrochemical methods including high sensitivity, simplicity of operation, and good temporal and spatial control (63,64). Jiang et al. (65)designed a cell-to-cell electrochemical microfluidic chip for food allergen detection via measurement of food allergen-induced cell morphological changes. ANA-1 macrophages and RBL-2H3 mast cells were seeded at a density of 10^6 cells/mL and cultured in parallel channels, followed by injecting 0.1 ng/mL dinitrophenylated bovine serum albumin (DNP-BSA) of allergen solution to stimulate macrophage cells and mast cells. Metabolite detection was performed on an electrochemical workstation via real-time monitoring and analysis of impedance signal

changes in the microfluidic chip. The electrochemical microfluidic chip accurately monitored real-time allergenic responses in the cell and provided a general platform for food allergen detection.

4.3.6 Bio toxins

Bio toxins refer to toxic substances produced by a living organism that may seriously threaten the health or life of humans and livestock if they exist in raw or processed foods (54). The poisonous effects of bio toxins (i.e. mycotoxin, marine toxin, phytotoxin, and animal toxin) (66)can be acute even at a very low intake dosage. Therefore, government agencies and food administration institutes have set extremely strict maximum residue limits on bio toxins in food. Microfluidic chips are capable of conducting both analyte transportation and sensing, its rapid sensing time, low sample consumption and high compatibility make them widely used in bio toxin determination. Recently, due to the requirement for high volume and high-throughput on-site detection, numerous rapid sensing methods have been developed. Microfluidics-based platforms present significant advantages in homemade portable micro-instrument development of rapid and high-sensitivity bio toxin determination. Recently, Guo et al.,(67) summarized the application of microfluidics to the detection of mycotoxins in agricultural and food products. Olcer et al.,(68)developed a real-time microfluidic electrochemical profiling method for on-site detection of deoxynivalenol (DON) in wheat. Two sets of electrode arrays were fabricated on a silicon dioxide wafer and cut to 10 × 20 mm^2 to form the sensor chips. A poly (methyl-methacrylate) (PMMA) sensor cassette was then fixed to the sensor chip by means of double-sided sticky tape to form a microfluidic channel. An assay was performed by applying 0.1V potential to the electrode array followed by continuous current measurement. Samples of wheat spiked with DON were assayed by microfluidic electrochemical profiling as well as conventional ELISA. A good correlation between these two methods was obtained with an R^2 value of 0.97.

4.4 Other food concerns

Other concerns in food safety include pesticides, dyes and fungicides, antibiotics, persistent organic pollutants, and additives. Wang et al., (69)developed a colorimetric micro-device using plug-based microfluidics for the determination of organophosphate pesticides (OPs). The volume and position of the liquid plugs (substrate and a solution containing enzymes and OPs) were formed at the T-junction by applying appropriate positive or negative pressure to the end of the flow channels. The two plugs merged in the main flow channel and then

flowed into the detection chamber. This method provided a novel colorimetric technique by using plugs of small volumes and microfluidics, thus minimizing the consumption of expensive reagents, while also improving reproducibility and precision. Using this method, the lower limit of detection (LOD) was 33 nM for Malathion and 90 nM for acephate, MEP, and diazinon was achieved.

Cardoso et al.,(70)reported a paper microfluidic device to determine nitrite levels in ham, sausage, and preservative water samples via colorimetric detection. The paper microfluidic device was fabricated using a stamping-based method. This method required a sample volume of 0.4 mL, and of the LOD was 5.6 μM. Liu et al.,(46)developed a chromatographic chemiluminescence microfluidic chip for determination of dichlorvos in fruits and vegetables. A linear relationship between 10.0 ng/mL and 1.0 μg/mL with a detection limit of 3.6 ng/mL was obtained. Guo et al.,(67)used a PDMS microfluidic impedance immunosensor to measure pesticide residue in vegetables. The PDMS microfluidic chip consisted of a main microchannel, a detection micro chamber of 6 mm × 0.5 mm × 0.02 mm, an inlet and outlet, and an interdigitated array microelectrode (IDAM) in the microchannel. Compared to other methods, such as immunochromatography and AChE-[BMIM] [BF_4] a- MWCNT/ CPb, the microfluidic impedance immunosensor had a broader linear range of 10-10^5ng/mL with a LOD of 1 ng/mL in the determination of chlorpyrifos.

4.5 Food processing

The use of microfluidics allows for streamlining workflow and other processes in the food and health sciences (71). Microfluidic technology has been applied to online process monitoring and process efficiency improvement in fermentation processes in the food and beverage industry (72). Hypochlorous acid (chlorine) is a widely used sanitizer for washing fresh produce. When developing science-based food safety regulations and practices, minimum free chlorine concentration needs to be strictly monitored and controlled in order to prevent pathogen cross-contamination. Zhang et al.,(66)utilized a mixer-based approach for free chlorine concentration determination using the inactivation kinetics of E. coli O157:H7. The micromixer was composed of three mixers (Y-injection mixer, Dean's vortex mixer, and chaotic mixer), three inlets for dispensing bacterial, chlorine, and dechlorinating solutions, and one outlet. Pathogen inactivation kinetics, time, and dose-dependent responses of pathogen inactivation using free chlorine were assessed by the micromixer. The researchers found that E. coli O157:H7 inactivation was significantly affected by the free chlorine

concentration and a 5-log10 reduction in viable bacterial cells could be obtained by exposing the culture to a solution of 1.0 mg/L free chlorine for at least one second. This method provides an efficient way to determine the minimum free chlorine concentration required to prevent pathogen survival during fresh produce washing operations. Due to the comparable size of microfluidics to the structural elements of foods, microfluidic devices are suitable for developing novel food macrostructures (52). Emulsions are one of the most common components in processed food products, and the control of features such as the texture and interfaces within the food is critical to design innovative microstructures and obtaining a wider variety of functional characteristics of food products (73). Although microfluidic emulsification has been extensively investigated in research laboratories, commercialization is difficult due to challenges in scaling up for larger throughput ((73).

5. CONCLUSION

In this review we have discussed several advantages of Lab on chip systems starting from pre-processing of sample fluids by integrating microfluidics application which can improve and widen the scope of lab on chip in food safety sensing. It can also ease of some of the rigid requirements under which food sensing systems must be worked on. Still there are some intrinsic drawbacks of biosensing platforms including costlier sensing element and its increased tendency of fouling. These two factors can limit the activity and stability of biosensors which in turn affects its lifetime. Hence advancement in this aspect should be the focus in future. One of the important advancement made in current scenario is that lab on chip concept, which improved the sensitivity of biorecognition element. Now for more development, research should be focused on materials that can potentially execute variousrole like providing structural support, compatible with transduction chain, and avoid fouling and interferences in biorecognition process. There are also some innovative materials like nanomaterials,graphene and conductive polymers along with already known paper based LOC. More technological advancement and research is to be doneon LOC based biosensors especially in field of food safety for precise qualitative and quantitative analysis.

COMPETING INTERESTS

The author have declared that no competing interests exist

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