Microfluidic-Based Sensors

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Abstract

Off lately, there has been an extensive growth and development in microfluidic technology. This trend is likely to be continued in near future as well. Microfluidics has emerged as a powerful tool for the fabrication of sensors in fields, like diagnostics, clinical analysis, electronics, material science, and drug discovery, owing to their capabilities of using minimal sample volume, accurate and precise flow control, high integration, etc. New innovations, particularly in the interaction of materials with biological systems, hassled to the development of point-of-care testing microdevices. The microscale confinements of the reagent volumes have made these devices quite cost-effective. Furthermore, the emerging concept of organ-on-chips that fabricate microengineered model system of human organs has led to new pathway of disease and infection analysis, drug metabolic and toxicological studies, etc. Likewise, the lab-on-chip concept has made clinical diagnosis rapid and easy to handle. Further, lab-based clinical procedures can now be carried out instantly at home comfort using these microfluidic sensors. These sensors have bridged the gap between the electronics and physiological systems. Presently, the microfluidic-based wearable electronics sensors made up of flexible materials have drawn substantial attention of researchers in diagnosis and healthcare sector. The great impact of microfluidics over various types of sensor systems, material fabrication, etc., has revolutionized the sensor technology and has a tremendous future scope. This chapter focuses on different aspects of microfluidic-based sensors including their fabrication procedures, materials applied, emerging trends in different types of microfluidic sensors, and their

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widespread applications. It also discusses the future outlook and its impact in sensing systems.

Keywords

Microfluidic · Sensor technology · Lab-on-chip · Point-of-care

7.1 Introduction

The emerging trends in sensor technology and the growing demand for point-of-care technology (POCT)-based sensors in various fields, like biomedical, clinical analysis, environment monitoring, defense, aviation, automobile, industries, drugs synthesis, metabolic sensing, marine biology, security, and safety, have enhanced the significance of microfluidic technology. Otherwise termed as lab-on-a-chip sensors, the microfluidic devices are portable and easy to fabricate. Since their first advent in 1990s [1], there has been considerable advances in not just fabrication procedures but also the applications of various types of microfluidic sensors. Small chip-based sensors with specified dimensions ranging from millimeters to centimeters help to perform laboratory-based quantitative, qualitative analysis and detections with ease and handy operating procedures. Microfluidics proffers accurate and controlled flow of analytes in the reaction zones; hence, it gives easy sensing mechanisms and reduces the dependence on bulky instrument. In addition, the flow in these devices can be altered and adjusted as per the desired rate owing to which this approach is suitable to develop miniaturized sensors [2]. The advance research in microfluidic techniques has paved a pathway for developing varied analytical detection platforms for sensing antigens, pathogens, biomarkers, drugs, etc. Unlike the conventional bulk sensing methods, these devices offer added advantages like less requirement of sample and reagent volume, low raw material consumption, safer handling and storage, enhanced accuracy and portability, therefore, cost-effective [3].

Microfluidic-based sensors are systematically designed to control the flow and mixing of analytes and reagents in the microchannels so as to obtain uniform and high sensitivity even with less sample volume. Also, efficient mixing in the microchannels provides good interaction between reagents and analytes, hence, giving more sensitivity. Recently, microfluidic biosensors for biological elements like proteins, biomarkers, DNA, RNA, tumor cells, drugs, and tissue engineering have been fabricated [4]. In addition, there has been extensive growth in concept of disease-on-a-chip and organ-on-a-chip. These devices can biomimic the natural organ with in vitro stimuli [5]. Owing to the fact that there is a widespread need and growth of microfluidic sensors, more approaches for their fabrication are being explored. Apart from paper, glass, and silicon-based sensors, various polymer sheets like polyimide, elastomers like poly(methyl methacrylate) (PMMA), polydimethylsiloxane (PDMS), cyclic olefins, and polycarbonate are also being used as base materials for manufacturing these sensors [6]. Various techniques, like photolithography, soft-lithography, 3D printing, inkjet printing, screen printing, molding, embossing, laser ablation, and lamination, are adapted widely for microfabrication. The use of these micromechanic techniques for fabrication has made tremendous advancements to develop cost-effective and point-of-care microfluidic-based sensors. The idea of sample in and result out sensing platforms has made this area of research attractive. Recent trends of smart phone-based devices for health management, food industries, and environmental monitoring integrated with microfluidic platform have resulted in reducing testing time and complexities [7]. These sensors have evolved in many aspects ranging from fabrication technologies to materials used, integration of automation, internet of things (IoT), etc. [8]. Microfluidic sensors have established as a standalone discipline with salient features like robustness, user-friendly, high sensitivity, and specificity, instant response [9].

This chapter discusses recent advances in the field of microfluidic-based sensors, their fabrication methods, reported applications, and advances. Although there are significant advances, yet the POCT devices in fields like analytical chemistry, medical diagnosis, biotechnology, agricultural, and environmental monitoring are to be explored more. This chapter also deliberates the limitations and future aspects of microfluidic-based sensors.

7.2 Materials for Microfluidic Sensors

The materials used for fabricating these devices play a key role in achieving the best performance. The materials chosen for making these sensors have to be scrutinized on parameters like total cost of fabrication, ease of modification, integration, and functional output. The advances and progress in this domain depend upon developing novel materials that offer enhanced sensory parameters and reliability. Since the inception of the microfluidic device, silicon and glass, as base, were the pioneer materials. Later on, various kinds of papers, polymers and hydrogels were also adapted [10]. Owing to their feature of high stability and availability, glass and silicon were preferred commonly; however, these materials were a little higher on the costing; hence, their usage for commercialization and large-scale production is limited. Off lately, a cost-effective liquid glass has been designed using silica nanopowder and monomer without clean room and ambient temperature [11]. In addition to this, less expensive polymers, like polymethyl methacrylate (PMMA), polydimethylsiloxane (PDMS), polystyrene and polycarbonate, have also been employed. Among this, PDMS, being less expensive, easy to modify, permeable to gas, has become the most popular material and used widely. Furthermore, PDMS also gives greater biocompatibility and is ideal to be used in flexible electronic device. There are certain limitations like it is challenging to reinforce elements with PDMS and long-term stability of the modified surface. Other polymers like polyimide can be used to fabricate microfluidic sensors by low-cost laser ablation method. This approach is not only scalable but can also be used over various materials.

Furthermore, paper as a base material for microfluidic sensors has also gained significant attention. Due to the porous nature, flexibility, capillary action, wettability, and high surface area, the paper-based microfluidic sensors are potential candidates or bioassay and immunosensing [12]. Electrospun nanofiber-based membranes, because of their large surface area, high porosity, are other potential materials that can be used to design microfluidic sensors. The major advantage of using this is that they provide good sensitivity and lesser signal-to-noise (S/N) ratio. Materials like conductive filaments, for example, poly lactic acid (PLA), polyethylene terephthalate (PET), poly vinyl alcohol (PVA), and acrylonitrile butadiene styrene (ABS) are some of the other materials used for making these devices via 3D-printing approach. While paper and plastic-based microfluidic sensors are more useful on the commercial and industrial front, the silicon, glass, conductive filament, and PDMS-based sensors are used in academia and research laboratories.

7.3 Fabrication Approaches

There are several fabrication approaches depending upon the base material, size, uniformity, and cost for designing the microfluidic-based sensor. Figure 7.1 gives the pictorial representation of the various methods reported so far.

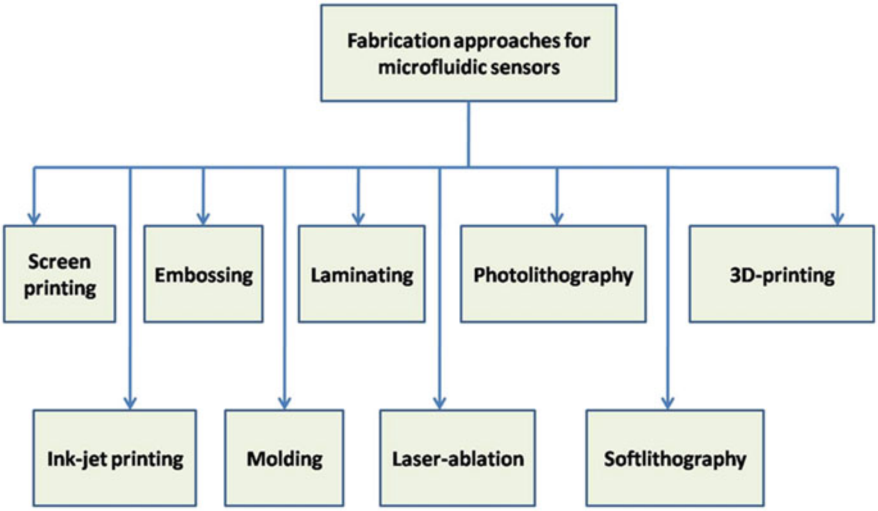

Fig. 7.1 Pictorial representation of the various fabrication approaches for microfluidic sensors used widely

7.3.1 Screen Printing

This method is used for making paper or other flexible substrate-based microfluidic devices. Herein, a wood-based frame is used over which the paper or the flexible substrate is affixed with the help of tape. Specially designed mesh or screen is made from either nylon or silk. These screens act as mask to give desired electrode patterns with specified dimensions. Over this, a conductive ink is poured and dried at temperatures ranging from 60 to 1000 °C to get desired electrode designs. Above this, a PDMS-based microfluidic channel is made and placed to give a uniform flow of analyte [13]. Figure 7.2 gives the schematic representation of the screen-printing procedure.

7.3.2 Inkjet Printing

This is comparatively a modern approach. Herein, a conductive ink of choice with desired viscosity is fed into the cartridge of the inkjet printer. The paper or glass substrate is placed on the base of printing machine and fixed using clamps. The design of the sensor electrodes is fed into the computer in a compatible file format. The distance of the nozzle of cartridge and substrate is adjusted. The printer makes the desired pattern over the substrate. This is then dried and used as sensor. Over this,

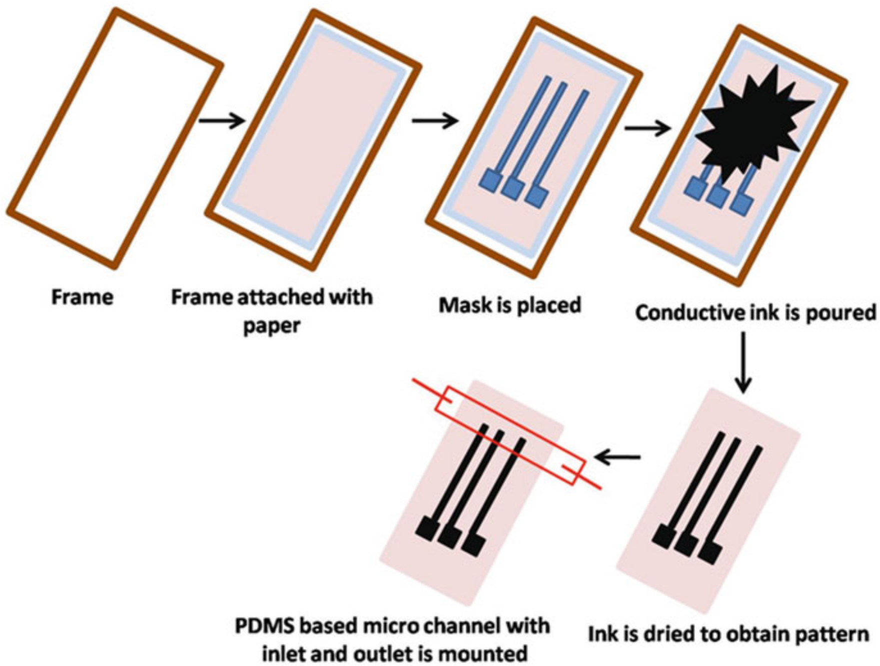

Fig. 7.2 Schematic representation of stepwise procedure of screen-printing procedure

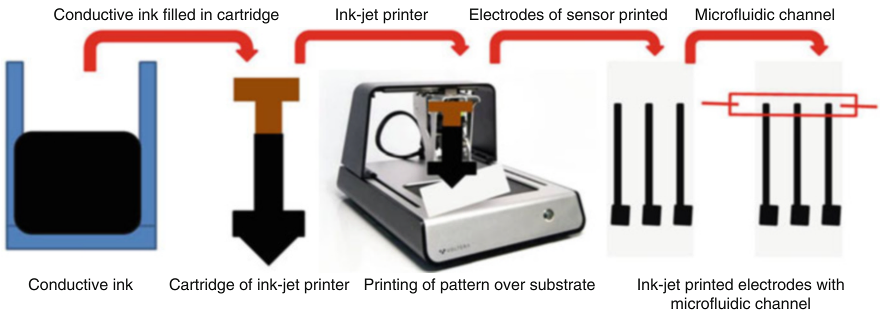

Fig. 7.3 Schematic representation of stepwise procedure of inkjet printing of sensor electrode with microfluidic channel

a PDMS-based microfluidic channel can be affixed [14]. Figure 7.3 is the diagrammatic representation of inkjet printing.

7.3.3 Embossing

Hot embossing is an emerging technique that has capability of reproducing a microscale device over thermoplastics. Herein, a mold of desired pattern of the microfluidic device is made with cavities for microchannels in a microfluidic device. A thermoplastic sheet is placed between this molds whose cavities are at room temperature. Slowly, the temperature is increased and pressure is applied. The thermoplastic melts and fills the cavity of the mold and when pressure is applied the molten thermoplastic takes the shape of the mold. Slowly the temperatures are cooled and the thermoplastic solidifies as the shape of the mold and is ejected [15]. Figure 7.4a is a diagrammatic representation of this method.

7.3.4 Molding

Molding is a technique wherein liquid polymers and thermoplastics are used in molted state. There are two categories in this approach: (1) Replica molding: where a master mold is made with lithography using materials like silicon, over this mold, molten polymer is poured, cured and the solidified. (2) Inject molding: a mold with cavities of microchannels is fabricated using lithographic method and hot molten polymer or thermoplastic is injected in the mold, cavity is filled with. Hot, molten thermoplastic is cooled down to room temperatures and it takes the shape of the microdevice and is ejected from the mold. Figure 7.4b is the schematic representation of the inject molding process [16].

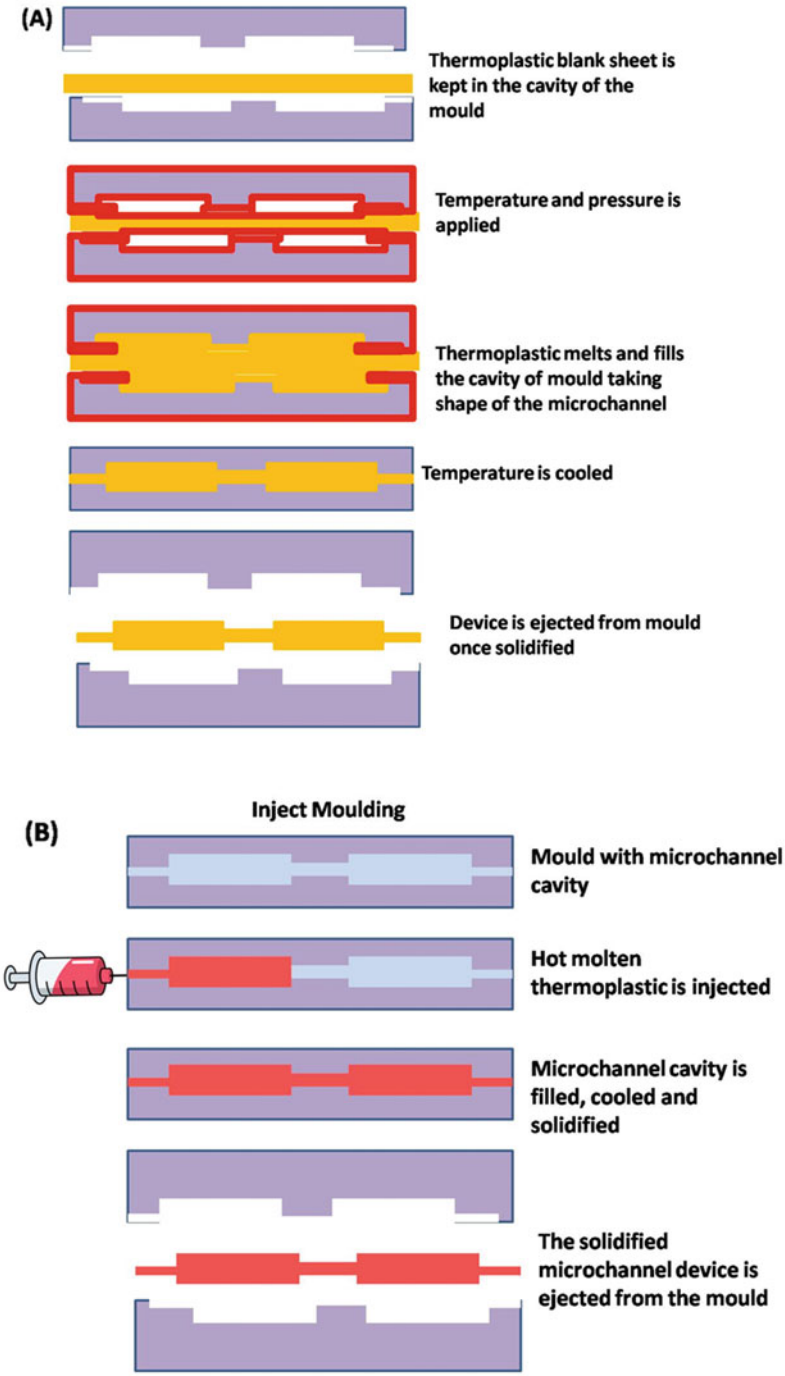

Fig. 7.4 (**a**) Schematic representation of the stepwise procedure of embossing technique. (**b**) Schematic representation of the stepwise procedure of inject molding technique

7.3.5 Laminating

This approach comprises of stacking independently cut layers and bonding them. These types of microfluidic sensors possess three layers: bottom layer, intermediate layer (with microchannel), and a top layer. These layers are bonded to form a firm microdevice integrated with sensor. The number of layers stacked and bonded depends upon the requirement of the device. There are major steps in this procedure: (1) Selection of type of material, (2) cutting the channels on the layer, and (3) bonding the stacked layers. Materials like glass slides, polymers like PMMA, polycarbonate, and PLA adhesive transfer tapes are the materials adapted widely. Knife plotter or laser cut approach (commonly CO_2 laser) is employed for making desired microchannel patterns. Although laser cutting gives an accurate dimension, it is a bit costly and requires skill. In comparison, knife plotter is cost-effective. However, the cutting technique depends on the material used. The use of adhesives, for instance, double-sided tapes, and thermal bonding are the approaches for bonding the stacked layers. In thermal bonding, the temperature of the each layer is raised nearer to the glass transition temperature, then force is applied that bonds the stacked layers into functional firm device [16].

7.3.6 Laser Ablation

Several substrates, like silicon, paper, glass, carbon, plastic, and polymer sheets, can be exposed to laser ablation for designing laser-induced graphene electrodes and laser cut microchannels for sensors. Various types of lasers like CO_2, ultraviolet (UV), pulsed, and diode are employed. Furthermore, different parameters like speed, power of laser, distance, and chemical composition of the substrate also affect the device features and performance.

7.3.7 Photolithography

This method makes use of optical means for drawing desired microchannels on the base substrate. Also termed as optical lithography, it is employed to draw channels, patterns, electrodes of microsize for sensing purpose on thin film or bulkier substrates. Earlier, projection of photolithographic techniques can design patterns on smaller substrates like ~250 nm. Nevertheless, the modern photolithographic approach uses soft X-ray, e-beam, focused ion beam, UV beam and can make patters up to 100 nm size as well [16]. Figure 7.5a is the schematic representation of this method.

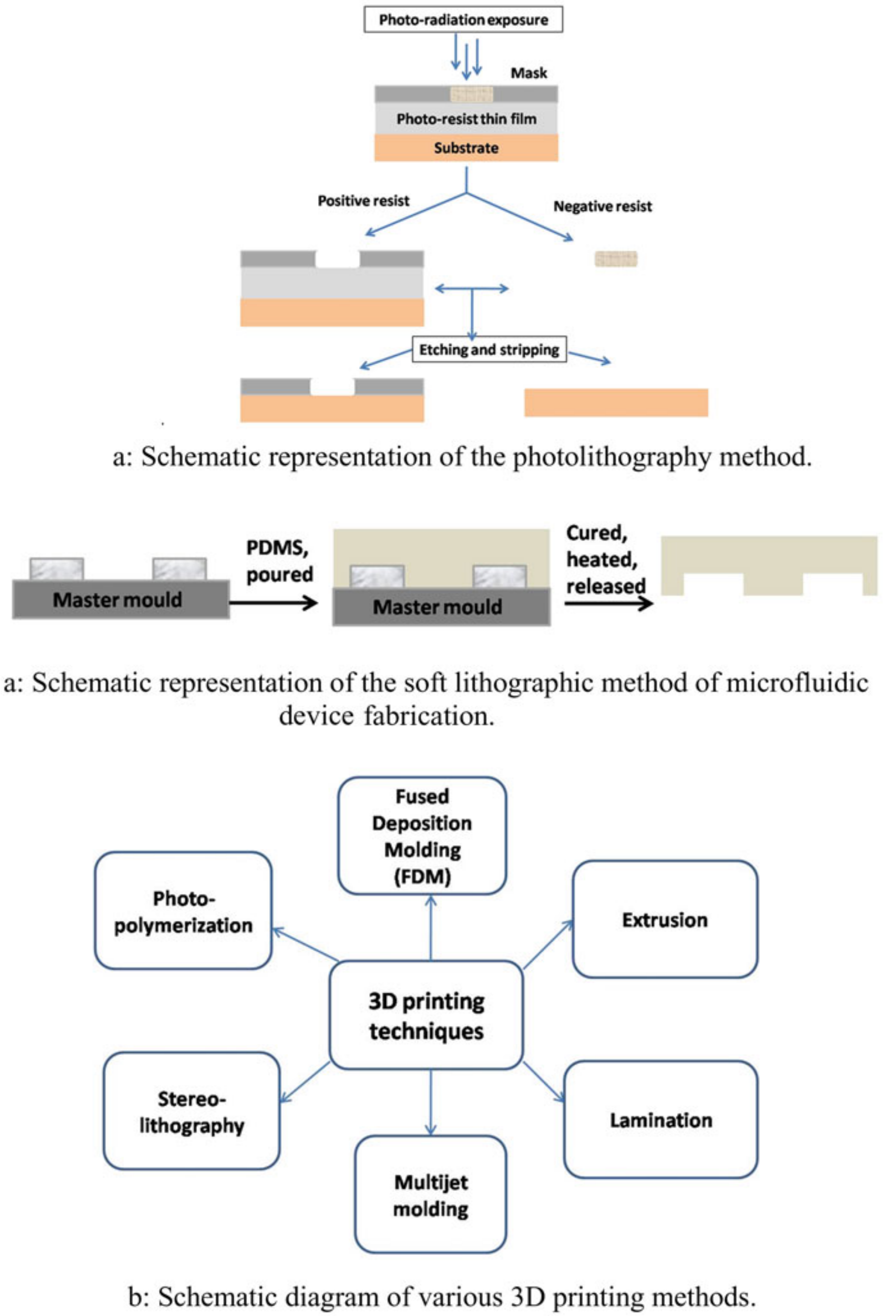

Fig. 7.5 (**a**) Schematic representation of the photolithography method. (**b**) Schematic representation of the soft lithographic method of microfluidic device fabrication. (**c**) Schematic diagram of various 3D printing methods

7.3.8 Soft Lithography

This is the most commonly used method of fabrication of microfluidic devices since 1998. Polymers like PDMS are used as a base material here. This is an advance method of self-replicating or replica molding. Herein, liquid materials like polymers (PDMS, polyimide, etc.) will be used to form solid elastomers. PDMS stamp or a master mold is prepared via micromachining. Liquid polymer is mixed with curing agent and poured onto the master with that has device design engraved over it. Elevated temperatures are applied that solidify the liquid. The prepared device is ejected once ready. Figure 7.5b is the schematic representation of this method [17].

7.3.9 3D Printing

This is also termed as additive manufacturing. It is a method of layer-by-layer deposition of desired material. Materials used are the conductive filaments like butadiene styrene (ABS), ploy lactic acid (PLA), polyethylene terephthalate (PET), acrylonitrile wood fiber (Cellulose + PLA), poly vinyl alcohol (PVA). The general procedure includes designing a 3D microfluidic device using a computer aided design (CAD) software. This designed model is converted into a standard triangle language (STL) file that is compatible with the 3D printer software. This software develops a 3D image into a sequential 2D layer giving a G-code file that then the 3D printer can print the device by material deposition. Figure 7.5c gives a summarized diagram of various 3D printing models used [16].

7.4 Microfluidic Sensors

Figure 7.6 gives the general classification of different types of microfluidic sensor. Each type of sensor has a different sensing mechanism. Broadly, microfluidic sensors are of two main types: (1) Microfluidic devices wherein the measurement or sensing of analyte or parameters are measured inside the device, (2) measurement of analytes or parameters externally. Both these mechanisms can be used for preparing physical parameters like pressure, flow, and temperature and biochemical sensors for developing chemical and biosensors. Herein, a few of the remarkable works reported in this chapter for each category are discussed.

7.4.1 Flow Rate Sensors

These microfluidic devices sense the flow rate of different liquids based on their viscosity, time of flow, etc. There are different approaches adapted for these. These sensors are based on principles like pressure, capacitance, and thermal changes as the function of flow rate. For instance, Yu et al. reported a PDMS-based microfluidic

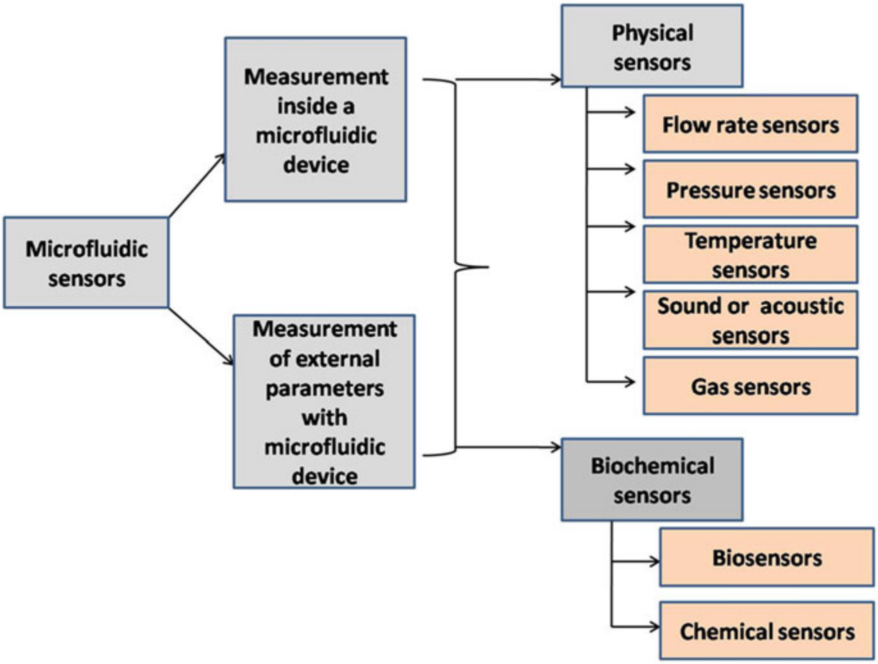

Fig. 7.6 Schematic representation of broad classification of various types microfluidic sensors

sensor for measuring the flow rate based on time of flight. The microdevice has two electrodes placed inside the microchannels. Electrodes are kept at a distant gap allowing the liquid to fill the gap between electrodes. With the help of syringe pump, conductive liquid is made to flow in the microchannels and when it is between electrodes, the resistance will increase. This change in resistance is measured as a function of flow velocity [18]. Dijkstra et al. developed flow sensor based on calorimetric principle. Herein, a microchannel with a temperature cavity is made over substrate. When the fluid is in temperature cavity, it is heated. The temperature changes are measured with the two resistors as a function of flow rate [19]. In another work, Jung et al. developed an integrated microflow sensor. The principle behind this is capacitive pressure of microgas flow. This microfluidic sensor has capacitors that calculate the pressure at the inlet, outlet, and at the microchannel. With the flow in the microchannel, there will be pressure difference that changes capacitance. This is measured as a function of flow [20]. Likewise, Czaplewaki et al. designed a microfluidic flow meter device. Herein, a micromechanical plate of about 100 m^2 was attached with a laser deflection mechanism. Various liquids with different viscosities and flow rates between 2.1 and 41.7 L/min was examined. Syringe pump was used to inject the fluid in the microdevice. Laser deflection was measured as it was directly proportional to the flow rate [21]. Navi et al. developed an underwater microfluidic sensor. It has a dome shaped container with an electrode. The flow of the fluid initiates a drag force to the container and gives displacement and allows the liquid in the microchannels to flow. The electrode attached converts the displacement observed into the flow rate [22]. Although many approaches are reported but many of these have limitations for practical applications and have a lot of future scope.

7.4.2 Pressure Sensors

One of the significant parameters of microfluidic devices are pressure as the flow of liquid in the microchannels depends upon the pressure. Gauge is the most common method used for measuring pressure but these cannot be applied in microdevices. In these devices, membrane is used in the sensing microchannel, wherein pinching of electrolyte filled microchannels is done. This gives pressure that deforms the elastic membrane. In turn, there is a change in resistance along the microchannel due to membrane deflection [23]. Sekimori et al. fabricated microfluidic chip-based pressure sensor. In this, a 1 mm^3 size pressure sensing element in a glass microchip with diaphragm. This was coated with polycrystalline-SiC. A capacitive sensor is placed. Pressure is measured with change in capacitance in the gap near distortion of the diaphragm [24]. Chen et al. designed a polyimide-carbon nanotube composite-based microfluidic pressure sensor. Multiwalled carbon nanotube (CNT) was used here. The electrical resistivity of this composite material changes with change in pressure and it is used to measure the pressure [25]. Thus, either by measuring the capacitance or resistivity of the microdevices upon applying strain, pressure sensors are developed.

7.4.3 Temperature and Acoustic Sensors

Microscale thermocouples are often used for measuring the temperature. Thin film-based microthermo couples with more spatial resolution are easily fabricated using glass rending excellent performance [26]. Usually, these are embedded into the metals for obtaining firm structure. Herein, wet etching of silicon, electroplating and SU-8 patterning was employed. Nickel metal was used for embedding thermocouples. The changes in the temperature are directly proportional to the thermoelectric output. Their fabricated device was compared with standard thermocouple (K-type) and was found to be same with no error and faster response time nearly 46 ns [26]. Kim et al. designed an integrated microfluidic sensor using a thin film of metal and microchannels for real-time monitoring of parameters like temperature, salinity, and conductivity. The microdevice has a AC voltage supply through power board and DC through 9 V battery a sensing board, mote for wireless connection [27]. In another work, Yang et al. fabricated a microsensor for temperature that was implantable. It was a size of capillary with about 300 μM. The transient temperature of the sensor was analyzed. This device could be used for biomedical diagnosis of hyperthermia [28]. Ye et al. fabricated a novel light-emitting diode

(LED) package with microfluidic temperature sensors that gave precise measurement of temperature [29].

Microfluidics is also being used for developing surface acoustic wave sensing. Earlier, bulk materials based on piezoelectric like lithium and quartz, were used. However, these materials are quite brittle in nature henceforth it becomes difficult to integrate them with electronics for processing the signal. Further, these materials are not useful with multiple modes of waves. Usage of thin films for these sensors makes the integration of electronics with lab-on-a-chip on different substrates including glass, silicon, and polymer. Zhou et al. reported aluminum nitride-based microacoustic devices. Silicon substrate was used here. The prepared device had Rayleigh mode and a higher guided wave mode frequency of wave at 80.3 and 157.3 MHz, respectively [30].

7.4.4 Gas Sensors

Microfluidic gas sensors are used for qualitative and quantitative estimation of specific gases present in the environment in point of care setting. Such sensors are useful to identify gas leakages for integration of a control mechanism for automatic shutdown. The portable microgas sensors have widespread applications in diversified fields like clinical analysis, chemical identification, medical diagnosis, safety, food industry, and defense. Certain significant applications include detection of toxic gases in the environment especially due to emissions from industries, automobiles, etc., safety and security in estimating poisonous gases due to smoke, explosions, fires, etc. Food packaging industries leverage such sensors for detection of gases from rotten food, etc. The literature has some of the benchmarking reports for gas sensing applications. For example, Martini et al. fabricated ammonia gas microfluidic sensor comprising of heater and trioxide tungsten (WO_3) film. This film exhibited selective analysis of ammonia. For this, they subjected the sensor to the test chamber wherein temperature controller maintained the temperature while the concentration of gas was varied. A linear range of 1–100 ppm at 0.2 L/min flow rate was tested. With the decrease in concentration of ammonia, the resistance of the sensor also decreased, that is, resistance was directly proportional to concentration [31].

In another interesting work, Gao et al. developed a microfluidic chlorine sensor via gas–liquid interface using chemiluminescence-based detection by employing luminol alkaline reagent. This liquid solution was trapped in the microchannel due to the applied surface tension. The chlorine gas was introduced into the microchannel that reacts with luminol to form ClO– that emits chemiluminescence. This emitted luminescence was analyzed by a photomultiplier tube in a response time of 30 s. The microdevice exhibited linear range of 0.5–478 ppm with the limit of detection of 0.2 ppm [32]. Yang et al. designed a unique capillary optical fiber-based gas sensor as a ring-shaped waveguide. The inner part of the fiber was coated with organosilicone gel that gave luminescence based on oxygen ratiometry. The oxygen concentration was measured by seeing the luminescence spectra of the optical fiber [33]. Zhu et al. developed microfluidic sensor for water monitoring by using tin oxide (SnO_2) film-based gas sensor with silicon base microhot plate, which was integrated into a polymer. The device was made via lithography and the SnO_2 was self-deposited. The principle for this sensing was desorption kinetics for different gases in the atmosphere [34]. Ozasa et al. made a unique lab-on-chip device, wherein live microbial cells trapped in the microaquarium helped in gas sensing. The device was made with PDMS. It had a microaquarium with two microfluidic channels. Euglena bacterial cells were present in the microaquarium releasing two gases, that is, air and CO_2 separately. The bacteria cells moved away from CO_2 toward air and this movement was observed with an optical microscopy. This was used to study the concentration gradient of CO_2 [35]. Cooney and Towe demonstrated microfluidic blood gas sensing to monitor CO_2 and O_2 in blood with microdialysis through optical analysis [36]. There is still a large scope for research in this regard as selectivity is an issue in gas sensing. With more precise matrix, materials, enzymes, redox mediators, etc., their sensitivity can be improved.

7.4.5 Microfluidic Biosensors

Biosensors are electrochemical devices that make use of various biological moieties like enzymes, antibodies, cells, microbes, etc., to detect both quantitatively and quantitatively different analytes. These biosensors aim to develop electrical signal that are dependent on the concentration of the analyte. These sensors have three parts: bioreceptor (biological entity), transducer (signal converter), and output reader (analog display). Literature has many biosensors mentioned, wherein bulk volume of reagents and sample is used. However, these are difficult for real-time practical applications. To overcome this, microfluidic biosensor devices are being explored. These microdevices have continuous monitored flow with the help of pumps. These devices have inlets for collecting sample, reaction with reagent, analysis of the reaction, and then signal output readout. There has been immense research for integration of these microfluidic biosensors in day-to-day lives. In this regard, significant reports are there in the literature. The advent of microfluidics has given significant growth in the field of biosensing and there are different types of microfluidic biosensors developed. A few of them that are applicable for real-time application are discussed here.

7.4.5.1 Wearable Microfluidic Biosensors

Emerging trends, like micromachining, microfabrication, and novel material fabrication, have aided the development of wearable microdevices for biosensing that can be worn over skin. The pioneering microfluidic devices were developed for measuring external parameters like pressure, temperature and pH. The new techniques have led to development of wearable microdevices for quantitative and qualitative analysis of various physiological chemicals and biochemicals for monitoring health conditions. For example, Koh et al. developed flexible material based soft, stretchable microfluidic device that can adhere to skin with no chemical and mechanical means along with wireless integration. The sweat from skin moves through microfluidic network into the reservoir of device. The device has colorimetric reagents for detection of biomarkers in sweat like chloride, glucose, lactate, and hydronium ions. Quantification is achieved by wireless interface that has digital hardware for image capture. The device was tested for real-time analysis on human while straining physical activity like cycling in indoors and outdoors. The device could measure accurately, the pH, lactate, and chloride concentration, sweat rate a sweat loss [37]. Similarly, Cho et al. fabricated capillary action-based soft, microfluidic device that can be mounted on the skin. This device attached to the skin supports collection of sweat sample in the reservoir. Pressure from sweat glands allowed the flow of about 1.8 μL of sweat sample. This device enabled the detection of sodium, potassium, and lactate in sweat [38]. The devices made by the aforementioned groups had three major components. Firstly, an adhesive layer for skin-friendly adhesion, secondly, a PDMS-based microchannel and reservoir containing colorimetric reagents and thirdly a magnetic antenna for wireless transmitting of signals. The four separate reservoirs have serpentine channel for flow of sweat and has reagents for lactate, pH, glucose, and chloride. The outlet on the device top layer avoids the back flow [37, 38]. Sekine et al. made a fluorometric device with smartphone imaging for sweat analysis of biomarkers [39].

7.4.5.2 Paper-Based Microfluidic Biosensors

Paper-based microfluidic devices aim to provide a zero-costing diagnostic tool. In 2010, Martinez et al. developed paper-based diagnostic devices [40]. These devices require hydrophobic barrier for the analyte to flow. The porous nature of the paper due to cellulose allows the fluid to move with capillary action. Various principles like colorimetry, fluorescence, electrochemical, chemiluminescence, and electrochemiluminescence have been used. Among this, colorimetry is widely adapted due to simple and minimal handling and instrumentation. Some of the remarkable paper-based biosensors are discussed here. Gootenberg et al. designed multiplexed RNA and DNA analysis using CRISPR enzymology [41]. This device was applied for real-time detection of ZIKA and Dengue virus RNA with limit of detection as 2aM. This microfluidic platform could also detect mutations in virus from patients' samples. CAS enzyme-based method is expected to have great scope in future. Wang et al. made a pop-up paper-based electroanalytical microdevice for estimation of beta-hydroxybutyrate (BHB) that is a biomarker for diabetes. It was made with a single sheet of paper folded as greeting card into 3D structure. It was made up of a three-electrode system, wherein working electrode was enzyme modified. It was coupled with commercial glucometer and gave detection of glucose and BHB as well [42]. Similar way, Teengam et al. demonstrated a microdevice for DNA, RNA, and colorimetric detection. This was employed for testing DNA of *Mycobacterium tuberculosis*, Middle East respiratory syndrome coronavirus, and human papillomavirus [43]. Ali et al. developed *Escherichia coli* sensor using a composite ink. Herein, a fluorogenic DNA probe was sued. This probe can identify the *E. coli* DNA and gives a fluorescence. A remarkable limit of detection of 100 cells/mL was achieved [44]. Cheng et al. developed paper-based enzyme-linked immunoassay (ELISA) microdevice. 96-microzone paper-based plate with hydrophobic polymer and hydrophilic paper was made. This device was highly sensitive, robust, and lesser cost [45]. Pollock et al. fabricated a multiplexed device for analysis of biomarkers aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the serum for liver functioning. The device gave response in 15 min. About 223 real-time samples blood and serum samples were analyzed. The results obtained from the device matched the clinical trials with 90% accuracy henceforth, has potential for real-time analysis [46].

7.4.5.3 Other Substrate-Based Microfluidic Biosensors

Apart from flexible substrates and paper-based microfluidic biosensors, other substrates like PMMA and PDMS are used for fabrication. For example, Sueng et al. developed a PDMS microfluidic chip for detection of Adenosine triphosphate (ATP) in real time. Herein, an aerosol condensation system is employed. The microchannel has ATP bioluminescence transducer as a mediator. The aerosol microbes were settled, bacterial ATP from the cell and concentration is found by bioluminescence. The chip was made through soft lithography with microchannel thickness as 100 μM. There were four inlets of 100 μM, one outlet of 400 μM, mixing channel, detection zone of 6 cm [47]. Hesam et al. designed a PDMS microfluidic device for detection of cancer cells based on the principle that the cancer cells will have lesser mobility than normal cells. Benign and early stage of cancer cells for both breast and ovarian cancer cells. A steady flow rate is maintained and cells are allowed in the microchannels through syringe pump. When one cell passes through the microchannel, another cannot pass. Using an inverted lens microscope, there movement is studied [48]. Using soft-lithography technique, a PDMS device is fabricated for detection of cell flow. The flow causes the changes in conductivity in the microchannel. A printed circuit board is used for realizing electrode plates. Microreservoirs are faced at these plates. The sample with cells is inserted into the microreservoirs, passes through the channel and comes out of other microreservoir. The change in impedance during this process is measured as a function of cell flow [49].

Wisitsoraat et al. developed a PDMS/glass-based microfluidic chip device based on flow injection. It was a three-electrode system device with working electrode as functionalized CNT, silver as a reference, and platinum as a counter. Chemical vapor deposition and sputtering method was used. Cholesterol oxidase was entrapped over CNT in channel. Chronoamperometry was the technique used. The sensor could detect 60 samples. The linear detection range was 50–400 mg/dL. No interference from other co-existing biochemical, like ascorbic acid, glucose, uric acid, and acetaminophen, can be useful for practical application [50]. Nguyen et al. designed interdigitated electrodes with carbon nanotube-polyaniline composite for detection of cholesterol. Potassium ferricyanide is used as a redox mediator. The mediator causes shuttling of electrons. The linear range of cholesterol was 0.02–1.2 mM [51]. Rodrigues et al. developed a glucose biosensor over a PDMS substrate. Herein, gold electrodes with glucose oxidase enzyme were used. Nafion was used to protect the enzyme. The current obtained was directly proportional to the glucose sample

[52]. Li et al. gave detailed review on preparing microfluidic devices with threads. Owing to the capillary action, threads can be employed in microdevices as lesser cost, lesser volume, and simple substrate. These can be employed with paper, PDMS, PMMA and as standalone devices. They have given recent advances in the applications of versatile thread-based microfluidic devices in areas like health monitoring, clinical diagnosis, food industries, and environment monitoring [53]. Thus, advent of microfluidics in the biosensing has significantly enhanced the real-time practical applications.

7.4.6 Microfluidic Chemical Sensors

Microfluidic platforms for various chemical detections are also being realized. For instance, a detailed review on recent advances in microfluidic devices for monitoring environmental pollutants and parameters like pH, heavy metals, nitrite, nitrate, bacteria, phenols, pesticides, and herbicides [54]. Shen et al. fabricated electrochemical microfluidic platform for detection of heavy metals. It was a paper-based device with three-electrode system, wherein pure graphite foil was used as a working electrode along with reference and counter. This device was tested for detection of cadmium and lead. A remarkable detection limit with 1.8 and 1.2 μg/L for lead and cadmium was found respectively. The device was highly reproducible up to ten times [55]. Yin et al. designed a microfluidic sensor for chemical oxygen demand detection. Herein, a silicon-based device was used which consisted of, Ag/AgCl as a reference electrode, platinum as a counter electrode, and PbO_2 modified working electrode. The device was 8 mm × 10 mm dimension. Phthalate derivative detection was performed in the linear range of 4.17–200 mg/L. The limit of detection was 2.05 mg/L. The fabrication of sensor was through microfabrication mass production approach, hence has potential to commercialize in low cost. In further, this sensor has IoT integration facility [56]. Gomez et al. demonstrated detection of Arsenic in water samples using a silicon-based microfluidic device. A three-electrode system comprising of gold nanoparticles gold film electrode as working is employed. The device was fabricated with lithographic method and gave linear detection in the range of 1–150 μg/L with limit of detection as 10 μg/L [57].

Kochli et al. developed microfluidic device integrated with electrochemical sensing for detection of lead and chlorophenols. Lamination was used as the technique of fabrication technique with laser machined polyimide sheet [58]. Wang et al. fabricated a microfluidic device on an acrylic substrate with a microchannel of 1 mm width, 7 mm length and 150 μL volume. The microchannel was coated well with silica gel. Post it dried, *o*-phenylenediamine reagent is coated. The reagent is colorless when NO_2 gas comes in contact with reagent becomes yellow in color [59]. Rérolle et al. demonstrated colorimetric microfluidic pH sensor for real-time application to sea sample. Minimal reagent volume was required [60]. Bowden and Diamond fabricated a microfluidic colorimetric phosphate sensor. Vanadomolybdophosphoric acid complex formation approach was used. The chip was three layered, wherein center layer of Si oxide is kept between glass sheets. The chip has sample inlets, mixing channels, and optical detection cuvette. UV-LED was used for optical detection and a spectrophotometer [61]. Delany et al. demonstrated electrochemiluminescence on a paper substrate. A screen-printed electrode as a disposable sensor prepared by inkjet printing was used. Ruthenium bipyridyl reaction that gives orange luminescence was employed. Nicotinamide adenine dinucleotide (NADH) and 2-(dibutylamino)-ethanol were the analytes detected. A smartphone-based analysis with digital images was done [62]. Wei et al. designed PMMA-based microfluidic chip for detection of benzoyl peroxide using chemiluminescence. The microchannel had 200 μM width, 100 μM depth, 67 mm length. Luminol was used as the reagent to react with benzoyl peroxide to give chemiluminescence. The real sample of flour was used [63]. Cheng et al. developed an impedance-based microfluidic sensor for highly sensitive detection of perfluorooctanesulfonate [64]. There have been several such reports for microfluidic sensing of various chemicals and biochemicals.

7.5 Future Aspects and Conclusion

Microfluidic technology is an interdisciplinary area of research emerging every day and is yet to be explored to its fullest. Alliance between fluid mechanics and various research areas is needed for future growth. Although significant advances have been done, yet commercialization of microfluidic devices is at the beginning stage. The future and upcoming application of microfluidic-based sensing is the growth in microsystem technology. For instance, implantable microdevices were used for monitoring biological components. Last couple of decades have seen significant growth in microbiodevices. Fields like flexible electronics, wearable electronics, drug analysis, tissue engineering, and biochemical and biomarker detection can revolutionize the applications. The upcoming decades are expected to be exciting for field of microfluidics. Microfluidics in lab-on-chip, organ-on-chip also has greater future prospects. Even though these are closer to real-time living cells, still they face difficulty in fabrication. In the near future, microfluidics is a potential tool for integration with human body for health monitoring and disease diagnosis. In addition to this, microfluidic sensing in environmental monitoring, agriculture science, space research, etc., also has enormous impact on daily life. Some of the significant examples for this are smart contact less sensors, noninvasive detections, tattoo-based sensors, etc. In a couple of decades to come, lab-on-chip and POCT are likely to show more commercialization. This chapter has summarized various advanced microfluidic-based sensing approaches. It also gives details about the fabrication methods and materials used for these types of sensors. Furthermore, types of microfluidic-based sensors and their recent applications have also been discussed.

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