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Recent Developments in Polymer Microfluidic Devices with Capillary Electrophoresis and Electrochemical Detection

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Abstract: We review recent work on the development of polymer microfluidic devices using capillary electrophoresis (CE) for fluid driving and separation and electrochemical detection (ED). A variety of commonly used off-chip and integrated electrochemical detection approaches, including amperometric, conductimetric and potentiometric detection approaches, have been given. We describe fabrication approaches for the creation of microfluidic architecture in a polymer substrate and electrode integration. The methods for polymer surface modification to enhance the microfluidic device properties are also described as well as developments in power supply for the creation of a robust CE-ED microfluidic device system. A variety of applications are described for the CE-ED systems.

Keywords: Microfluidic device, electrochemical detection, polymer microfabrication, surface modification, capillary electrophoresis.

1. INTRODUCTION

Micro total analysis system (μ TAS) has developed rapidly in the past decade since it first appeared in 1990 [1, 2]. More generally this area has become known as microfluidics and implies the ability to manipulate fluids in a chip format. Capillary electrophoresis (CE) on a microfluidic device offers fast and highly efficient separation of small inorganic and organic species as well as large biomolecules. Numerous recent reviews exemplify the different applications of capillary electrophoresis [3-17]. Many detection methods have been employed in CE microfluidic device, these include laser induced fluorescence (LIF), nonfluorescence optical detection, electrochemical, chemiluminescence, electrochemiluminescence, Infrared [18], Raman [19] and surface plasmon resonance [20]. Much work has been done on the use of capillary electrophoresis separation on microfluidic device with laser-induced fluorescence for detection [21-25]. Laser induced fluorescence is attractive for the high limit of detection (LOD), but is limited to compounds which fluoresce or are amenable to derivatization with a fluorophore. In recent years, electrochemical detection has also attracted interest because of its advantages in cost, design flexibility, ease of miniaturization and its sensitivity and selectivity. There is increasing interest in the use of polymer substrates for microfluidic device development because of the advantages of cost and amenability for high replication [26- 28]. This review will focus on recent developments in polymer based microfluidic devices with electrochemical detection.

2. ELECTROCHEMICAL DETECTION ON MICROFLUIDIC DEVICE

Three electrochemical detection modes, amperometry, conductimetry and potentiometry have been commonly used for detection in capillary electrophoresis on microfluidic device [29- 31]. Amperometric detection is an attractive because of its high sensitivity and the ease with which it can

be integrated as a detection element in a microfluidic device system. It does, however, suffer from interferences from the high voltage (HV) used in electrophoresis which is commonly used within for sample separation and transport within microfluidic device. There is, therefore, often a need for decoupling to ground the separation voltage prior to the detection cell and much work has been done in this field in the past few years. There is increasing interest in using conductimetry for detection. It can be used to detect substances that do not have any electrochemical activity and is therefore a complementary technique to amperometric detection. Conductimetry does, however, suffer from lower sensitivity.

2.1. Amperometric Detection

In 1998, Wolley *et al.* first reported amperometric detection techniques for μ -CE chip [32]. The technique can be implemented in either a three-electrode (working, auxiliary and reference) or two-electrode (working and reference) systems [33]. In amperometry mode, the potential of the working electrode is set at a constant value and only those substances that are oxidized or reduced at the set potential are detected as they emerge from the micro channel [34]. Although amperometry is the most commonly used electrochemical detection method in microfluidic devices; two shortcomings limit its commercial application. Firstly, decoupling is required to minimize the high voltage electric field, (in the order of several hundred V/cm) at the end of channel, before the species reach the detector where the working electrode (WE) holds a constant potential below 2.0 V. Secondly, there is need to improve the reproducibility of the detection current. The reproducibility of the detection current greatly depends on the stability of the WE and the reproducibility of the position of the WE to the outlet of separation channel.

Three decoupling methods, end-channel (Fig. 1), off-channel (Fig. 2) and in-channel detection (Fig. 3), are typically used and these differ in the relative position of the WE to the channel outlet (29).

2.1.1. End-Channel

In the end channel mode, the working electrode is typically placed several tens of micrometers away from the end

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of channel. The gap between the outlet and the WE can effectively isolate the high separation voltage from the detector [32] (Fig. 1a). The end channel detection mode was adapted from the end-column detection mode for conventional capillary electrophoresis with capillaries of internal diameter less than 5 μm [35]. Based on conventional end column detection mode, microfluidic device CE-ED with end-channel detection mode is a popular detection mode. Different electrode materials such as gold, platinum, copper, carbon in different forms (paste, glassy, fibre, ink, pyrolyzed photoresist film, nanotubes and diamonds) have been reported. The alignment of the working electrode can be either on-chip or off-chip. In off-chip mode, the WE is fixed in an extra apparatus, such as a screen-printed electrode on a substrate [36], a hand-made microelectrode controlled by a three dimensional adjuster [37, 38] or alignment of the WE and the outlet through a guide tube [39-42]. In the three dimensional adjuster, the probe microelectrode which is also known as the tip electrode is precisely positioned several micrometers away from end channel [43]. The distribution of electric field (E) at the end channel is strongly dependent on the microelectrode potential, tip-to-channel distance, and separation potential [44]. Scanning electrochemical microscopy (SECM) coupling imaging has been used to detect the electric-field distribution at the end of the separation channel [45]. The off-chip mode has the advantage that the WE can be replaced, if fouled, without the need to expensive disposal of the whole microfluidic device and the chip microfabrication is simplified. The off-chip mode does, however, suffer from relatively poor current reproducibility. The peak current partly depends on the distance between the channel outlet and the WE and the poor current reproducibility arises from the difficulty in reproducibly positioning the WE. The extra device for fixing and alignment of the WE limits the degree of integration and miniaturization of the microfluidic device CE-ED systems. This is not a problem for the on-chip mode where generally, the WE is microfabricated on the substrate and its position is easily controlled. There is now an increasing interest in the use of the on-chip mode.

The end-channel detection mode is relatively simple and only needs to adjust the distance between the exit of the separation channel and the surface of the working electrode. However, a residual electric field will exist in the end-channel detection reservoir which will lower sensitivity, shift the detection potential [46] and lead to broadening of the electrophoresis peaks. To improve the efficiency of end-channel detection, Ertl *et al.* [47] proposed CE chips with a sheath-flow supported electrochemical detection system. Gravity-driven buffers flow along the sheath-flow channels (Fig. 1b), that join the end of the separation channel from each side, and carry analytes to the electrochemical detector instead of use of electro osmotic flow (EOF) [48]. The detection limit of a standard sample of catechol is 4.1 μM with a distance of 250 μm from the outlet of the separation channel to the working electrode; this is about 5 to 10 times longer than is the case normally. At this long distance, the separation voltage is considered to be effectively isolated. Sufficiently small inner dimensions of separation channels with wider outlet are an alternative approach to diminish the HV-field interference in electrochemical detection. Wilke and Büttgenbach introduced a 1000 μm width channel outlet in

the fully integrated micro machined capillary electrophoresis chip to isolate the interference [49]. This sudden change in channel geometry can decrease the resistance of the end channel and thus greatly reduce the electric field in the detection region (Fig. 1c). Analyte diffusion appears between the end of the separation channel and working electrode which limits the separation efficiency and detection sensitivity [50, 51]. The electrophoretic current will produce an iR drop at the detection reservoir which alters the potential of the WE with shifts in half-wave potential of the hydrodynamic voltammogram. Shifts of +130 mV in the half wave potentials for both dopamine and catechol has been reported when the applied separation voltage was increased from 15 kV to 30 kV [46]. In the end-channel detection mode, an increase of the cross-sectional area of the separation channel positively shifts half wave potential for oxidizing dopamine and catechol [52]. For dopamine at the field strength 288 V/cm, increased cross sectional area shifts half-wave potentials from 285 mV to 330-400 mV. The gap between the WE and RE has a pronounced effect on the HV field interference and detection performance [32]. The positioning of the WE and RE on an equi-potential surface eliminates the HV-field interference [53]. A gap of 50-20 μm between the WE and the separation channel was shown to produce a positive (+15 mV) shift in half-wave potential for dopamine [53]. An increase of channel-to-electrode distance from 20 μm to 50 μm significantly increases both the migration time and peak widths with a decrease in peak heights. The working-to-reference electrode spacing is more critical as compared to the working-to-channel distance when considering background noise, detection potential shift, detection sensitivity and separation efficiency. An integrated reference electrode situated close to the WE dramatically reduces the noise caused by the HV field. The half wave potential of the oxidized analytes shifted from +160 mV to +470 mV when the working-to-reference electrode spacing increased from 100 μm to 500 μm . In end channel CE-ED, the 100 μm gap between the WE and RE partially reduced the HV-field interference and increased sensitivity [54]. An array of working electrodes at the end of the separation channel significantly decreased the background current to ~ 1 nA [50]. Recently, Álvarez and co-workers have developed various end-channel designs for integration of gold wire electrodes in CE-ED microfluidic device [40, 41, 55-60]. Álvarez *et al.* introduced guide channel at the end of the separation channel for the working electrode wire. In this approach, the 50-100 μm gold wire is in contact with the solution at the end of the channel [56]. Epoxy resin adhesive tape fixed the position of the working electrode wire at the end channel and reduced the capacitive currents [56, 61]. Hydrogen peroxide, ascorbic acid and uric acid were measured simultaneously in 70 s with good reproducibility. Single and dual-channel (Π -design) microfluidic device electrophoresis with end channel electrochemical detection system has been reported for dopamine, p-aminophenol (pAP), hydroquinone (HQ) [57, 62]. Recently, Castaño-Álvarez *et al.* reported neurotransmitter detection using SU-8 based microfluidic device electrophoresis with integrated end channel electrochemical detection [63]. The space between the gold working electrode and separation channel was 20 μm for high separation efficiency. Previously, the same group reported end channel capillary electrophoresis microfluidic devices made of various materi-

als, e.g., poly(methylmethacrylate) (PMMA) [58, 60], thermoplastic olefin polymer of amorphous structure (TOPAS)[55, 59], and Polydimethylsiloxane (PDMS) [62]. Klett *et al.* [53, 64] developed an end-column design in conventional CE. An array of gold microband electrodes on a detection chip were placed at a distance of 10 μm between the working and reference electrodes (Fig. 1d). This design ensures that both electrodes are identically affected by the presence of the CE electric field and thus no shift in the half-wave potential when the CE high voltage was applied. In a similar approach, Baldwin [65] suspected an effect on the reference position. The discrepancy may be due to the different micro device design. End channel electrochemical detection mode is very successful and effective for the analysis of real samples [66, 67]. Recently, Peng and coworkers placed the WE 25 μm away from the separation channel and the detection limits ranged from 1×10^{-8} to 2×10^{-7} g/mL for phenolic Compounds [68, 69].

2.1.2. Off-Channel

In the off-channel mode, the analytes first pass through a decoupler, before they reach the WE. In the absence of decoupler, bubbles are continuously formed in the front part of the WE when a separation voltage is higher than 1200 V and a + 0.7 V potential (vs Ag/AgCl) applied to the WE [70, 71]. A decoupler can ground the separation potential and protect the EC detector from damage arising from surges in current. In capillary electrophoresis with ED, a bare or coated fracture near the end of capillary has been presented as decouplers. Coatings can be made from porous glass [72], graphite [73] and polymers such as Nafion [74]. Zhang *et al.* [75] used a Teflon tube as a decoupler for amperometric detection of ofloxacin and pasiniazid in urine. Decouplers can also be from Pd tube [70], because Pd can effectively reduce H^+ and absorb hydrogen. This allows hydrogen, generated from the hydrolysis of water at the cathode during separation, to diffuse faster before the formation of hydrogen bubbles. Furthermore, etched holes or scores which are filled with lower conductivity materials such as epoxy [71] or cellulose ace-

tate [76], near the end of a capillary have been employed as decouplers. This design separates the capillary into two parts, and isolates the detector from the interference of high voltage electric field. Indium tin oxides (ITO) material was found to decouple the electrochemical detection circuit from the interference of a separation electric field and measured dopamine, catechol, DNA ladder, and hydrogen peroxide [77]. Recently, Sha *et al.* [78] used porous etched joint decoupler on the EC detection. The porous joint successfully eliminates the electrophoretic high-voltage field on the carbon fibre working electrode. The detection limits of propyl gallate (PG) and tertbutylhydroquinone (TBHQ) was recorded 2.51×10^{-6} and 4.88×10^{-6} mol L^{-1} .

In microfluidic device with electrochemical detection, the decouplers employed have mainly followed the design concepts used in conventional CE. On-chip decoupler has the advantage of no dead volume or sample leakage and can be micro-fabricated as part of the overall chip. Before 2002, there were relatively a few papers on off-channel detection with a decoupler design. Yin reviewed off-channel design with decoupler in electrochemiluminescence cells [79]. Rossier *et al.* [80] proposed an array of micro-holes of 5–10 μm in diameter made from UV excimer laser as a decoupler in a poly (ethylene terephthalate) (PET) microchannel (Fig. 2a). The shift of the half-wave potential of analytes is only about 15 mV under an electric field of 50 V/cm when the separation current was 5 μA [81]. The limit detection is around 5 μM for aminophenol. Chen *et al.* [82] obtained a better LOD of 0.29 μM for catecholamine and 0.47 μM for dopamine on a polymethylmethacrylate (PMMA) chip with a 3 mm width deposited Pd film decoupler just 1 mm before the working electrode. In this study, the electric field strength was recorded to reach as high as 714 V/cm.

We have seen development in new design and optimization in decoupling (Fig. 2b). Lai *et al.* [83] found that 700 \AA thickness of a Pd film is sufficient for most solutions in a PDMS/ glass chip. The chip was used for routine detection for dopamine with an LOD of 0.25 μM and a maximum al-

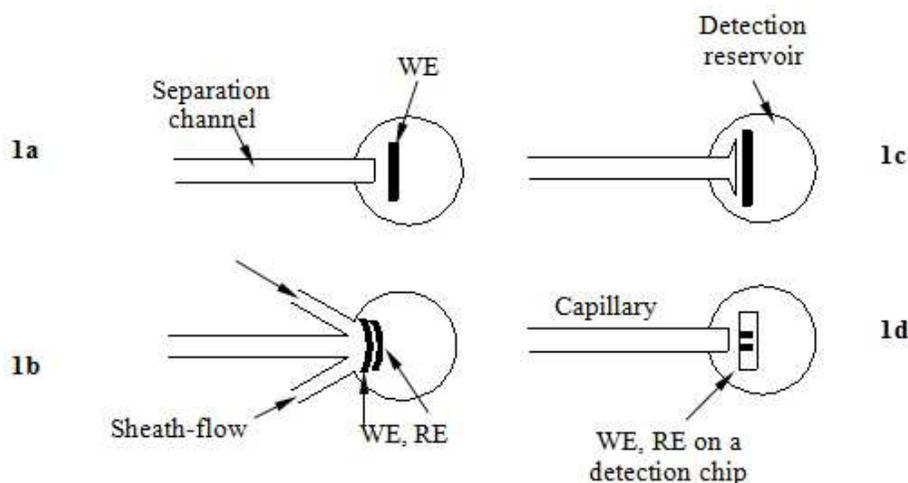


Fig. (1). End-Channel Configuration.

(1a). Basic end-channel configuration (32). (1b). Sheath-flow driven design (47). (1c). Widened channel outlet (49). (1d). micro band array electrodes with distance of 10 μm between the WE and RE in conventional CE (53). (To simplify the drawing, not all the electrodes are included; same in Fig. (2) and Fig. (3)).

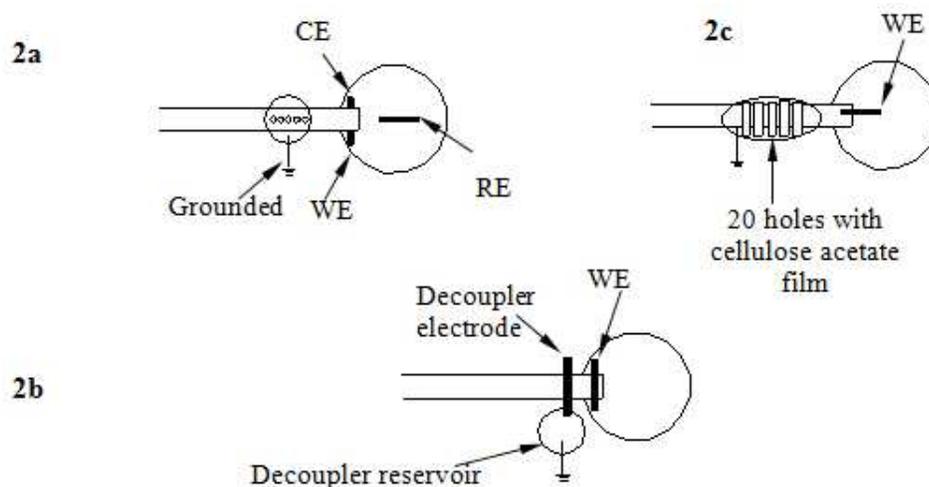


Fig. (2). Off-Channel Configuration.

(2a). Drilled holes near the end of a separation channel [80]. (2b). Designs with Pd or Pt decouple electrode [82-85]. (2c). Holes array with cellulose acetate film [86].

lowed electric field strength of reach 800 V/cm. A Pd microwire with a 50 μm gap between the separation and electrode channels isolated the electrode channel from the separation channel [84]. Lacher *et al.* [85] optimized the Pd decoupler size and the spacing between the decoupler and the working electrode. A maximum electric field of 1200 V/cm was used in this PDMS/ glass microfluidic device giving a plate number of 248000 /m. The LOD for dopamine was around 0.5 μM . Dawoud *et al.* [87] electroplated palladium nanoparticles on the gold microelectrodes and the concentration detection limit for 8-hydroxy-deoxyguanosine DNA adduct (8-OH-dG) is in the order of 100 nM. Kovarik *et al.* [88] reported their work on coupling a carbon microelectrode with a Pd decoupler. The LOD for dopamine is estimated to be 2.3 μM with a linear range from 5 to 200 μM . In the amperometric detection of the 8-hydroxy-deoxyguanosine (8-OH-dG) DNA adduct, electroplated Pd nanoparticles integrated on gold decoupler provides significantly improved detection limit, separation efficiency, and resolving power [89]. Wu *et al.* [90] tried electrodeposited Pt nanoparticles as a decoupler and pseudo-reference electrode. The potential shift was found to be nearly cut to zero and a LOD of 0.125 μM for dopamine was achieved. The maximum electric field and plates are around 85 V/cm and 4800 /5 cm (96000 plates/m), respectively, which are far lower than with the use of Pd as a decoupler. This is mainly due to better adsorption of hydrogen on Pd metal surface than a Pt surface. As a consequence of this a higher voltage can be applied before interruption of the channel by bubbles. Du *et al.* [91] reported the fabrication of a Pt decoupler coupled with copper WE on a PDMS-glass hybrid microfluidic device. Glucose in human plasma was successfully determined with a linear response from 10 μM to 1 mM. Recently, Lin *et al.* used Pt decoupler and a renewable working electrode (Cu) for the electrochemical detection of dopamine and catechol analytes over the concentration range 10–1000 μM [92]. In the CE chip, the Pt and Cu wires were aligned horizontally on the separation channel. The distances between the decoupler and the end of separation channel and the centre of the WE electrode was fixed at 1000 μm and 200 μm respectively. Embedded

gold nanoelectrode ensemble (GNEE) working and Pt decoupler electrodes provide a significantly higher signal response than unmodified electrode [93]. For dopamine analytes, the GNEE decoupler electrode reduces the amplitude of the charge current (3.5 nA vs. 18.7 nA) and the baseline drift. Compared to the conventional Pd decoupler, the baseline current drift measured with GNEE decoupler is three times smaller [94]. In CE microfluidic device, for a mixture of 1 mM Dopamine and catechol, response with GNEE decoupler electrode almost five times higher than conventional Pd decoupler.

Lunte *et al.* [86] developed a chip-based cellulose acetate decoupler for electrochemical detection (Fig. 2c). The decoupler is constructed by etching a series of twenty 30 μm holes using a CO₂ laser in the cover plate of the microfluidic device, and filling the holes with a thin film of cellulose acetate. The decoupler shows excellent isolation of the detection circuit from the separation electric field. Field strength of 1700 V/cm can be applied with noise level of less than 1 pA at a carbon fiber electrode, and gives the lowest reported detection limit for dopamine in a microfluidic device CE with electrochemical detection of 0.025 μM up to date [86]. Arnett *et al.* [95] used laser etched decoupler and carbon fiber working electrode for the electrochemical detection of 8-oxoguanine and 8-hydroxy-2-deoxyguanosine in the rat cerebral cortex. An alternative approach to reduce the electrophoretic current is to bypass the current by a field decoupler near the end of the separation channel. This additional pathway provides a junction for the electrolyte and ground the separation current just before the working electrode [96]. There is, however, a need to improve the mass production of this design.

2.1.3. In-Channel

In the in-channel detection mode, analytes migrate over the electrode while they are still confined to the channel, which allows low analyte diffusion and higher sensitivities. The main drawback of the in-channel detection mode is the necessary isolation of the high separation voltage from work-

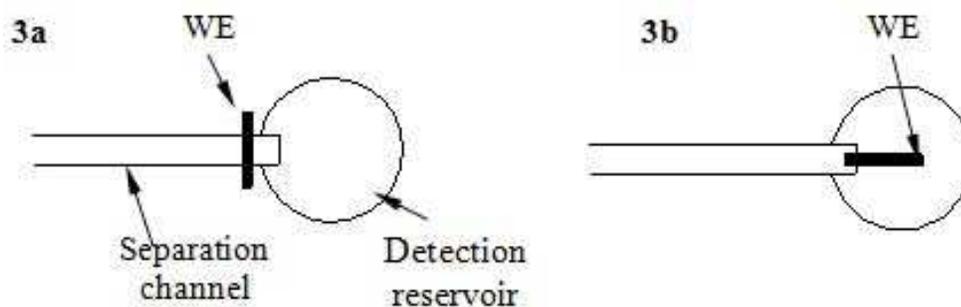


Fig. (3). In-Channel Configuration.

(3a). WE is perpendicular to the channel, detected by a floating potentiostat [97]. (3b). WE faces the flow [98].

ing electrode. Employing an electrically isolated potentiostat as electrical isolation approach [97] can allow placement of the working electrode inside the channel (Fig. 3).

This avoids the difficulty in fabricating a decoupler in off-channel detection and the loss of efficiency and band broadening with end-channel mode [99]. A floating potentiostat was designed and data are transmitted over an electrically isolated RS-232 port while the detection circuitry is not grounded. This design enables the placement of the WE directly in the channel and a separation performance in plate height and peak symmetry can match the result by Laser Induced fluorescence (LIF) [97]. However, the LOD for catechol is 4 μM mainly due to the background noise from the non-shielding potentiostat. For the same analytes, in-channel amperometric detection mode decreased the total plate height by a factor of 4.6 compare to end-channel mode [100]. A similar tendency was observed for small, inorganic ion nitrite. Single carbon fiber electrode introduced in the end part of the micro channel directly detected electroactive and non-electroactive analytes in-channel amperometric mode [101]. This group also reported in-channel amperometric detection mode for the analysis of inorganic anions in CE chip [102]. Low-noise algorithms, amplifies and improved layout will lead to a better result. No gap between the channel outlet and the working electrode prevents the analyte dispersion, increases peak resolution and sensitivity for the amperometric detection [60, 103]. A very low separation voltage (below +500 V) allows placement of the working electrode within the separation channel (20 μm away from the outlet [55]. In in-channel detection mode, low separation voltage offers low baseline noise level with reduced Joule heating. Recently, Chen *et al.* [104] used a dual in-channel configuration for amperometric detection in microfluidic capillary electrophoresis chip. They applied two parallel separation channel containing the working and reference electrode separately. The WE and RE are placed equally exactly 200 μm from the outlets and the counter electrode was placed 100 μm from the channel outlet. Separation voltage causes a potential shift between the working and the reference electrode and deteriorates the detection signals significantly. An amperometric signal (0.1 pA) was measured without any potential shift with the LOD 1.8 nM for dopamine. An increase in coulometric efficiency (C_{eff}) of an in-channel amperometric detector was reported with gold particle deposition [105]. 10 lines of gold working electrodes (50 μm wide and 50 μm spacing) were fabricated in channel to

enhance the separation efficiency and limit of detection. An external electric field induces a potential difference between array of microband electrodes and enables in-channel electrochemical detection of electroactive species such as ascorbic acid and $\text{Fe}(\text{CN})_6^{4-}$ [106]. The induced potential difference between the electrodes can be controlled by the external electric field and can isolate the separation voltage in CE microfluidic device. Besides this, in-channel fabricated single carbon fiber electrode was reported to efficiently separate Pb^{2+} , Cd^{2+} and Cu^{2+} with in 80 seconds [107]. The detection limit of Pb^{2+} , Cd^{2+} and Cu^{2+} were 1.3, 3.3 and 7.4 μM with the theoretical plate number of 1.2×10^5 , 2.5×10^5 , $1.9 \times 10^5 \text{ m}^{-1}$, respectively.

2.2. Pulsed Amperometric Detection

Though constant potential amperometry is the most widely used electrochemical detection mode in microfluidic chip, other electrochemical detection methods such as pulsed amperometric detection (PAD) and voltammetry are also used.

Direct current (DC) amperometry detection is limited to a small number of easily oxidizable or reducible analytes. However pulsed amperometric detection is an alternative waveform that can increase the number of electrochemically detectable analytes in real samples. Besides this, in the constant potential amperometry mode, working electrodes are easily fouled because of adsorption of oxidized products on the electrode surface, especially for noble metal electrodes. This problem is obviated in PAD since a high potential is first applied to clean the electrode surface followed by switching to a negative potential to regenerate the electrode surface, and finally setting to a potential for analyte detection. PAD has found wide application in the detection of compounds containing amine, alcohol, or sulfur moieties, which can easily foul metal electrodes in capillary electrophoresis [108, 109]. Wen [110] studied waveform shape, waveform frequency and various signal analysis methods in order to get improved S/N in PAD in conventional CE. They found the addition of a multiple-step potential waveform to a bipolar pulse could enhance the S/N up to 10 times.

Fanguy *et al.* [111] gave the first report on the use of PAD at a platinum working electrode in a PDMS/glass microfluidic device. Glucose, maltose and xylose were separated and measured with a detection limit of 20 μM for glucose. Garcia *et al.* [112] determined underivatized carbohy-

drates, amino acids and sulfur-containing antibiotics with PAD through the end-column configuration. A gold microwire working electrode was aligned at the end of the separation channel in a perpendicular channel to isolate the detector from the separation current. Detection limits of 6 fmol (5 μ M) for penicillin and ampicillin, and 455 fmol (350 μ M) for histidine were obtained. Garcia *et al.* [113] proposed the use of post-column pH modification in microfluidic device electrophoresis for glucose determination with PAD. Sodium dodecyl sulfate was used to stabilize flow rate and enhance the detection signal. A linear relationship between the peak current and the concentration of glucose was found between 10^{-2} - 10^{-15} M, with a limit of detection of 1.2 μ M. This group further applied PAD to nitrogen-containing compounds such as creatinine, creatine and uric acid [114]. The results obtained with urine samples were comparable with the standard clinical assay based on the Jaffe reaction. They also developed analysis method for levoglucosan from smoke samples that can be used to fast locate forest fire or air pollution sources [115]. In the presence of 30 mM sodium dodecylsulfate surfactant, pulsed amperometric detection method successfully detect the antioxidants propyl gallate, octyl gallate, lauryl gallate (LG), and nordihydroguaiaretic acid (NDGA) [116]. Four synthetic antioxidants were analyzed within 2 min and the limit of detection was recorded 1-4 μ m by microfluidic device-MEKC (Micellar electrokinetic chromatography) with pulsed amperometric detection mode. Besides, phosphatidic acid and deoxycholate enhanced electrochemical response for glucose, penicillin, phenol, and homovanillic acid [117]. 25 μ m width Au electrode simultaneously measured three phenolic pollutants in base medium which addition of alkyl sulfates improved the reproducibility of the migration times (t_M) and peak currents (I_p) [118]. Pulsed amperometric detection mode allows detection of 5 nM for dopamine, 74 nM for glutathione, and 100 nM for glucose in CE microfluidic device [84]. A Pd microwire acts as a decoupler and isolates the separation voltage from the Au/Pt working electrode. Pulsed amperometric detector based on boron-doped diamond (BDD) thin film electrode successfully detects 1.0-100 μ M salbutamol, terbutaline and clenbuterol [119]. Garcia *et al.* [120] reviewed pulsed electrochemical detection mode for capillary electrophoresis. They also reported integrated pulsed amperometric detection (iPAD) coupled with microfluidic device electrophoresis to the analysis of various carbohydrates [121]. Manica *et al.* [122] utilized electrical potential waveforms similar to PAD to clean Pt working electrodes. This method was applied in the analysis of histamine and serotonin, which can absorb strongly to metal surfaces and gave detection limits of 78 nM and 17 μ M for serotonin and histamine, respectively. Repeated use of the Pt electrode and application of electrochemical treatment did not affect the noise, metal adhesion and physical appearance of the electrode. Garcia *et al.* used unmodified gold electrode for stable detection of phenolic pollutants in base medium on a PDMS microfluidic device [123]. The electro-oxidation of phenolic compounds depends on the pH, concentration and temperature and a thin insulating polymeric layer [124, 125]. Ding *et al.* [126] demonstrated CE microfluidic device with PAD for the analysis of phenolic acids in water samples. Separation potential, buffer pH and composition, injection time and PAD parameters were optimized for the separation and detection of six pheno-

lic acids. PAD applies three-potential waveform to the working electrode and the redox cycle serves to regenerate a clean, oxide-free noble metal surface for the electrochemical detection, allowing high signal stability and even real-time monitoring of nonsteroidal anti-inflammatory agents in serum [127].

2.3. Voltammetry

Voltammetric detection appeared early in microfluidic chip design with the work of Rossier [128]. Rossier studied the electrochemical response of carbon microband electrodes placed in a microchannel by cyclic voltammetry and chronoamperometry. Ueno *et al.* [129] used voltammetry, chronoamperometry and computer simulation to evaluate the electrochemical response in polymer microchannels. It was found that the electrode responses in the microchannel chip were best described by one-dimensional diffusion along the channel length. The restricted space and speed of solution flow in the channel greatly affected the collection efficiency. Holland *et al.* reviewed fundamental concepts of amperometric and voltammetric detection techniques coupled with CE chip [130]. Recently, Du *et al.* [131] used linear potential and chronoamperometry in capillary electrophoresis to reveal the oxidation mechanism of thiosulfate. Cyclic chronopotentiometry (CCP) detection mode in end-column CE chip was used to separate and quantitatively detect sugars in honeys [132]. Earlier, Henley *et al.* [133] modelled mass transport and potential distribution of electro osmotic flow in the microfluidic devices. Linear sweep voltammetry detector in a microfluidic channel demonstrated the effects of IR drop on the voltammetric response of working electrode. Forry *et al.* [134] used fast-scan cyclic voltammetry (FSCV) at carbon-fiber microelectrodes to probe electric fields inside microfluidic channels. FSCV also takes the advantage of measuring electro active analytes that are not separated in the channel.

A technique related to FSCV is sinusoidal voltammetry (SV). In the case of SV, a large amplitude sine wave is used as the excitation waveform with data analysis performed in the frequency domain [135]. SV is becoming increasingly popular in Microfluidic device based CE because of its improved sensitivity, lower background noise and wide application of substances. Hebert [135] *et al.* compared amperometry and SV and found that SV is about an order of magnitude more sensitive than constant potential amperometry. Carbohydrates were studied with SV at a planar copper electrode with mass detection limits of less than 200 amol for glucose and sucrose [136]. Planar carbon electrodes made from pyrolyzed photo resist films are integrated on a PDMS/quartz hybrid microfluidic device [137]. SV detection of various neurotransmitters at these carbon electrodes demonstrates that the electrodes are stable with low capacitance and have high sensitivity; the detection limit for dopamine is 100 nM. Single nucleotide polymorphism (SNP) has been screened by capillary gel electrophoresis with SV detection in the same group [138]. This chip-based screening system takes the advantage of accuracy of the thermostable polymerase with the help of an electrochemically labeled chain terminator in the single base extension reaction. The terminator is incorporated only when its Watson-Crick complementary base is present at the mock SNP site.

Other voltammetry detection methods such as square-wave and adsorptive-stripping voltammetry have also studied on microfluidic devices [139]. Square wave voltammetry is a sensitive electrochemical method for the detection of absorbed ion on the electrode surface. In square-wave voltammetry a potential wave is applied to the working electrode. Ramaley and Krause [140] invented square-wave voltammetry but Osteryoungs [141] extensively developed the method. Gerhardt *et al.* [142] used modified Osteryoung SWV techniques in capillary electrophoresis. In this modified methods, instrument collects current data during the entire square-wave cycle. Recently, Lindsay *et al.* [143] reported droplet-based electrochemical digital magnetofluidics system for automated clinical diagnostics and drug discovery. Square-wave voltammetry and chronoamperometry was used for rapid measurements of microdroplets containing magnetic microparticles. CE chip integrated with square wave voltammetry successfully quantifies avidin in transgenic plant [144].

Anodic stripping voltammetry is an extremely sensitive and popular electrochemical technique for measuring heavy metals. Stripping analysis consists of two step processes, electrolytic deposition of trace amount heavy metals on the working electrode and dissolution (stripping) of the deposit. In the conventional anodic stripping voltammetry (ASV), mercury (Hg) or mercury precursor acts as a working electrode. For disposable *in situ* sensing applications, mercury or mercury precursors is not ideal for working electrode. Recently, Zou *et al.* [145] introduced bismuth (Bi) as an alternative working electrode for *in situ* heavy metal ions measurement. They used square wave anodic stripping voltammetry in CE chip for Pb (II) and Cd analysis and the limit of detection was recorded 8 ppb and 9.3 ppb, respectively. Naseri *et al.* demonstrated catalytic adsorptive stripping voltammetry [146] and stripping voltammetry [147] in an electrochemical micro-flow cell. Bismuth-film working electrode detected Ni (II) by square wave adsorptive stripping voltammetry in disposable CE microfluidic device [148].

2.4. Conductimetric and Potentiometric Detection

Microfluidic devices with electrochemical detection have been mainly based on the amperometric mode because of its high sensitivity and simplicity of integration with the microfluidic device. This approach is, however, limited to the detection of electrochemical active species and therefore has limited applications. Conductimetry and potentiometry are good complementary approaches since they are more universal for ionic species [149-151].

In conductimetric detection, differences in the conductivity or impedance of analyte zones and the background electrolyte are measured when they flow through the detector fabricated on microfluidic devices. This is a universal detection approach, applicable to all charged species, that has been applied in CE on microfluidic device in either the galvanic [152-154] or the contactless mode [155, 156]. Conductimetric detection has been used in the analysis of metals ions, amino acids, protein and DNA. In conductimetric detection systems, usually background electrolytes exhibit a comparatively lower specific conductance from those of the analyte ions. However, high concentration of background

electrolytes is necessary to reduce electrodispersion effect in CE chip. Background electrolyte suppressor technique prior to detection can enhance signal-to-noise ratio. However, it is difficult to miniaturise the suppressor in CE-EC systems. Conductivity detection method work best for small, mainly inorganic ions with high mobility. Contact conductivity and contactless conductivity are the two main approaches of the conductivity detection (CD) mode. In the contact conductivity that is also known as galvanic mode, a pair of sputtered or platinum wire electrodes is placed in the channel as the detector. Contactless detection is preferred to galvanic detection for several reasons including obviation of gas bubbles and fouling of electrodes, effective isolation from high electric separation fields and easier alignment of electrodes and detector. Contactless conductivity, which is also known as capacitive coupled contactless conductivity detection (C^4D), has experienced a rapid attention in recent years. The detector is placed outside or close to the channel instead of inside which makes the alignment of the electrodes much easier. No contact between the electrodes and the buffer in the channel, thus no gas bubbles are formed at the electrodes and no fouling of the electrodes. This mode can especially isolate the separation high voltage electric field from the detector. In CE microfluidic device, capacitatively coupled contactless conductivity detection mode enhanced detection limit down to ppb level [157]. A review on contactless conductivity in CE can be found in reference [158, 159]. Kuban *et al.* [160] found that the sensitivity of detection can be improved by applying lower frequency, high excitation voltage, and widen gap between electrodes to get lower stray capacitance. Hoffmann *et al.* reported high sensitive DNA detection by capacitively coupled contactless conductivity measurement in CE microfluidic device [161]. CE chip was fabricated and characterized by several polymeric substrate, such as PMMA, polystyrene, polycarbonate, cycloolefine copolymer, polyether ether ketone (PEEK) [161, 162]. Recently, several review articles were published concerning different aspects of capillary electrophoresis with the contactless conductivity detection [163-164].

Wang [166] used a combination of conductivity and amperometric detection on a single microfluidic device for the simultaneously determination of both ionic explosives and electroactive nitroaromatic species. This group has also designed a new injection layout to achieve simultaneous measurements of anions and cations on a PMMA microfluidic device [167]. In order to understand the separation process, Wang *et al.* [168] created a movable detection system by placing the detector at different points along the micro channel; and this design allowed the optimisation for the detection of low-energy ionic explosives as well as nerve agent degradation products. Recently, Vázquez integrated dual contactless conductivity and end-channel amperometric detection on PDMS/glass CE microfluidic device [169]. Laugere *et al.* [170] proposed a four-electrode contactless conductivity detector for CE microdevices. This configuration was found to be more sensitive in detection in varying conductivity of background electrolyte without the need for adjustment of the detection frequency. Generally, when buffer is changed, there is a need to readjust the measurement frequency to get optimal sensitivity, linearity and accuracy. An LOD of around 5 μM was obtained for potassium.

Recently, Kuban used external contactless conductivity detector in CE chip [171]. Two copper electrodes were placed in anti-parallel position and the gap between the electrodes was 0.5 mm. A Faraday shield was placed between the two copper electrodes to reduce direct capacitive coupling between the electrodes.

Contactless conductivity detection on chip has also been used to determine aliphatic amines in nonaqueous background electrolytes that are UV absorbable [172]. Acidic background electrolyte increases the sensitivity and the detection of limit in the order of 1 mM [173]. Tanyanyiwa [174] developed capacitively coupled contactless conductivity detector to measure heavy metal ions with detection limits of 2.1, 2.8, and 6.8 μM for Mn^{2+} , Zn^{2+} , and Cr^{3+} , respectively. Citric and lactic acids in food and beverage and three antiinflammatory nonsteroid drugs have been also analysed with good results. Contactless conductivity detection on a PMMA microfluidic chip was used to determine underivatized anionic sulfonates, carboxylates and artificial sweeteners, and cationic dopamine, ephedrine and metanephrine [175]. Amino acids and sugars were measured in a glass micro channel because the poor chemical resistance of PMMA chips under strong alkaline conditions. The detection limits for the species examined are in the range of 1 to 30 μM [175]. The sensitivity of contactless conductivity detection mode for bio molecules, such as amino acids, peptides and proteins, depends on the background electrolyte and the pH range [176]. Recently we have seen contactless conductivity detection of chlorhexidine digluconate [177], polyhexamethylene biguanide [177], salbutamol [178], and tobramycin [179]. Tuma *et al.* [180, 181] reported contactless conductivity detection (C^4D) systems for free amino acids in the amniotic fluid. The background electrolyte was consisted of 1.7 M acetic acid and 0.1% hydroxyethyl-cellulose (pH 2.15) and the LOD values were between 1.5 μM (arginine) and 6.7 μM (aspartic acid). Electrophoretic separation of phenolic acids (derivatives of benzoic and cinnamic acids) was measured with contactless conductometric detection in less than 6 mins [182]. Cu wire acts as a shield for the indirect conductometric measurements and the LOD was recorded 2.3 μM to 3.3 μM . External contactless conductivity detector in CE chip is quite popular for the detection of biochemical species, such as amino acids, peptide, proteins, immunoglobulin and DNA [171], inorganic ions [183], small amines [184], vitamin C [185], benzoate [185], sorbate [185]. Other applications, such as enzymatic assay of organophosphate nerve agents [186], nitrogen mustard degradation products [187], lithium in whole blood [188] and basic drugs [189] have been released recently on microfluidic devices with conductimetric detection.

Conductivity detection undertaken by direct current is termed as potential gradient detection (PGD) [190]. The technique is based on the measurement of variations of electric field strength between zone boundaries during electrophoresis [191]. The difference in mobility of ions due to different charges produces various migration zones and is detectable by PGD. Feng [192] separated three metals in 1 min with plate numbers of 60400 plates/m, 64150 plates/m and 77700 plates/m for K^+ , Na^+ and Li^+ , respectively; this is competitive with conductivity detection on a microfluidic device [193]. Determination of alkaloids, strychnine and

brucine in nonaqueous CE is applicable as well in Feng's work [192]. A novel potential gradient detection system coupled with a portable CE chip separated DNA fragments in polymer solution [194]. Feng *et al.* [195] also applied PGD to non-UV active compounds detection. This group also detected native neomycin components in a portable CE chip without any derivatization step [196]. CE coupled with potential gradient detection method separated and detected enoxacin, ofloxacin, fleroxacin, and pazufloxacin in 2.8 min with the detection limit of 23 to 65 ng/mL [197].

In CE microfluidic device, potentiometric detection is less widely used than amperometric and conductivity detection but is a useful alternative for non-electroactive ions. Potentiometry is based on ion-selective electrodes coated by semi-permeable membranes that allow access to specific ions and produce a potential signal that can be related to the ion concentration described by the Nernst equation [198, 199]. Chloride ion-selective electrode (ISE) potentiometrically analysed liquid food samples near and below the lower end of the linear (Nernstian) response region without any pretreatment [200]. Water-soluble anionic, cationic and non-ionic surfactants generate pore in the molecular sieves and modify surfactant sensors for the potentiometric detection [201, 202]. A novel potentiometric chip sensor for Ba^{2+} ions based on a solvent polymeric membrane has been designed to overcome technical problems of ruggedness for industrial processes [203]. This mode has been rarely coupled with a microfluidic device since ion-selective electrodes are not typically used in the detection of multiple species simultaneously. Sekula *et al.* [204] used conductive rubber phase coated ion-selective electrodes for potentiometric detection of organic amines, drugs, and biogenic amines. The semi-permeable coating was constructed by potassium tetrakis(p-chlorophenyl) borate (TCPB), bis(2-ethylhexyl) sebacate (DOS), and high molecular mass poly(vinyl chloride) (PVC). Non-nernstian $\text{SmFeO}_3\text{Pt}/\text{YSZ}/\text{Pt}$ sensor potentiometrically detected volatile organic compound (VOCs) in CE chip [205]. A potentiometric approach has some advantages for CE based microfluidic device including no requirement for electrical decoupling and simplification of fabrication of the detector. The latter often arises from the independent nature of the detector signal and the geometrical size of the electrode.

2.5. New Detection Schemes

Klett *et al.* [206] developed a potentiostatless detection scheme for CE by using two gold microband electrodes which were positioned 10 μm apart and 50 μm out of the capillary tip. The potential difference (ΔE) and current between these two electrode were recorded when the CE separation high voltage was applied. High voltage induced ΔE is found a function of the applied separation high voltage and that the current between the electrodes depends on the CE voltage and concentration of a redox couple $\text{Fe}(\text{CN})_6^{3-} / \text{Fe}(\text{CN})_6^{4-}$ which is similar to that in three-electrode potentiostatic setup. This approach can minimize the whole instrument size for amperometric detection and is of great potential for application in portable CE microfluidic devices.

Xu *et al.* [98] found that non-electroactive species can be determined by indirect amperometry through a single carbon fiber electrode which was aligned in the end part of a micro-channel (Fig. 3b). The potential difference induced by the CE separation electric field between the WE and the RE brings about the change of the reduction potential of dissolved oxygen, which can be used as an electroactive indicator to determine non-electroactive analytes. This mode takes the advantage that the adverse effect of separation electric field on detector can be turned into a universal analytical method and decoupling between CE and electrochemical detector is unnecessary.

3. FABRICATION OF POLYMER MICROFLUIDIC DEVICES:

Microfluidic device systems have followed developments in micro electromechanical systems (MEMS) which have wide applications in a variety of sectors. Many of the processes used in the semiconductor industry are widely applicable for lab-on-a-chip developments. A variety of substrates, including glass, polymers and silicon, are used for the development of microfluidic device systems. Glass substrates have the advantage of transparency to visible light wavelengths, no fluorescence and good chemical stability. Microfluidic devices based on glass are difficult to manufacture in large volumes and therefore are expensive. In recent years, polymers and plastics substrates have become more popular materials for microfluidic devices because of their low cost, relatively simple fabrication process [207], potential of disposable use, ease for high replication and availability of a wide variety of materials with different physical and chemical properties.

Replication and direct writing are two major approaches to fabricate polymer devices in μ TAS (Micro Total Analytical Systems). Replication methods using polymer substrate often use a moulding master. Metals and alloys are the most commonly used materials for the manufacture of micro moulding master [208]. Because of good mechanical properties such as high strength, hardness and durability, metal withstands the sheer force in the moulding process. Silicon is also used as a mould material and has the advantage of allowing fine feature replication [209]. The success in the replication technology mainly depends on the mould structure and surface property of the mould. The key factors include, surface roughness of the mould and the ability to separate the mould from melted substrate.

Several methods are employed for fabrication of master moulds, these include:

- Electroforming mainly (LIGA) based (lithography, electroplating, molding) technologies (LIGA, UV-LIGA, IB-LIGA, EB-LIGA);
- Mechanical techniques such as CNC (Computer Numerical Control) milling, micro electrical discharge machining (μ EDM), micro mechanical milling and electrochemical machining (ECM) using ultra-short pulses
- Excimer and ultra-short pulse laser ablation
- Silicon wet etching
- Reactive ion etching

Mechanical techniques such as CNC micro milling machine offer long master lifetimes with good geometrical definition at reasonable cost [210]. CNC milling is ideal for the large features (above 100 μ m) and has tolerances around 10 μ m [211, 212]. CNC milling can be limited when there is requirement for highly complex and fine feature fluidic architectures. Aluminium and stainless steel are the most popular materials for the CNC milling mould [213]. Micro electro discharge machining (μ EDM) offers the fabrication of quasi three-dimensional structures in conducting materials [214, 215]. The protocol offers high degree of flexibility in terms of substrate and geometries, but the mould surface is comparatively rough. Considering current micromachining techniques and suitable thermal properties, silicon is a good material for the casting and embossing mould. Wet etching process combined with the lithography process offer a low and high aspect ratio structures. In hot embossing, a silicon mould significantly reduces the fabrication time compared to a metal mould. Non-rectangular shape in the microstructure is the only drawback in the easy process. Deep reactive ion etching (DRIE) offers better high aspect ratio structure with vertical walls [216, 217]. Fast reactive ion etching causes high surface roughness and poor de-embossing characteristics.

Conventional lithography combined with electroplating offers very small and complex structures in the replication technology [218-220]. In the lithography process, a photoresist coated substrate with a conducting electroplating seed layer is exposed to the light and consequently developed. The developing process removes the photoresist from the expected electroplated area. The substrate is later placed in the galvanic bath for the electroplating. Migration of ions between the bath and the conducting seed layer, allows metal growth in the resist free area. The thickness of the electroplated layer is dependent on the applied current, charge, mass, density of the bath, temperature and pH. Considering Faraday's Law,

$$x = \frac{1}{\rho} \frac{m}{q} \frac{1}{A} t \quad (1)$$

Where x is the film height, ρ is the density of nickel, I is the plating current, A is the surface area plated, t is the applied time and m and q are the mass and charge of one mole of metal. Nickel is a popular metal for electroplating since it can provide a very smooth with good surface chemistry. A LIGA based mould can be used for more than 1000 cycles with the negligible surface roughness (<10 nm)[221]. In LIGA, poor adhesion to the substrate seed layer and non uniform deposition are the two main issues for consideration. X-ray LIGA also offers very small, complex features with very high aspect ratio structure [222-224].

Polymers can be used as alternative moulds materials and have the advantage of reduction of cost, complexity and fabrication time. Casted PDMS polymer is alternative mould material for the hot embossing and soft lithography process [225]. PDMS is thermally stable and inactive substrate at the 200°C processing temperature, offering a soft mould for the soft embossing process. The operating parameter for the soft embossing is almost identical of hot embossing, except the applied force. Usually very weak force (50 N) force is ap-

plied in the soft embossing process [226]. Double casted PDMS layer much more stable at the elevated high temperature. Introduction of various polymers such as polyurethanes, epoxies and Teflon increase the thermal stability of the PDMS layer. Negative photoresist SU-8 has been reported as an injection mould and replication parts in polycarbonate and polypropylene [227, 228]. In de-embossing process, the poor adhesion of SU-8 to the base substrate causes very shorter life line. Micro contact printing [229], hot imprinting [230], X-ray lithography [231, 232] and ion beam lithography [233] are becoming more popular with an increasing demand for polymer micro fluidic devices.

Casting which is also known as soft lithography is a suite of non-photolithographic methods for replicating a negative master [234]. Because of the materials properties, process simplicity, replication accuracy and wide application, casting is one the most popular methods for relatively low volume replication. The polymeric microstructure offers good optical properties with high transparency and is applicable for biological systems. In the soft lithographic methods, a mixture of base elastomer and its curing agent are spread eventually over the mould microstructures. Addition of curing agent, a three dimensional bands are formed in the base elastomer [235, 236]. Vacuum desiccators with low vacuum (25-28 in mmHg) are sufficient for degassing and removal of air bubbles. The curing can take place at room temperature or at the elevated temperature. The curing time is directly related to the applied temperature. The temperature and the ratio of the curing agent determine the stiffness of the elastomeric layer. After curing, the soft/rigid elastomeric layer can simply be peeled away from the mould. The soft lithography process offers high replication accuracy at the ambient laboratory condition. Usual clean room environment facility is not essential for the casting process. Reservoir and detection holes can be punched or drilled into the cured materials. The cured materials have excellent adhesion property, which allows a wide choice of bond strength. Plasma treatment of the PDMS elastomer offers permanent bond between two PDMS layers which leads to layer-by-layer construction process. Casting process offers highly complex three-dimensional mixers, flexible valves and pumps within microfluidic channels which enables cell culturing and protein crystallization integrated on microfluidic devices [237-239]. Recently, soft lithography process developed thermo set polymer devices with stable surface properties and good chemical compatibility [240]. Addition of active electronic components into base elastomer and curing agent alters the physical and chemical properties of polymers. Compared to other replication methods, casting has the advantage of easily obtaining high aspect ratio or 3D channels [241-245]. This is especially true for elastomers though it suffers from longer curing time and low mass-yield. A simplified casting method has been developed to produce PMMA channel without specialized instruments [246]. A pre-polymer solution is cast against a silicon master and then polymerised under UV, akin to fast prototyping of PDMS devices [247].

Hot embossing is a popular approach for the fabrication of polymeric microstructure [216, 236]. In the hot embossing process, the polymer wafer and the master structure are heated above the glass transition temperature and a controlled force is applied under vacuum. The assembly is

cooled gradually below the glass transition temperature with the applied force and vacuum for the demoulding. The success of the replication process depends on uniform temperature distribution, high vacuum and good surface quality of the mould. In hot embossing, cycle time plays an important role for the mass production of the polymeric microstructure. Typically, the cycle time is 4 to 15 mins for a 4 inch/8 inch wafer. The large thermal mass of the insert mould causes the long cycle time for the embossing process [248]. In the recent years, a number of different mould heating methods have been developed including hot gas heating [249], optical heating [250], infrared radiation (IR) [249] and ultrasonic heating [251] for shorter cycle time. A mould with low thermal inertia (LTI) is capable of rapid thermal response in a fraction of seconds and reduces dramatically the cycle time [252].

Nowadays, the low aspect ratio microstructure and rapid production microthermoforming are quite popular [253]. Hot embossing equipment can perform the microthermoforming with negative mould and counter plate. The counter plate is integrated with vacuum and pressure ports. A thin polymer foil is clamped and heated in the mould. Above the glass transition temperature, the elastic film is stretched by a compressed gas pressure and replicates the mould structure [254]. Compared to the hot embossing, the replication accuracy is limited with low aspect ratio structure [255].

Injection moulding is widely used for high polymer fabrication and has the advantage of very short cycle time, which enables a high volume manufacture at low cost [256]. The dried polymer materials are introduced into a hopper and screws are used to transport the polymer from the hopper to the moulding tool. In this section, because of high temperature, the polymer melts and exhibits a pseudo-plastic behaviour [257]. Melted polymer is then injected under high temperature and pressure into the micro structured mould. The liquid polymer flows within the complex microstructure of the mould. For a good aspect ratio structure, a holding time and pressure is applied. In the demoulding process, the mould and the substrate cool together. A good replication of the mould is dependent on, mould temperature, injection speed, injection pressure, holding time and pressure [258]. The injection speed and pressure favour the degradation of the thermoplastic polymer. Microinjection moulding techniques offer high aspect ratio structure but suffers from the requirement of a mechanically complicated moulding tool.

Injection compression moulding process offers compact disc (CD)-based fluidic platform with high aspect ratio in shorter cycle time [259]. This process is a combination of injection moulding and hot embossing within the compression process. In this process, the melted polymer is injected in the flat cavity mould with a piston for compact thin polymer devices. The drawback to this approach is that it is only applicable for very thin micro fluidic devices.

Direct techniques allow rapid fabrication of single microfluidic devices without the need for fabrication of a master mould. This process is fast for the prototyping of single microfluidic device, allowing a wide variety of design alternatives to be considered. The approach is, however, less amenable for mass production since it can be time consuming.

Photolithography is a popular approach for microfluidic device fabrication. Computer aided design (CAD) programmes such as Macromedia Freehand or Autodesk AutoCAD can be used for the design of the mask. In recent years there has been increasing interest in the use of a thick SU-8 photoresist for polymer fabrication [260]. EPON SU-8 is a negative tone epoxy patternable resist that is mechanically reliable, optically transparent, chemically resistant and hydrophilic. The thickness of the photo resist changes with the spin coating speed and spin time [228]. A thicker photoresist can offer a good structural height for devices. Initially the base substrate is coated with the photoresist and exposed to light, typically g or i-line, through a photo mask [261]. Development of the photoresist thus leads to the three dimensional micro channels. The oligomers in SU-8 photoresist have high density of epoxy-groups that can form tightly cross-linked structure during curing [262, 263].

Recently, direct lithography followed by deep plasma etching of polymer has been reported for the fabrication of polymer based microfluidic devices [264, 265]. Instead of a stencil mask, structured photoresist is used as a mask for the activated plasma to etch the polymer substrate in the plasma-exposed region [265]. The implementation of this method overcomes essential requirements of mould fabrication and simultaneously offers surface modification of the microfluidic channel. Anisotropic plasma etching alters the physical property of the microfluidic channels, in terms of surface roughness and the hydrophobic/hydrophilic nature of the surface. Hydrogels are photostructurable polymers that can show significant volume change depending on the polarity of the solvent or the pH environment [266]. Hydrogel and other photosensitive pre-polymer mixture can thus be used to create micro channel structure in the presence of controlled exposed light [267]. In the lithography process, unexposed or un-reacted pre-polymers remain in liquid form and easy to be removed. Gelatine is a popular as sacrificial materials to form hydrogel micro fluidic network [268].

Laser based technologies for microfabrication involves the use of UV laser pulses that are absorbed by the polymer, leading to bond breaking by either thermal degradation or photo degradation [269]. The micro channel depth depends on the absorption depth of the polymer, heat of vaporization of the work material, laser wavelength and the laser pulse duration [270]. The geometry of the microstructure was realised by using a mask or moving the substrate base controlled from a CAD file. Usually a deep UV (< 480 nm) is utilized to ablate polymers. Shorter wavelength Excimer lasers, offer higher precision of features. It is relatively easy to produce channels in a wide variety of commercial polymers such as polycarbonate (PC), Poly methyl methacrylate (PMMA), polystyrene (PS), Polyethylene terephthalate (PET) and poly tetrafluoroethylene (PTFE) [271]. The interaction between the laser light and polymer materials alter the hydrophilic/hydrophobic nature of polymer surface which can be of benefit for electro osmotic flow. A potential drawback is a higher surface roughness than alternative approaches.

Stereolithography allows a real three-dimensional micro fabrication process. In this process a light sensitive liquid polymer is used with two high intensity light beams. The light beams penetrate through the liquid resin and cross link-

ing polymerization only occurs at the point where the two light beams meet. Usually the laser focuses and scans in the X-Y direction, and the resin container moves in Z direction. The height of the structure is determined by the exposure length and dose. The main advantage of this technique is that it is relatively easy and fast for fabrication of a single chip. However, the process is time consuming and not amenable to high replication, additionally cross-linked polymers have a relatively high surface roughness.

Plasma etching is a relatively new approach for the fabrication of microfluidic devices [272, 273]. The plasma of a diluted gas contains highly reactive gas radicals. The chemically aggressive radicals can react preferentially with organic materials and generate reaction by-products, which are subsequently desorbed from the surface. Channels and even holes can be made by plasma etching with an appropriate mask. Recently, Gogolides *et al.* reported PMMA and PEEK fabrication technology using lithography and plasma etching [265, 274, 275]. Deep anisotropic O₂ plasma etching, controls micro channels roughness and emphasizes stable-in-time (non-ageing) super hydrophilic nature [265, 274]. Ion beam lithography is a powerful technique for manufacturing microstructures directly without a mask. In this technique, a small beam spot of megaelectronvolt (MeV) ions is scanned over the polymeric substrate and generate a latent image of the pattern. Gonin *et al.* [276] have used the technique to fabricate 3D PMMA micro channels. Recently Whitlow *et al.* [277] have used 56 MeV ¹⁴N³⁺ and a 3 MeV ⁴He²⁺ beams from K130 cyclotron and a 1.7 MeV Pelletron accelerators to fabricate microfluidic patterns on PMMA.

A wide variety of methods of devices bonding have been described, including thermal [278] and pressure bonding [279]. Common bonding methods for lidding of polymer channels include plasma [272, 247], glue [280-282], lamination [283-286], UV/ozone surface treatment [287], laser welding [288] and solvent bonding [289-296]. A successful bonding process is justified with preserved channel integrity, geometry and structure with high bonding strength. Detailed reviews of the approaches and issues for bonding have been described [269, 271].

3.1. Polymer Properties for Lab-on-a-Chip Development

The use of polymers as substrates for separation devices requires some consideration of their chemical and physical properties. The polymer channel must have chemical resistance to both the analytes and the running buffer. Becker *et al.* [269] has listed the chemical resistance features of several common polymers to different chemicals such as bases, acids and organic solvents. Polystyrene and polyvinylchloride can resist strong acids, bases and alcohols. PMMA, PC and polyester are not stable in strong bases or ketones and esters. These polymers are available for use in CE analysis when a limited pH range, around neutral, can be employed. Lee *et al.* [297] studied solvent compatibility in PDMS microfluidic devices. Other physical characters such as thermal conductivity, dielectric strength of polymers are also included in Becker's paper [269]. Good thermal conductivity enables better Joule heat dissipation and thus higher separation voltage can be applied which in turn leads to a higher number of plates. The dielectric strength properties of the polymer determines the voltage that can be applied across an insulator

before breakdown occurs. Polyethylene has the highest dielectric strength and thermal conductivity amongst commonly used polymers. Recently, Shadpour *et al.* [298] compared physicochemical properties of various polymers.

Understanding of the zeta potential or surface charge of polymers is important for the EOF in the channel [299]. Kirby *et al.* [300] proposed the use of pC (the negative logarithm of the counter ion concentration) as a useful normalization for the zeta potential (ξ) on polymer substrates in contact with univalent counterions (e.g. sodium, potassium). At high pH, PDMS, polycarbonate and poly(ethylene terephthalate)/poly(ethylene terephthalate glycol) (PETG) have ζ/pC in the range of -30 to -35 mV. In the case of poly(tetrafluoroethylene), PE, PVC and PS, the ζ/pC value are in the range of -20 to -25 mV for high pH. As a comparison, the ζ/pC value at high pH for silica is -50 mV. The higher the absolute value of ζ/pC is, the larger the ζ will be. This can be used to predict ζ potential of polymers and thus EOF.

The surface charge density and the EOF are greatly determined by the polymer material, surface treatment or modification methods and even the fabrication route. For example, PMMA channels from laser ablation have higher EOF than that from hot embossing because reactive carboxylate species are incorporated into the surface during the ablation process [301]. Pugmire *et al.* [302] found that microfluidic devices fabricated by laser ablation under different atmospheres show different surface properties. PETG, PVC and PC micro channels have been found to hold greater EOF and keep native chemical structures when the ablation atmosphere is oxygen rather than nitrogen or argon. In the case of PMMA, the ablation atmosphere was found to have no effect on its surface characteristic.

Most polymer substrates are hydrophobic and therefore have lower surface charge density, and consequently EOF, than that of glass and silica. A lower EOF will lead to lower efficiency because of longer migration time, and band broadening. Highly negatively charged glass channel walls do, however, have the disadvantage of adsorption of biological substances such as proteins, which results in peak tailing and highly asymmetric peaks [303]. Polymers have good biocompatibility but nonetheless in some situations adsorption of biological species on the polymer walls will lead to changes in the polarity and consequently change in the fluidic transport. Recently, Chen *et al.* [304] reviewed biocompatible polymer materials for the protein research. Much work on the surface modification of polymer microchannels has been developed and reviewed recently [305-308]. Environmentally sensitive polymers, also known as smart polymers, provide some interesting new properties that could be employed for bioassay in microfluidic devices [309].

Epoxy based microfluidic devices offer physical, chemical stability as well as biocompatibility [310]. SU-8 is epoxy based photoresist with high viscosity before curing and is inert to analytes after development. As is the case for a number of other thick photoresists, SU-8 is mechanically strong and optically transparent for wavelength above 350 nm [311, 312]. It does, however, suffer from a relatively high coefficient of thermal expansion that causes stress and fracture at elevated temperatures [313].

3.2. Surface Modification of Polymer Micro Channels

Surface modification mainly focuses on the improvement of electrophoretic separation by reducing the interactions between the analytes and channel wall, and the control of EOF, leading to a better peak shape, decreased analysis time and controlled EOF. The velocity (v) of the EOF depends on the dielectric constant (ϵ), viscosity (η) of the solution, applied electric field (E), and the zeta potential (ξ). The zeta potential value changes with the surface charge of the capillary (σ), pH of the buffer solution, counter-ion concentration and ionic strength, surface modifications, and the presence of adsorbed molecules [314]. Because of the lower surface charge densities and lower surface zeta potentials, EOF in polymeric devices is much lower than the glass-based fluidic chips. For the separation efficiency, polymeric microfluidic devices require some modification for higher surface zeta potentials. Adsorption of polyelectrolyte on the capillary surface provides non-uniform surface charge distribution. Recently, Danger *et al.* [315] reported non-uniform surface charge distribution and its effect on the EOF in CE microfluidic device. They also found that polyelectrolytes coated capillaries alter the magnitude and direction of the EOF and the hydrodynamic contribution to the total peak dispersion. For unmodified polymeric electrophoresis chip, pH is a dominant factor, this alters the charge of the channels surfaces and therefore the EOF [316, 317]. For unmodified polyethyleneterephthalat based microfluidic devices, electroosmotic flow changes from 1.71×10^{-4} to 4.35×10^{-4} $\text{cm}^2 \text{V}^{-1} \text{s}^{-1}$ over a pH range of 3 to 10 in a 50 mM phosphate buffer solution [318]. Besides this, the separation voltage, detection potential and injection time also hinder electro osmotic flow in CE chip [319].

Surface modification approaches are categorised according to the stability of the adsorbed layer, normally as described as dynamic, semi-permanent and permanent. Permanent modification involves the use of chemicals [320, 321], chemical reactions [322-325], physical treatment to polymer microfluidic devices such as by laser ablation [270, 302, 326] or plasma approach. The use of hybrid materials for the microfluidic device provide some interesting properties [327, 328]. A semi-permanent method involves the use of mixtures of double-chained, cationic (didodecyldimethylammonium bromide, DDAB) and zwitterionic surfactants (1, 2-dilauroyl-sn-phosphatidylcholine, DLPC) mixture which can provide a semi-permanent coat on the CE chip [329]. The surfactants require a conductive buffer which can lead Joule heating and the formation of bubbles [330-335]. The separation efficiency in capillary electrophoresis is strongly dependent on the Joule heating and heat distribution [336-344].

It is comparatively simple to control the EOF direction by dynamically modifying the channel surface with physically adsorbed chemicals, such as polyelectrolytes [320] and surfactants [321]. Two polyelectrolytes, poly(allylamine hydrochloride) and poly(styrene sulfonate) were alternatively coated to the surface of PS and PETG microfluidic devices [320]. Similar EOFs in PS or PETG microchannels have been obtained and the EOF direction can easily be controlled by the charge characteristic of the coating. Positively charged poly(allylamine hydrochloride) has also been used in a short PET microchannel to get a reversed EOF and

achieve the separation of three alkali cations, potassium, sodium and lithium [345]. EOF can be increased by adding the anionic surfactant sodium dodecyl sulfate in a running buffer. Anionic surfactant, poly(diallyldimethylammonium chloride) and montmorillonite coated fused-silica capillaries showed a highly stable μ EOF (run-to-run RSD less than 1.5%, $n = 20$) and high separation efficiency [346]. Similarly, polyanions of poly(acrylamide-co-2-acrylamido-2-methyl-1-propanesulfonate) (PAMAMPS) bi-layer reveal stable μ EOF ranges from -5×10^{-5} to $35 \times 10^{-5} \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ in the CE microfluidic device [347]. Cationic surfactant dimethyldioctadecylammonium bromide (DODAB) and polyoxyethylene (POE) stearate coated CE chip demonstrated a stable EOF and prevention of adsorption of basic and acidic proteins [348]. Usually in CE chip, the cationic surfactants are quaternary amines with anionic counter-ions (chloride or bromide) [349]. Decreased or even direction-reversed EOF can be achieved by using the cationic cetyltrimethylammonium bromide [321, 350]. Dou *et al.* [351] have enhanced the separation efficiency amino acids, carbohydrates and peptides separated by dynamically modified PDMS microchannels with 2-morpholinoethanesulfonic acid (MES). Their further work in modifying PDMS microchannels with non-ionic surfactant, Brij35, resulted in a hydrophilic surface and eliminated the adsorption of proteins on the PDMS surface [352]. In CE microfluidic device, 1-butyl-3-methylimidazolium dodecanesulfonate (BAS) [353] and 1-butyl-3-methylimidazolium tetrafluoroborate (BMImBF₄) [354] can act as supporting electrolyte as well as surface modifier and reduce protein adsorption within microfluidic devices. Dynamic coating of PDMS surface has been reviewed by Garcia *et al.* [117]. Tween 20 [355], phosphatidic acid (PA) [117], polyvinylpyrrolidone (PVP) [356] cetyltrimethylammonium bromide [355], n-dodecyl- β -D-maltoside [357], sodium dodecyl sulphate [358], didodecyldimethylammonium bromide [359], 1,2-di-lauroyl-sn-phosphatidylcholine [360], Triton X-100 [360] and palmityl sulfobetaine [361] have strong effect on the EOF. Sodium dodecyl sulphate is highly soluble in aqueous electrolytes easily adsorbed on the surface of the polymer and modifies μ EOF [300, 362, 363]. Garcia *et al.* compared the effect of SDS, DOC and PA on EOF and found that SDS coated polymeric microfluidic device provides the highest electroosmotic flow compared to DOC and PA [363]. Mixture of cetyltrimethylammonium bromide with sodium dodecyl sulphate alters the surface charge of PMMA substrate and suppresses protein adsorption [364]. Nonionic surfactant Pluronic F127 of very low concentrations interacts strongly with cyclic olefin copolymer and decreases the separation voltage with minimal Joule heating [365]. Modified surfaces of the microfluidic devices offer reduced migration time and increase peak skewness [366]. However, in the electrochemical detection systems, surfactants interact with the surface of the detection electrode and this facilitates the electron transfer process [367].

Physical treatments such as laser ablation to PMMA [301, 368], PETG, PVC and PC [302, 369], PS and PET [270], and oxygen plasma to PDMS [247] have been used to directly modify the channel surface. Sulphur dioxide plasma treatment introduces negative charge and modifies the inner surface of the PMMA micro channel and enhances EOF (~ 7

$\times 10^{-4} \text{ m}^2 \text{ V}^{-1} \text{ s}^{-1}$) over a wider pH range (4-10) [370]. Octafluoropropane (C₃F₈) and acrylic acid (AA) plasma have been shown to modify the EOF of PDMS microfluidic devices [371]. Argon plasma pre-treatment improves adhesion of the fluorocarbon (FC) and AA films in the modification process [371]. Polymerization of methyl methacrylate monomer (MMA) with modifying monomer molecules (methacrylic acid (MAA), 2-sulfoethyl methacrylate (2-SEMA), 2-aminoethyl methacrylate (2-AEMA)) changes the surface property of the acrylate layer [372]. The monomer is UV-initiated and polymerisation occurs at the atmospheric-pressure. Narrow band 254 nm excimer laser radiation increases the wet ability of the casted PDMS surface [373]. Water-plasma hydroxylation and UV-initiated photochemical reaction between PMMA and 1,1-bromoundecyltrichlorosilane improve EOF for PMMA channels [374]. Covalent immobilization of poly(ethyleneimine) onto PMMA substrates changes the direction of the electroosmotic flow [375]. UV irradiation forms a layer of carboxylic acid on the surface of the PDMS layer and increases electroosmotic flow [376, 377]. PDMS substrate can be modified with the conventional plasma treatment, but the oxide surface life time is very short and reverts to its hydrophobic nature. Extraction of unreacted monomer by a series of organic solvents can increase the EOF and the lifetime of the modified layer [378]. These treatments can improve surface charge density and thus EOF due to increased surface silanols and carboxylic acids. Svato group copolymerized methyl methacrylate with anionic and cationic alkyl methacrylate monomers, such as methacrylic acid, 2-sulfoethyl methacrylate, and 3-(N,N-dimethylaminopropyl)methacrylate (DMAPMA) for the protein analysis [379].

Permanently modifying glass channel surfaces mainly originates from silanization chemistry. A variety of robust approaches are used for permanent modification of polymer surface. As for polymer microfluidic devices, the method of surface treatment depends on the polymer materials. Many reports have been concentrated on formation of a layer of polymer coating [322-325, 380] or a monolithic as a sieving material [105] through ultraviolet graft reactions [381, 382].

PMMA surface was modified to be amine-terminated by using an aminolysis reaction where the surface methyl ester groups are coupled with a monoanion of α, ω -diaminoalkanes [322]. The modification resulted in a reversed EOF. Further reaction with n-octadecane-1-isocyanate enabled the polymer channel to perform reverse-phase separation of ion-paired double stranded DNA with better resolution. Brown *et al.* [383] examined different surface modifications techniques for the poly (methylmethacrylate) microfluidic devices. Wang *et al.* [382] added a chain-modifier monomer, methacrylic acid, 2-sulfoethyl methacrylate or 2-aminoethyl methacrylate (AEMA) to solution during copolymerization fabrication process. The EOF increases twice in 6% MAA-modified PMMA chips than native ones and is very stable and reproducible. A reversed EOF can be obtained through 3% 2-AEMA modification. Qu *et al.* [384] introduced silane functional groups (Si(OCH₃)₃) during craft copolymerization for fabrication of PMMA. A modified surface for protein analysis was obtained through silica sol-gel entrapped enzyme immobilization. Amphiphilic phospholipid copolymer of 2-methacryloyloxyethyl phos-

phorylcholine and re-butyl methacrylate (PMB) introduce the phosphorylcholine functional groups onto the PMMA surface [385]. The PMB-modified PMMA microfluidic devices exhibited more stable electroosmotic mobility compared with the untreated one.

PDMS surface was modified to be highly hydrophilic through ultraviolet graft polymerization with acrylic acid, acrylamide, dimedylactylamide, 2-hydroxyethyl acrylate, or PEG monomethoxyl acrylate [324, 386, 387]. Hu *et al.* [323] have also developed cross-linked coatings on the surface of PDMS by UV polymerization and obtained high separation efficiency for five peptides with theoretical plates up to 18600 /2.5cm. Their further work found that pre-treatment with a photoinitiator, benzophenone to the surface of PDMS micro channels, the rate of graft polymerization of monomers such as acrylic acid, poly(ethylene glycol) monomethoxyl acrylate, or poly(ethylene glycol)diacrylate at the surface was greatly accelerated [325]. A stable EOF was obtained and a better resolution for the separation of two fluorescein labelled peptides was achieved. Chemical vapour deposition of reactive gases on PDMS and followed by chemical reaction on the surface altered the physical and chemical properties of PDMS (388). Chen *et al.* reported chemical vapour deposition of poly (p-xylylene) [389], poly (4-aminomethyl-p-xylylene-co-p-xylylene) and poly (4-formyl-p-xylylene-co-p-xylylene) [390] on PDMS substrate. Xiao *et al.* reported a new atom-transfer radical polymerization to modify PDMS channels with a layer of covalently bonded polyacrylamide [391]. Lui *et al.* [392] employed surface initiated atom transfer radical polymerization (SI-ATRP) reaction for the PMMA surface modification. A PEG-functionalized monomer, PEG methyl ether methacrylate (PEGMEMA) was polymerized on the surface of PMMA in the SI-ATRP process. Lately, Sun *et al.* explored a similar process to grow a PEG-functionalized layer on poly(glycidyl methacrylate)-co-(methyl methacrylate) (PGMAMMA) micro channel surfaces using the SI-ATRP method [393]. Xiao *et al.* carried out SI-ATRP to graft a thin polyacrylamide layer inside the PDMS micro channel [391]. Recently, a new technique known as in-channel ATRP (atom transfer radical polymerization) to modify surface of the micro channel surface [394]. The modified microchannel surface exhibits low, pH-stable EOF and very much low protein adsorption with high efficiencies. A UV treatment of cyclic olefin copolymer (COC) and polycarbonate fluidic chips reduce the contact angle of water [395]. In UV treated microfluidic devices, lysozyme and cytochrome c were well separated within 35 s. Efimenko *et al.* [396] reported that UV treated PDMS in the presence of oxygen enhances the surface charge energies from 26 mJ/m² to 72mJ/m². Roman *et al.* [397] developed a sol-gel method to improve the hydrophilic of PDMS by homogeneously distribution of SiO₂ particles on it. Homogeneously distributed SiO₂ (~10 nm in diameter) within the PDMS polymer matrix by sol-gel method altered water contact angle from ~108.5° to ~90.2°. This also resulted in a surface with no adsorption of rhodamine B and doubling of EOF from the native PDMS. Wu *et al.* [398] treated PDMS surface with oxygen plasma and then coated with multilayer poly (vinylalcohol) (PVA) under high temperature. Lysozyme, ribonuclease B, bovine serum albumin, P-lactoglobulin and fragments of dsDNA have been

separated and detected in the PVA modified microchannels with the plates more than 1,000,000/m. *In situ* surface-initiated polymerization process were shown to produce super hydrophobic PDMS surfaces with a contact angle of water at 155° [399].

Metal and metal oxide coating on the microfluidic devices can effectively tailor the surface energy of polymer surface. Sputter-coated titanium dioxide (TiO₂) on PDMS substrate decreased water contact angle from 105° to 25° [400]. The coating materials are transparent but metal cracking results in the change of the surface properties. Sputtered gold (< 1.0 nm) on PDMS surface decreased water contact angle to 25° without cracking [401]. Sputtered SiO₂ thin film on COC surface offers high optical transmission properties with high solvent resistivity [402]. *In situ* fabrication of gold nanoparticles on PDMS substrate can alter the physical and chemical properties of PDMS substrate [403]. Activated PDMS surface with an Ar plasma followed by sputter coated aluminium film (44 nm thick) prolonged hydrophilicity up to 30 days [404]. Metallic nanoparticles functionalized with chemical and biological surface coatings offers stable EOF with enzyme reactors, immunoassays and other biochemical analysis on microfluidic device [405, 406]. Immobilization of poly(diallyldimethylammonium chloride) and TiO₂ nanoparticles on PDMS surface through layer-by-layer assembly technique favours the separation of biomolecules (Arginine, phenylalanine, serine and threonine) [407]. A detailed review of PDMS surface modification methods for the microfluidic device application has been carried out by Zhou *et al.* [408].

Base hydrolysis of hot or wire embossed fabricated PETG channels can yield carboxylic acids and alcohol groups on the surface where amine or fluorescent groups can be integrated through further coupling reactions [230]. An improved EOF was obtained. Permanently modified polycarbonate surface has been studied through chemical reaction with poly (vinyl alcohol) or polyethylenimine during injection moulding when the plastic melts [409].

Electrophoresis separation in channels with a sieving matrix formed from photo initiated polymerization reactions has attracted more attention because of the high efficiency in DNA analysis and protein mapping [381]. Recently, Liu *et al.* reviewed permanent surface modification techniques for the protein analysis [410, 411]. Lai *et al.* [328] have developed resin-gas injection technology for bonding and surface modification of polymer microfluidic devices. A layer of dry monolithic stationary hydrogel was formed on the walls of a PMMA microfluidic device, serving as a sieving material for electrophoresis separation of DNA fragments. Local modification of the channel surface with the help of masking during UV exposure is another highlight of this work. Porous polymer monoliths have been formed on the plastic surface through a photo graft reaction followed by UV-initiated *in situ* polymerization [412]. Adhesion of the monoliths on cyclic olefin copolymer tubes or polypropylene micro channels was dramatically enhanced.

Hybrid materials have often been used to construct a microfluidic device [413-415]. As an example PDMS with glass has the advantages of fast and inexpensive prototyping of a microstructure on polymer material and enhanced EOF

because the glass surface holds more negative charges and thus improves EOF for the whole channel. Polymerization of butyl methacrylate (BMA) and poly(ethylene glycol) methyl ether methacrylate (PEGMA) introduced a PEG layer on the PMMA microchannel surfaces and reduced protein absorption [416]. Absorbed Teflon solution on a PDMS microfluidic channel increased the hydrophobicity of the channel outlet and generate hydrodynamic droplet for bioanalytical analysis [417]. Epoxy polymerisation and followed by aminopropyl silanization of the PDMS polymeric channels resisted nonspecific protein adsorption [418]. Grafted perfluorooctyltriethoxysilane onto oxidized PDMS substrate forms fluorinated micro channel and separate fluorescein-tagged proteins [419].

A microfluidic channel outlet has been recently used to generate separation efficiency in hybrid channels. However, it was limited by the nonuniformity of the surface charge density due to different materials, and increased dispersion caused peak broadening and tailing [420]. Chen *et al.* [327] have reported a solution to nonhomogeneous electroosmotic flow in PDMS/glass microchannel. The channel surface was dynamically modified with a stable poly(dimethylacrylamide) coating on both the PDMS and glass surfaces. Improved hydrophilicity on the PDMS surface was observed and the separation of flavin adenine dinucleotide (FAD) and fluorescein with a high efficiency of 105,000 plates /m was obtained. Zangmeister [421] reported an approach to spatially immobilize DNA-containing polyacrylamide hydrogels in a PMMA/PC hybrid microchannel. A 3D DNA selective separation matrix was created by ultraviolet/ozone photopolymerization. The lifetime of the gel plugs increased nearly 2.5 times over unmodified channels. Poly (ethylene-oxide) (PEO) has been used to coat PMMA channels to minimize the interaction of DNA with the polymer surface. Besides this, 2-hydroxyethyl cellulose, hydroxypropyl cellulose and polyvinyl pyrrolidone are also popular for PMMA surface coating [422]. Recently Munk *et al.* [423] reviewed approaches to chemically modify poly(methyl methacrylate), poly(dimethylsiloxane), polycarbonate and cyclic olefin polymeric chips. β -galactosidase (lactase) covalently attaches polyethylene films and dramatically changes the surface property [424]. Bioactive compounds covalently bond to the polymer surface and change the physical and chemical properties of the surfaces. Wet chemical [383, 424, 425], organosilanization [374], ionized gas treatment [378] and UV irradiation [324, 373] are the most popular techniques for the attachment of bioactive compounds on the functionalized polymer surface. Goddard *et al.* [426] recently reviewed covalent attachment of the bioactive compounds.

4. INTERGATION AND APPLICATION

Efforts in integrating micro devices have focused on miniaturizing the high voltage power supply or detector, improving the degree of automation in sample introduction [427], enhancing the throughputs and development of a standard interface for microfluidic devices [428]. The development of low cost electrodes in micro devices is particularly important for electrochemical detection. Here we mainly focus on the electrode fabrication approaches and the miniaturization of power supply for microfluidic device.

4.1. Electrode Fabrication for Microfluidic Devices and Application

Electrode fabrication methods for microfluidic devices involve photolithography together with material deposition techniques, screen-printing techniques, laser ablation, wet chemistry and conventional manual microelectrode fabrication processes. Photolithography with material deposition techniques, such as sputtering and evaporation, are widely used in manufacturing electrodes on microfluidic device, especially for metal electrodes such as Pt [32], Au [429], Pd [82, 85, 88], carbon or even boron-doped diamond [430]. The choice of the working electrode materials depends on the application. This approach has the advantage that it is relatively easy to locate the position of the electrodes within the channel, is capable of good reproducibility of electrode and amenable to large scale production of devices although costly for small production runs.

Carbon electrodes are most commonly used in CE electrochemical detection techniques for analysis of inorganic and organic species. Such electrodes exhibit attractive electrochemical properties, including wide potential range, low over potential and background noise, rich-surface chemistry, chemical inertness, minimal fouling, low cost and variety forms. Carbon electrode is available in carbon fiber [107], carbon glassy, graphite, carbon paste and film form. Screen-printed electrodes in a manner of end-channel ED coupled with microfluidic devices are low cost and capable of large-scale production [36]. Chemical modified screen-printed thick film carbon electrodes have been demonstrated to be flexible, simple with versatile applications [431-433]. Wang's group has accomplished analysis of various species such as carbohydrates, urine, vitamin C [434], amino acids [435], epinephrine [436], hydrazine [431] and organophosphate nerve agent [437]. Compared to the conventional metal electrode, electron transfer rates at carbon electrode are low. A cellulose-single-stranded DNA (cellulose-ssDNA) modified carbon electrode was fabricated to determine dopamine (DA), norepinephrine (NE), 3,4-dihydroxy-L-phenylalanine (L-DOPA), 3,4-dihydroxyphenylacetic acid (DOPAC), and ascorbic acid [438]. The modification of the working electrode improved the sensitivity about 12 times higher than bare one. Earlier, a glass microfluidic device has been developed with single-wall carbon nanotube modified working electrode based on screen-printed carbon electrode. Lower detection potentials were applied in determining hydrazine, phenol, purine and amino acid compounds. Carbon nanotubes were found to promote electron-transfer reactions and impart higher resistance to surface fouling [439]. Integrated microfluidic device with single-wall carbon nanotube modified electrode has a great potential for environmental and bioanalysis applications. Screen-printed electrode modified with multi walled carbon nanotubes (MWCNTs) detects water-soluble vitamins (pyridoxine, ascorbic acid, and folic acid) [440]. Pumera *et al.* reported comparative study of single-wall and multiwall carbon nanotube for CE microfluidic device [441].

Liu *et al.* [43] used micro moulding facilitates for simple and sensitive multiple different metal electrode. A LOD of 100 nM for dopamine was obtained without a decoupling consideration [442]. Carbon paste [443], carbon fiber [444,

445] and carbon ink [88, 446] have also been used as concave filling electrode materials on micro devices and widen the application of a chip. An indirect method for monitoring nitric oxide by determining nitrate and nitrite at such a carbon fibre electrode on micro device with electrochemical detection has been developed by Lunte's group [445]. This method involves directly amperometric detection of nitrite following a CE separation and conversion of nitrate to nitrite by chemical reduction through Cu-coated Cd granules. Gawron's work improved the detection selectivity through the dual-electrode detection of a Cu (II) peptide complex (444). Hebert *et al.* [137] obtained a pyrolyzed carbon film through pyrolysis procedure for sinusoidal voltammetry detection of neurotransmitters.

Recently, Walker *et al.* reported a new approach to fabricate microelectrodes on polymeric substrate using airbrush [447]. The airbrushing tool patterns the conductive inks as a thin film on the substrate. The pressurised air atomizes the ink into very tiny droplets and a very fine nozzle tip allows the ink to spread uniformly. As is the case for screen-printed electrodes, airbrushed electrodes separate peak for ferrocyanide at 0.34 V.

Pt is one of the most widely used metals for electrochemical detection. Early in 1996, Ewing [448] developed a glass micro device with electrochemical detection. Arrays of 100 working Pt microelectrodes were fabricated by photolithography and analyzed samples continuously introduced through a moving sampling capillary. As a noble metal, Pt electrode surface offers favorable electron transfer kinetics and large anodic potential range. Low hydrogen overvoltage is the main drawback of the Pt working electrode and restricts cathodic potential window. Low hydrogen overvoltage range causes formation of oxide layer /hydrogen layer on the electrode surface and alters kinetics of the electrochemical reaction. Pulse amperometric detection mode can overcome the problem by cleaning the absorbed layer on the noble metal electrode surface [449]. An integrated microfluidic glass device with electrochemical detection was reported in 1998 [32] in which Pt working and counter electrodes were fabricated by photolithography coupled with plasma sputtering. The Ag/AgCl reference electrode was placed in a detection reservoir. Indirect electrochemical detection with end-channel mode has been adopted to determine DNA restriction fragment and PCR product sizing with LOD of 28 zmol for fragment 603-bp of Φ X174. This micro device with a matching detector initially achieved the concept of microfluidic device. Xia *et al.* used Pt ultra microelectrode integrated on a three-dimensional adjustor for the electrochemical detection of benzenediols and related pharmaceutical compounds [316]. Pt microelectrode (10 μ m) sealed with Pyrex tube was placed at the end of the separation channel with Pt counter electrode and Ag/AgCl reference electrode. End-channel platinum working electrode successfully evaluated H₂O₂, l-ascorbic acid, *p*-aminofenol in a CE microfluidic device [58, 59]. Pt working electrode as well as gold nanoparticles enhanced electrochemical detection of roxithromycin [450].

Martin *et al.* [429] made a PDMS/glass microfluidic device in which dual gold electrodes were lithographically fabricated on glass. A linear response from 10 to 500 μ M with a LOD of 4 μ M was obtained for catechol. Fully integrated

microfluidic devices with ED have been created with all Pt electrodes by Baldwin's group [65] and six gold electrodes by Wilke [49]. In these systems, both CE and detection have been incorporated on glass substrates by using MEMS based approaches of photolithographic patterning, wet chemical etching, sputtering, and thermal wafer bonding. This represents a maturing of fabrication techniques for micro devices. Compared to Pt, Au electrodes are more inert with high hydrogen overvoltage range. The Au electrode is also convenient for self-assembled organosulfur monolayer and stripping voltammetric analysis. Single-wall carbon nanotubes modify the electrochemical property of the bare gold working electrode and exhibits low noise levels for aminophenols and neurotransmitters [451]. Electrochemically prepared mercury/gold electrode offers fast, sensitive and reproducible detection of nitro aromatic explosive compounds [452].

The excellent electrochemical properties of diamond make it a very attractive material for use in the electrochemical detection. A boron-doped diamond thin film WE was fabricated through microwave plasma-assisted chemical vapor deposition [119, 430, 453]. At the selected detection potential, boron-doped diamond microelectrode offers low and stable background current with enhanced sensitivity [454]. This diamond electrode has the advantage of lower noise, strong resistance to fouling and high sensitivity to environmental pollutants [455, 456]. The LODs for 4-aminophenol and 2-aminonaphthalene are 2.0 and 1.3 μ M, respectively. Boron-doped diamond microelectrode integrated in CE chip detected the level of endogenous norepinephrine in several tissues [457]. Chen *et al.* reviewed the potential application of boron-doped diamond microelectrode in CE chip [458]. Recently, Gao *et al.* [459] reported the fabrication method of Boron Doped Diamond Microelectrode (BDDME) for microfluidic devices and electrochemical characteristics of BDDME such as wide potential window, low background current, high electrochemical stability for biological detection as well as detection of trace substances.

Applying laser pulses directly to polymer surfaces forms a defined concave in the bottom or the sides walls of the channel, and carbon paste or ink can be filled in to construct an electrode [81, 128]. The desired microstructure was produced using plasma etching of a sandwich copper/polyimide/copper circuit board combined with chemical etching of copper [273]. It has the advantage of fabricating holes for the flow control, as well as electrodes from gold or other metals in a batch process by means of electroplating at copper etched position. This method enables the mass production of low cost and disposable polymer microfluidic device with electrochemical detection.

A few reports have described fabrication of working electrodes through wet chemistry such as chemical deposition of gold at channel outlet [460], electroplating Au or Cu electrode on a microfluidic device [461]. Yan *et al.* [352, 462] obtained a PDMS/glass micro device with gold or copper electrodes for electrochemical detection. They used soft lithography of PDMS to define the geometry of the microelectrodes and followed by electroless chemical deposition process, which included silane and sensitizing of the glass surface first, forming a layer of nanoscopic Ag particles, then the copper formed through reduction of Cu²⁺ by formalde-

hyde, and finally a layer of gold can be produced. The similar electroless chemical deposition process has been used to construct gold nanoelectrodes through a model template of polycarbonate membrane [463] and first report of nickel WE to detect alcohols and sugars on a glass microfluidic device [464]. Recently, photo-directed electroless plating combined with electroplating techniques was used for the fabrication of Au microelectrode [465]. In this technique, gold nanoparticles was deposited on the patterned microstructure and later the nano-particles served as the catalyst for the electroless plating. Scanning electrochemical analyzer electroplates the gold microelectrode and generates Ag/AgCl reference and Pt counter electrode for the electrochemical detection techniques [466]. Electrochemical deposition of gold particles on the working electrode increases the surface area of the Au sensing microelectrode and offers well-resolved separation of dopamine and catechol in less than 60 s [105]. Absorption of self-assembled monolayer (SAM) of 3-mercaptopropionic acid modifies the gold working microelectrode and enhances the limit of detection of dopamine [467]. Electroless plating and interface rotation of laminar flows with three multiphase fluids with density difference allows single and dual silver working electrode in a microchannel [468]. Electrodeposited Prussian blue film on the indium tin oxide, electrode catalyzes redox reaction and enhance electrochemical sensitivity [469]. Prussian blue film coated ITO electrode detected 0.1 mM dopamine and catechol in a CE microfluidic device.

Metal wire [41, 58, 470], carbon fiber [38, 471] or bundle micro disk electrode [472, 473], and nano material [474] are applicable for integration with micro devices. Usually a guide tube [39, 39, 475] or 3D adjuster [38, 476] is used to place the WE accurately to get good reproducibility.

4.2. Miniaturisation

A report on a portable capillary electrophoresis instrument with amperometric, potentiometric and conductometric detection is given by Kappes *et al.* [477]. Static high voltage power supply is essential for the stable EOF and pumping [478, 479]. In addition to the detection method, it is also necessary to consider development of a compact, small and portable HV power supply. HV power supply's dimensions, weight and power are the key parameters for the miniaturization and portability. Field portable miniaturized capillary electrophoresis instrument reduces the time, cost of the analysis, and avoid sample decomposition during transportation and preparation. A simplified detector with two electrodes for amperometric detection on microfluidic device appeared in 2001 [461]. In order to facilitate portable use, a number of efforts have focused on miniaturizing of the HV power supply by means of cell battery. Baldwin *et al.* [480] integrated the portable HV power supply and the electrochemical detection circuits for microfluidic device based capillary electrophoresis which lasted for 15 hours without charging. The compacted power supply and detector circuit, 4 in. × 6 in. × 1 in. in size and 0.35 kg in weight is ideal for microfluidic device applications. The efficiencies for dopamine and catechol were 54200 and 100400 plates/m, respectively under the electric field of 200 V/cm. The maximum electric strength of 500 V/cm could be available. A miniaturized HV power supply for portable application has been de-

veloped by Erickson *et al.* [481]. Pinched and gated injection modes have been achieved by a 3-channel HV power supply that ranges from 0 to ±4000V [482]. Kuban *et al.* developed battery powered portable capillary electrophoresis instrument with voltage capabilities up to 15 kV for more than one working day [483]. The miniaturized HV power supply integrated with capacitively coupled contactless conductivity detection successfully separated and detected inorganic cations and anions [163, 483]. Gärtner *et al.* designed miniaturized CE instrument consists of miniature regulated unipolar power supply modules and CE chip holder with proper connection [484]. The total dimension of complete CE instrument was 19 × 12 × 8 cm³.(length × width × height). Maximum voltage of the miniaturized power supply was recorded 4 kV with current output 250 μA. Recently, Makarotseva *et al.* reported a miniaturized portable CE instrument equipped with a CCD detector and various injection devices for the analysis of the composition of degradation products of chemical warfare agents (CWA) [485]. The power supply system was based on 10 common AA size rechargeable batteries with an operating run time up to 4 hours without recharging. Valdez *et al.* reported wireless control microfluidic device based capillary electrophoresis and a mobile unit for chemical analysis [486]. The system consists of an embedded processor that is designed for digital control, decoding and applying of wirelessly transmitted test parameters, data acquisition and mobility control. Field programmable gate array (FPGA) board of the mobile platform performs all CE tests including high voltage power supply, injection, separation, pulsed amperometric detection and transmission of the data [486].

CONCLUSION

This review has surveyed recent developments in capillary electrophoresis within microfluidic devices with electrochemical detection. Approaches to channel fabrication, surface modification for polymer microfluidic architecture, electrode manufacture and miniaturization of analytical system was discussed. Much work remains in optimizing of fabrication protocols, interfacing to the outside world and system integration. Developments within microfluidic devices will lead to low cost and rugged microfluidic systems that have high sensitivity and selectivity for a wide range of applications.

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