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Mini Review

Droplet-Interfaced Separations as an Emerging Tool for High-Throughput Microchip Electrophoresis

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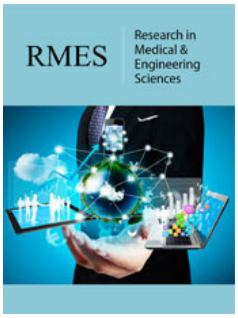

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Abstract

Electrophoresis is a powerful analytical separation technique to analyses biological sample fragments such as nucleic acids, biomarkers, proteins, enzymes etc. Microchip electrophoresis (MCE) is a miniaturised form of electrophoresis and offers fast, robust and low-cost analyses and portability. However, the current format of MCE operates only in the single channel, which limits the throughput of the separations. Droplet-based microfluidics, on the other hand, offers simplicity, robustness and multiplicity in microchannels. Therefore, it has a great potential for droplet-based high throughput electrophoretic separations of DNA fragments, proteins and biomarkers from biofluids such as saliva, blood, dialysate etc. and the ease of operational procedures could further lead this for the Point-of-Care (POC) diagnostics in healthcare.

Keywords: Microchip electrophoresis; Electrophoresis; Droplet-interfaced separations; Gel electrophoresis; Droplet microfluidics

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Electrophoresis is a powerful analytical technique to separate and analyse biological samples such as separation and detection of nucleic acid fragments (DNA, RNA) and cell proteins, immuno-separation of biomarkers and enzymes, etc. Traditional slab gel electrophoresis (SGE) and capillary electrophoresis (CE) are among the most common forms of electrophoresis and have widely been used in biochemistry laboratories. However, the requirement of higher voltages (300V/cm) and longer capillaries (40cm) [1,2] makes the CE system challenging for portable POC devices. With the advancement of microfabrication technologies, electrophoresis has been miniaturised to achieve on-chip electrophoretic separations known as microchip electrophoresis (MCE). MCE offers many advantages over conventional electrophoresis techniques such as integration of different separation functions onto the chip, consumption of small amounts of sample and reagents, faster analyses and efficient separations, etc. [3]. The working principle of the MCE is based on the mobility of charged molecules due to the electrostatic force acting on them under the presence of an electric field [4]. The type of charge on the particles and electric field strength determines the electrophoretic movement of charged particles. MCE has the potential to be adapted for portable point-of-care and clinical diagnostics. A particular interest of research in this area is the sample injections in MCE systems. Reliable and reproducible sample injection into the separation channel is significantly crucial for resolving a mixture of biomolecules such as nucleic acids, proteins, and amino acids, etc. Sample injection in MCE involves containment of the sample on the same microchip as opposite to CE where the sample is injected separately. The majority of the MCE systems have used one of the two conventional sample injection methods, i.e. electro kinetic or hydrostatic injection. Hydrostatic sample injection technique controls the fluid flow in the small microchannels via pressure control and requires sophisticated microvalve systems due to which it has limited throughput [5].

In electro kinetic injection method, the sample is mobilised electrophoretic ally, and a fraction of the sample is dispensed into the separation channel [6,7]. The MCE cross-chip consists of two channels, i.e. the sample loading channel and the separation channel. Firstly,

the channels are filled with a buffer solution, and the sample is electrophoretic ally driven in the sample loading channel in the presence of an electric field. This step is known as the sample loading step. Secondly, a sample plug from the intersection of the cross-channel is injected into the separation channel under an electric field. This step is known as sample dispensing. Separation occurs as the sample moves along the channel and separates into small bands. Finally, the sample enters the detection point where the electropherograms are recorded. Electro kinetic mode of sample injection may introduce bias as different analytes have different electrophoretic mobilities, and the sample is dispensed from the cross-junction. More than 90% of the sample goes to the sample waste reservoir. Therefore, the injected sample may not reflect the concentration and composition of the original sample [8]. Jacobson et al. [9] described the pinched and floating sample injection methods into the separation channel. Cross-chip design injects the sample into the separation channel via the intersection, and the width of the channel intersection controls the volume of the sample injection. To reduce the sample bias, a higher volume of sample can be injected into the loading channels. However, because of the diffusion in the channels, this increases the band-broadening effect in the separation channel. This method only uses the electrokinetic movement of the sample in the loading channel known as the floating sample injection [9].

Droplet-based microfluidics encapsulates samples into discrete droplets and allows the manipulation of droplets in a high-throughput format. Therefore, it has been applied to inject droplets into the separation channels such as Edgar et al. [10] developed a microfluidics device to inject droplets into the separation channel. The authors fabricated the chip with integrated droplet generation part and separation region and introduced the membrane between these two parts. The droplets were generated in the channels and then transported towards the separation channel where aqueous droplets were diffused into the separation channel by the aqueous membrane. In contrast, Niu et al. [11] fabricated a droplet connector for two-dimensional separations of peptides. These droplets were generated after the first-dimension separation (via capillary HPLC) and then merged with the separation channel buffer. Pillar array was used which automatically extracted the oil at the injection part, and the droplets were merged to the separation channel by the electric field. The connector injected entire droplets into the separation channel reproducibly. In another development, a K-shaped device was fabricated by Rowan et al. [12] to inject the sample into the separation channels. The authors used the V-shaped flow channel in which the sample was moved towards the separation channel, and a plug of the sample was injected into the separation channel. The serial injection of the amino acids was performed by using this device, and a controlled separation was achieved.

In another study, Niu et al. [13] developed a droplet-based platform for separation of analytes encapsulated in droplets. The platform allowed serial injection of pL to nL droplets into the separation channel. The sample droplets were generated in Teflon tubing and injected into the separation channel. Droplet generation was achieved by using inert oil (FC-40), and the oil was removed with the help of an oleophilic membrane. The electric field was then applied to the separation channel, and the droplets were merged in the separation channel. The droplets of 50bp DNA step ladder were injected into the device and separated into its fragments. The results were comparable with the standard electropherograms from capillary electrophoresis and agarose gel separations provided by the company. This method allowed sequential injection of droplets into the separation channel, and each droplet is separated into its components within a time frame of 1-2min, i.e. the device is capable of analyzing hundreds of droplets sequentially. Although this platform provided separation of multiple droplets, the sequential format of the device limited the throughput. Hassan et al. [14] developed droplet-interfaced separation chip based on the slip chip concept and injected multiple samples into the separation channels. The device was capable of injecting 30 samples in a single slip of the chip into the separation channels without the requirement of the electrodes/external pumps. DNA ladder fragments were injected into separation channels, and an electric field of 100V/cm was applied while the detection was carried out at 1.3cm using a single electrode for 30 channels. The ease of operational procedures can lead this device towards quantitative separations of biomolecules in parallel.

Electrophoresis is a standard technique to separate macromolecules and has become a routine method for DNA size fragmenting and separating protein mixtures in most laboratories around the world. Microchip electrophoresis (MCE) is a miniaturised form of capillary electrophoresis. MCE offers application of higher voltages to achieve fast and efficient electrophoretic separations. Droplet-based microfluidics offers a promising platform for high-throughput sample injections into separation channels. This review demonstrates that the high-throughput MCE device with user-friendly and straightforward operational procedures can lead towards the development of inexpensive POC diagnostics in healthcare.

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