Capillary-Driven Flow Microfluidics

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Point-of-care (POC) or near-patient testing allows clinicians to accurately achieve real-time diagnostic results performed at or near to the patient site. The outlook of POC devices is to provide quicker analyses that can lead to well-informed clinical decisions and hence improve the health of patients at the point-of-need. Microfluidics plays an important role in the development of POC devices. However, requirements of handling expertise, pumping systems and complex fluidic controls make the technology unaffordable to the current healthcare systems in the world. In recent years, capillary-driven flow microfluidics has emerged as an attractive microfluidic-based technology to overcome these limitations by offering robust, cost-effective and simple-to-operate devices. The internal wall of the microchannels can be pre-coated with reagents, and by merely dipping the device into the patient sample, the sample can be loaded into the microchannel driven by capillary forces and can be detected via handheld or smartphone-based detectors. The capabilities of capillary-driven flow devices have not been fully exploited in developing POC diagnostics, especially for antimicrobial resistance studies in clinical settings. The purpose of this review is to open up this field of microfluidics to the ever-expanding microfluidic-based scientific community.

microfluidics | point-of-care diagnostics | antimicrobial resistance | lab-on-a-chip | capillary-driven flow | capillary action | detections | smartphone imaging

1. Definition

Capillary-driven flow microfluidics, on the other hand, is a type of microfluidics which works on the principle of capillary action that allows the movement of fluids in capillaries or microchannels without the requirement of external pumping mechanisms [1]. This type of microfluidics offers the possibility of pre-coating of reagents into the microchannels, bringing forward ready-to-use devices for POC diagnostics ever promised by the scientific community for decades. The ideal type of capillary-driven flow-based device for POC diagnostics must provide results within a few hours or even minutes while the patient remains in the clinic, and on-spot diagnostic decisions can be made almost instantly.

2. Recent Advances in Capillary-Driven Flow Microfluidics

Capillary-driven flow microfluidics has been developed predominantly for biomedical applications, e.g., numerical modelling of capillary-driven flow for polymerase chain reactions (PCR) inside capillaries was performed [2]. The

authors modelled PCR in hydrophobic polydimethylsiloxane (PDMS) microchannels via computational fluid dynamics (CFD) which were also experimentally tested to compare results, as shown in Figure 1a. PCR mixture was introduced into the microchannels, and the liquid meniscus was recorded to fill all the channels in 12 s, which matched well with the modelled meniscus movements. In another development, capillary-driven flow devices were built to measure the viscosity of the fluid based on capillary action in microchannels [3][4]. A micromachined polymethyl methacrylate (PMMA) chip was used to create a capillary flow inside microchannels, and the meniscus was monitored via an automated optical system (Figure 1b) [3]. In this study, a small volume (26 µL) of the sample was loaded into the microchannels, and viscosity was measured by recording the fluid travel time between two fixed points. In contrast, Lee et al. [4] developed a capillary flow microfluidics device to measure zebrafish blood viscosity in microchannels (Figure 1c). The device was able to use small sample volumes (2 µL) and conduct continuous measurements to study the viscosity changes during embryonic development. Furthermore, the device was able to draw up fluids at higher shear rates, and the measurements were achieved in less than 2 min. Such optically enabled capillary flow systems have the capacity to be used as portable systems for POC diagnostics and analysis in chemical/pharmaceutical industries.

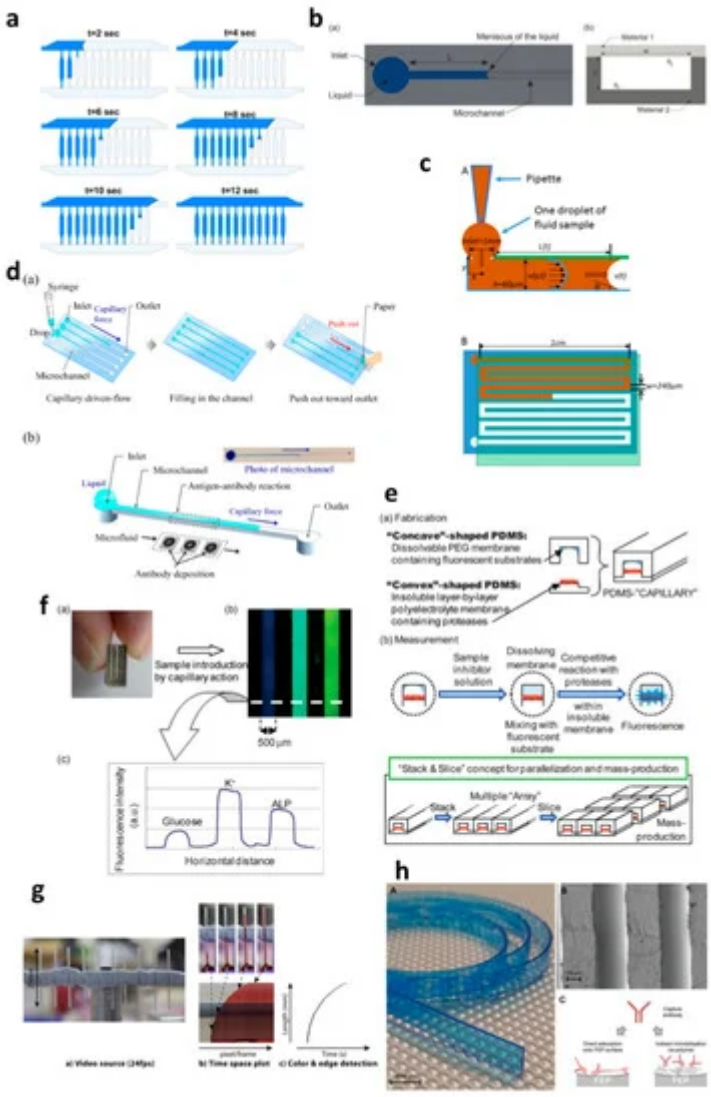

Figure 1. Applications of capillary-driven flow microfluidics. (**a**) computational fluid dynamics (CFD)-modelled filling of microchannels at multiple time points. Reproduced with permission from [2]; (**b**) Optical viscometer. Schematic of the microchannel with the capillary flow (**a**), illustration of the microchannel fabrication with two different substrates (**b**). Reproduced with permission from [2]; (**c**) Capillary flow pressure-driven zebrafish-blood-loaded microchannels. Side and top view of the sample pipetting and fluid flow in the microchannel (**A**,**B**). Reproduced with permission from [4]; (**d**) Illustration of the antibody immobilization process (**a**) with single-channel schematic (**b**). Reproduced with permission from [5]; (**e**) Combinable-polydimethylsiloxane (PDMS) capillary sensor array concept illustration. Reproduced with permission from [6]; (**f**) Combinable-PDMS capillary sensor array analysis of serum components via imaging (**a**) and fluorescence microscopy (b-c). Reproduced with permission from [7]; (**g**) Blood volume collection using glass capillaries. Capillary filling with EDTA blood (**a**) with the capillary filling plot of time−space (**b**) and color threshold levels and edge detection (**c**). Reproduced with permission from [8]; (**h**) Fluoropolymer microcapillaries illustration with flat ribbon blue dye-filled (**A**), field emission gun scanning electron microscopy (FEG-SEM) image (**B**), and capture antibody immobilization strategies (**C**). Reproduced with permission from [9].

Polymethyl methacrylate was also used to fabricate a capillary flow device for nucleic acid biosensing applications having small microfluidic channels consisting of sealed reagent-loaded pads . The system was incorporated with magnetic nanoparticles, which were released upon sample entry into the microchannel, and horseradish peroxidase (HRP) and hydrogen peroxide were mixed in a channel yielding potentiostat detectable species. This type of biosensor based on capillary-driven flow has the potential of miniaturization and commercialization for POC applications. Open microfluidics channels have also been developed for capillary flow [10], but they have disadvantages, such as sample evaporation, contamination and handling difficulties. Therefore, open microfluidics is not discussed further in this review, which is instead focused on capillary flow inside closed microchannels and capillaries.

Several biomedically relevant biomarkers were studied via capillary-driven flow microfluidics [5][6][7][11][12][13]. A capillary flow immunoassay microchip was developed by Fuchiwaki et al. [5] to quantify procollagen type I C-peptide from blood samples. Laser ablation was used to immobilize the antibody on the surface of the PMMA microchannels, which allowed the reaction via movement of liquid in the channels, as shown in the schematic (Figure 1d) [5]. The liquid sample was dropped on the channel inlets which travelled towards the antibody-coated region via capillary force, incubated and flushed out via the outlet and paper absorption. Different concentrations of the peptide (0–600 ng mL^{-1}) were calibrated by multiplexing the channels on a single platform and injecting them into parallel microchannels (Figure 1d). Enzyme inhibitor assays were also developed on capillary flow systems to enable single-step analysis and multiplex them for commercial purposes (Figure 1e) [6]. The device was made of polydimethylsiloxane (PDMS) and was named a “combinable PDMS capillary sensor”. In this study, fluorescent substrates were immobilized on the membrane in the microchannels and the enzyme inhibitor solution is drawn into the microchannel via capillary force. The inhibitor solution dissolves into the membrane where the reactions occur, and detection is performed in an optically clear microchannel. This method shows the potential to multiply the assays by simply cutting long PDMS microchips coated with reagents and flowing samples in parallel. A similar PDMS capillary flow device [7] was also developed for the detection of serum biomarkers, such as glucose, potassium and alkaline phosphate assay (ALP). In this device, the PDMS was mixed with a black reagent (India

ink) to render the PDMS black, and the channel surface was coated with silver layers to enhance the fluorescent signals and sensitivity of the assay (Figure 1f). The sample was introduced into the microchannels via capillary flow, and the intensities of three biomarkers were attained in parallel (Figure 1f).

Huang et al. [11] developed a capillary flow device for DNA probe detection using ordered silicon microcapillary array to control the flow of the liquid. The authors simply placed a drop of sample on the inlet (20 µL) which travelled in the microchannel with DNA probe spots (100 nL) and achieved rapid DNA detection. Recently, Soares et al. [12] developed an ultrasensitive and single-step capillary flow device for biosensing applications. The authors used bead-based technology to control the capillary flow and performed a competitive assay using only a 4.5 µL sample. The system is robust and bears a huge potential for POC diagnostics due to its turn time of 70 s per assay.

Additionally, the capillary flow has also been used for blood plasma separation in microfluidic channels [13][14][15], such as that developed by Madadi et al. [13], to separate plasma using 5 µL of the sample, generating a plasma of 0.1 µL for diagnostic applications. The authors used microchannel-integrated micropillars to confine red blood cells and validated the separation via the detection of thyroid-stimulating hormone. Delamarche's group [14][15] further developed plasma separation attached with immunodiagnostic devices, where C-reactive protein (CRP) was quantified by using 5 µL of human serum extracted from a blood sample and 3.6 nL of reagents solution deposited on the chip [14]. The system was able to detect low concentrations within 3 min by flowing the liquid via capillary force in the microchannels. Furthermore, a capillary flow bead-based immunoassay device for diagnostics has also been developed by the same lab [15]. These types of devices offer multiple biomedical applications with a possibility of detection via smartphones or handheld devices.

Glass capillaries, which are widely available in the market, were also utilized for capillary flow. Lapierre et al. [16] used bare glass capillaries to collect blood samples in the capillaries. The authors generated profiles of blood movement in vertical capillaries, studied the effect of ageing of glass on the liquid rise and modelled the liquid rise parameters using standard equations (Equations (1)–(3)). However, fabrication of glass microchannels for POC applications is generally costly and requires tedious glass intrusions and solvent bonding. In contrast, fluoropolymer microcapillaries (FEP) have been coated with reagents to achieve hydrophilic surface inside the capillaries which can load aqueous samples rapidly [17][9][18][19][20]. Pivetal et al. [9] converted the surface of FEP microcapillaries by coating with a layer of polyvinyl alcohol (PVA) and cross-linked reagents for analyte detections (colorimetric or fluorescent), such as the detection of prostate-specific antigen (PSA) [18][19] and cytokines [20]. These FEP capillaries were injected with multiple solutions, such as PSA standard, detection antibodies, enzyme complex, washing solutions and enzymatic substrates, which were injected in all channels simultaneously. Additionally, FEP microcapillaries were placed vertically in the blood sample to draw up the liquid for ABO blood typing [17]. When the liquid rose into the capillaries, the reagents were released into the sample fluid and reacted with biomarkers to produce colour/fluorescent signal, which was detected via microscope or portable/smartphone systems. FEP microcapillaries illustrate a great potential for integration into point-of-care testing devices and offer the possibility of inexpensive biochemical analyses.

3. Conclusions and Future Challenges

Point-of-care (POC) diagnostics allow the testing of patients in real-time, such as lateral flow assays widely used in the home or clinical settings. However, they have limitations, including the analysis of active bacterial/pathogenic cells, and hence are not applicable for fluid flow applications. Microfluidics plays a vital role in the development of miniaturized POC devices, but handling and accessory requirements make it less practical for deployment in clinical settings. Capillary-driven flow microfluidics has emerged as an alternative to these cumbersome techniques and offers robust, cost-effective and simple-to-operate microfluidic devices. This type of microfluidics has potential for adaptation towards point-of-care diagnostics, especially for tackling antimicrobial resistance, and requires global scientific attention. Such devices can be pre-coated with specific reagents and multiplexed for multiple analyte detections at minimum costs and fewer labour requirements. Furthermore, the elimination of pumping and fluid control systems makes this technology suitable for smartphone/portable detection, as the devices can be simply inserted into the optical detection systems holders attached to smartphones.

One of the most prominent challenges for capillary-driven flow microfluidics is the stability and control of flow rates in microchannels. The flow rates largely depend on inlet pressures and are fixed during fabrication of microchannels. Several device modifications have been attempted to overcome this challenge, such as by varying the dimensions of microchannels to control fluid movement [21] and the incorporation of porous materials at the outlets to absorb the fluid and increase micropumping time [22]. Furthermore, liquid evaporation may also occur after capillary fill and depends on the microchannel dimensions and temperature of the devices [23].

Additionally, durability and stability of microchannels and chemicals also affect the micropumping capability of the capillary flow device, such as reagent degradation over time due to light exposure, moisture or temperature. To circumvent this, the printing of chemicals, freeze-drying chemicals into microchannels, laminations or vacuum sealing can be used [24][25][26].

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