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MICROFLUIDIC TECHNOLOGY AND ITS BIOMEDICAL APPLICATIONS

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ABSTRACT

Microfluidics is the field of handling small volume of fluids and/or manipulating micron-size and submicron-size particles in a microchannel. Microfluidic devices require only small amounts of samples and can run the process in a short period of time. These features have made Microfluidics a powerful technique in lab-on-chip and biomedical applications. These microsystems play important roles in tissue engineering, drug screening, determining the point-of-care diagnoses, and also generating clinically relevant tumor microenvironment for cancer studies. The current paper focuses on the studies conducted on transportation of fluids and particles in small scale systems. It will also introduce the latest developments of the microfluidic components and will provide several biomedical applications of such devices.

INTRODUCTION

Since 18th century, it has been known that liquid could be pass through a small channel by applying electric difference to the two ends of the microchannel [1]. This non-mechanical technique of handeling fluid or transporting particles by applying an external electric field to a microfluidic system is called Electrokinetics. Electrokinetics has found a large number of applications in many different fields of study such as engineering, energy, biomedical, and chemistry [2-4].

The origin of the surface in contact with the aqueous electrolyte solution plays an important role in electrokinetic-base devices. It has been shown that vortices forms around an electrically conducting surface (which is in contact with aqueous solution), once the external electric filed is applied. These vortices will change the flow pattern in a microchannel and dictate different behavior to the motion of the particle.

Consider an ideally electrically conducting particle with arbitrary geometry which is immersed in an aqueous solution (Fig. 1a). Once an external electric field is applied, an electric current generated in the aqueous solution and enters the conducting particle (Fig. 1b). Originally, the positive and negative charges in the conducting particle were randomly distributed so that particle was electrically neutral initially. These charges are affected by the current. The current drives the negative charges under the skin of the particle on one side and the positive charges to the opposite side; inducing equal and opposite surface charge. Simultaneously, the surface charges attract the counter-ions of the liquid. As a result of this charge rearrangement, a dipolar screening cloud adjacent to the solid-liquid surface forms. This new pattern of charge and ion orientation dose not let the current goes through the conducting particle. The particle and the dipolar screening cloud act like an insulator particle to the applied electric field. An induced dipolar double layer is formed (Fig. 1c) and a steady-state electric field is established. The above mentioned process happens very quickly, thus the transient charging process is usually negligible in comparison with the characteristic time of most microfluidics transport processes [5].

The induced charges on the surface of the conducting particle can be described as a function of the local applied electric field. Due to the variation of local induced-charges, the slip velocity of the flow changes its value and direction over the different locations of the particle. As a result, different vortices in opposite directions generate near the solid-liquid interface of the particle (Fig. 1d). These vortices for the first time were

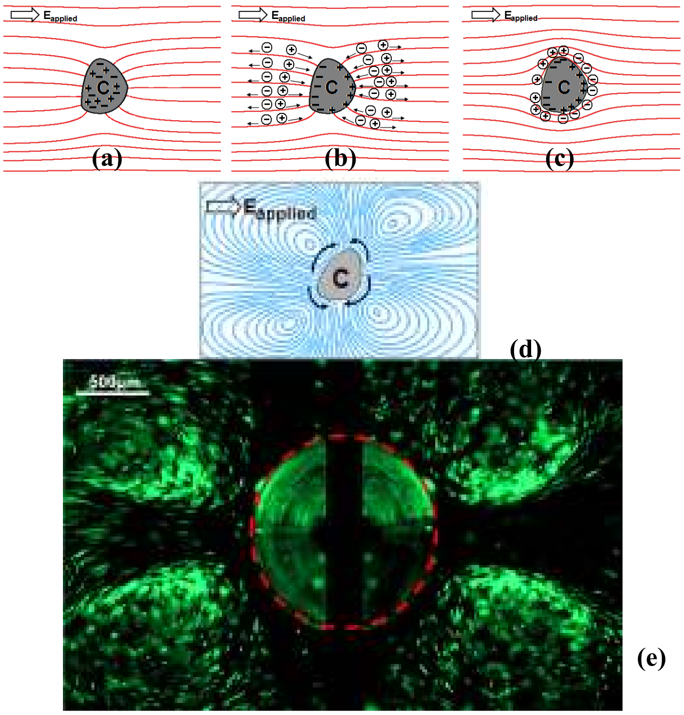

FIGURE 1 (A-C) CHARGING PROCESS OF AN ARBITRARY SHAPE CONDUCTING PARTICLE UNDER A UNIFORM APPLIED DC ELECTRIC FIELD (B) INDUCED-CHARGE ELECTROKINETIC FLOW FIELD AROUND A CONDUCTING PARTICLE. (E) FLUORESCENT PARTICLES WITH A DIAMETER OF 1.90μM ARE USED TO VISUALIZE THE INDUCED-CHARGE ELECTROKINETIC FLOW PATTERN AROUND A CARBON-STEEL SPHERE (DIAMETER=1.2MM). THE DC ELECTRIC FIELD (40V/CM) IS APPLIED FROM LEFT TO RIGHT. DASH LINE REPRESENTS THE PARTICLE BOUNDARY. THE IMAGE IS CAPTURED BY TE2000-E NIKON MICROSCOPE AT T=2S. REPRODUCED FROM REF. [6] WITH PERMISSION FROM ELSEVIER

experimentally visualized by Daghighi et. al. [6] using DC electric filed (Fig. 1e). These vortices are enormously used in microfluidic devices to improve many shortcomings of present microfluidic equipments.

MICROFLUIDICS AND ITS APPLICATIONS

Concentration of Diluted Solutions:

In microfluidic devices, the concentration of sample molecules directly affects the effectiveness of the biochemical reaction and the ability to detect the sample molecules (such as DNA and proteins) in the solution [7-9]. The ability of concentrating the sample molecules in one specific area is key to the success of many on-chip biochemical assays. DNA detection has become a key technology for various biomedical applications. Currently, polymerase chain reaction (PCR) has to be used to amplify the amount of DNA from the initial sample, before any DNA detection techniques can be applied. If the small amount of the DNA molecules from the initial sample can be concentrated and collected, this could enable many biomedical detection methods directly on a microfluidic chip [10].

An electrokinetically-driven concentration method in a straight, closed-end microchannel is shown in Fig.2. This method utilizes simple electric field applied via three electrodes along a microchannel to concentrate the sample molecules from a dilute solution in a well and then transport the concentrated sample molecules along the channel. This microfluidic chip is simple to make and easy to operate, and can increase the sample concentration significantly.

Mixing:

Mixing different solutions to obtain a homogeneous mixture in a short period of time is a key feature for many lab-on-a-chip (LOC) applications; which is not easily achievable. Poor mixing process produces a heterogeneous mixture and consequently influences the accuracy of the results. Mixing two or more fluid streams in microchannels without using micro-stirrer or mechanical micro-mixers depends on their molecular diffusions; since, the nature of flow in microchannels is laminar (no convective term assists the mixing process).

To improve the mixing results, some researchers proposed using microchannels with complicated geometries [12-14]. Disturbing flow to change the flow regime from laminar to turbulent is a practical approach to develop a reliable mixing process [15]. However, using the stirrer introduces moving parts in the micro-systems and has many operational drawbacks and fabrication difficulties. The alternative solution (to avoid moving parts) was implementing electrokinetic methods for mixing [16]. The induced-charge electrokinetics concept and induced micro-vortices can be employed to design an electric micro-mixer with high performance [17, 18]. The simplicity of such an ICEK mixing method has attracted considerable attention in the fields of microfluidics and LOC [19].

Fig 3 shows an ICEK micro-mixer using a conducting particle inside a micro-chamber. Two perpendicular DC electric fields with the same magnitude control the proposed ICEK micro-mixer. This ICEK micro-mixer which employs the induced vortices around the moving conducting particle is easy to be fabricated and is shown to produce 100% homogeneous mixture at the downstream of the fluid. This ICEK micro-mixer can be considered as a simple high-performance and accurate solution for problems of current micro-mixers.

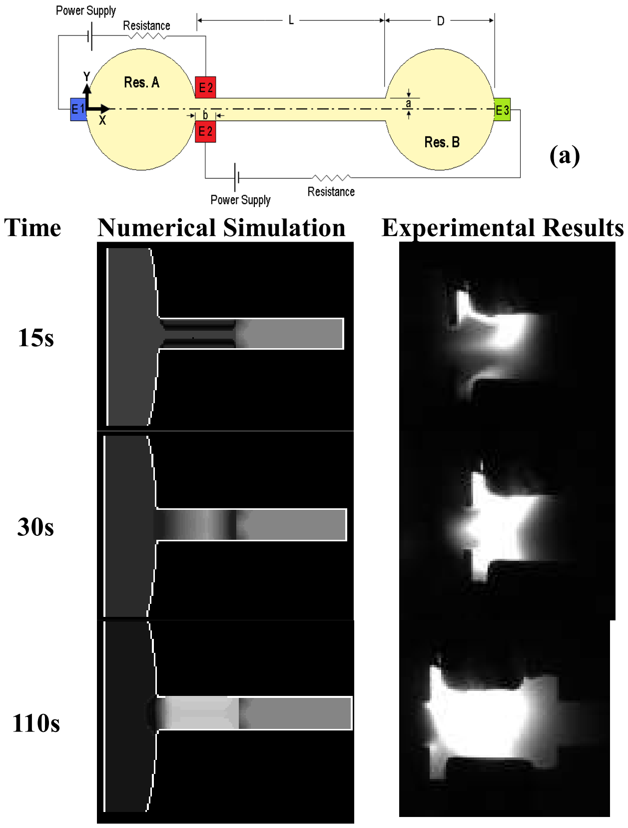

FIGURE 2 (A) TWO-DIMENSIONAL (X-Y PLANE) ILLUSTRATION OF THE CLOSED-END MICROCHANNEL USED IN THIS STUDY OF SAMPLE CONCENTRATION AND TRANSPORT. (B) COMPARISON BETWEEN THE NUMERICALLY SIMULATED CONCENTRATION PROCESS AND THE EXPERIMENTALLY OBSERVED CONCENTRATION PROCESS REPRODUCED FROM REF.[11] WITH PERMISSION FROM ELSEVIER

Micro-Valve:

The main function of a micro-valve is switching the direction of the flow at the desired time to control and regulate the fluid stream. Micro-valves are one of the most important components of integrated LOC devices. Using micro-valves with high performance the sequential loading and washing processes could be performs accurately and fast. Thus, a micro-valve capable of switching fluid flow fast with no leakage and less dead-volume is highly recommended. The first micro-valve was introduced by Terry [21], in 1979, which was the first magnetic MEMS micro-valve. Later on, his micro-valve was improved in several ways [22-24].

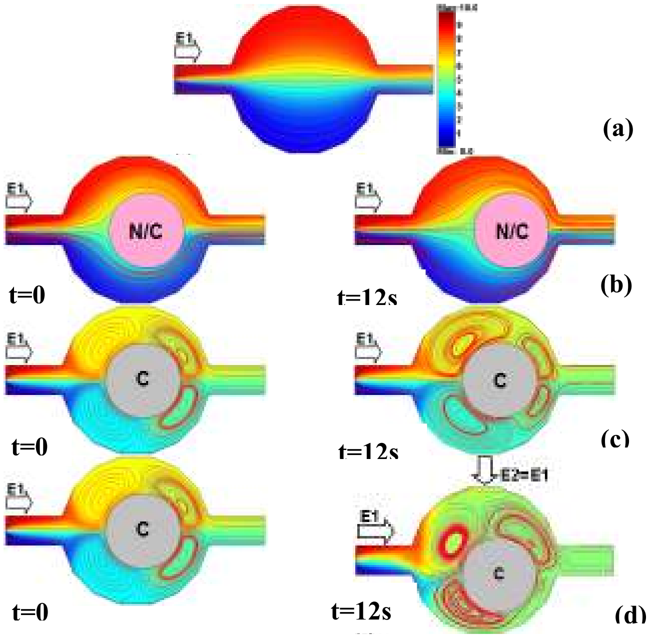

FIGURE 3 FLOW PATTERN AND CONCENTRATION DISTRIBUTION IN A MICRO-MIXER. THE FIGURE SHOWS A MICRO-MIXING CHAMBER (A) WITHOUT A PARTICLE INSIDE, (B) WITH A NON-CONDUCTING PARTICLE AND (C AND D) WITH CONDUCTING PARTICLE. ELECTRIC FIELD (E1=40V/CM) IS APPLIED FROM LEFT TO RIGHT AND E2=E1 IS APPLIED FROM TOP TO BOTTOM OF THE CHAMBER. REPRODUCED FROM REF. [20] WITH PERMISSION FROM ELSEVIER

Thermo-pneumatic, shape memory alloy, and bimetallic, flexible or rigid membranes micro-valves are the other types of micro-valve that developed after. The main drawbacks of such micro-valves are the response time, operating under high voltage. At 2000 a revolution in fabrication of micro-valves happened which solved many of the various MEMS-based micro-valves problems. However, the existing micro-valves still have lots of serious problems which are unsolved. Such as: complex fabrication, considerable dead volume, long response time, leakage, and stability.

x-z plane crossing the middle of the 3D micro-valve at different time steps. The flow pattern and vortices are shown by plotted streamlines. The normalized vectors show the direction of the fluid. The diameter of the Janus particle and the micro-chamber are 20µm and 40µm respectively. The height of the micro-chamber is 40µm. Reproduced from Ref. [26] with permission from The Royal Society of Chemistry.

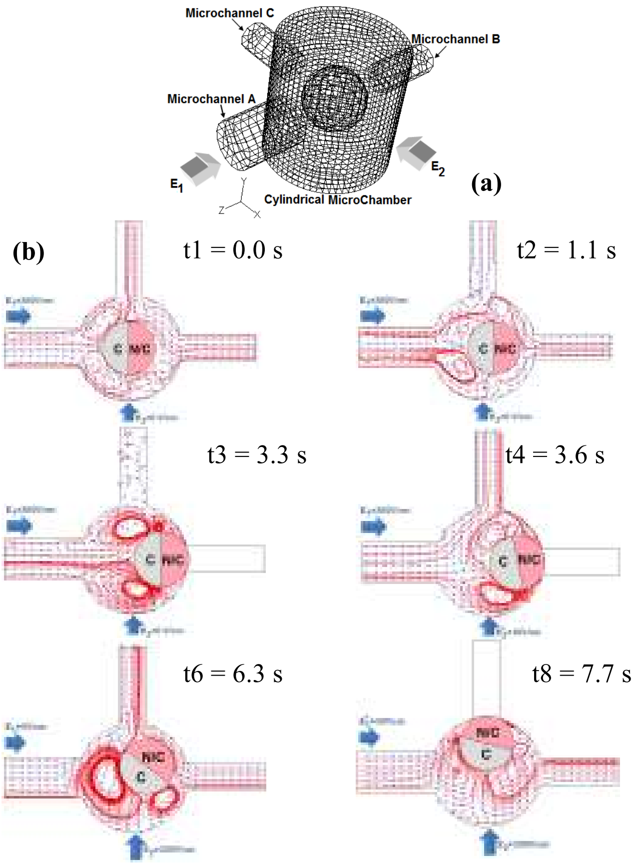

FIGURE 4 (A) ICEK MICRO-VALVE WITH A HETEROGENEOUS PARTICLE. E1, AND E2, REPRESENT THE EXTERNAL ELECTRIC FIELD DIRECTIONS (B)

Fig 4 presented a new design to develop practical and efficient micro-valves and overcome the current problems. This is an ICEK micro-valve using a heterogeneous particle inside a micro-chamber and could be easily controlled by applying two perpendicular electric fields. It has been demonstrated that a heterogeneous particle under the applied electric filed intents to be aligned with the direction of the electric filed [25]. Based on this theory, the location of the heterogeneous particle inside this valve can be simply controlled. Such designs would be a great step towards developing integrated LOC devices.

Micro-Motor:

Motor is a device that creates motion by converting the power (electric, aquatic, magnetic, etc) that it receives from an external source into mechanical energy. Faraday was the first person who could convert the electrical energy into mechanical energy by electromagnetic means in 1821 [27]. The first electromagnetic self-rotor was introduced in 1827 by Jedlik which used electromagnetic coils [28]. Such devices were unable to rotate continuously until Jedlik solved this problem by inventing commutator.

However according to Gad-el-Hak [29] the first micro-motor did not move even when large electric current was applied due to significant friction effect in small scales. To solve this problem, Fan *et al.* [30] introduced the integrated movable micro-structures which could be used for actuators and sensors. Based on their micro-mechanical structures, they reduced the area between rotor and the substrate using dimples on the rotor's surface [30].

Since fabrication of coils and iron cores for rotor/stator type mixer in small scales had not been developed yet, scientists were looking for an alternative. In 1987, Trimmer and Gabriel [31] proposed practical designs for an electrostatic micro-motor based on electrostatic-drive principles. An electrostatic motor works based on the attraction and repulsion of electric charges and for the first time were developed by Gordon [32] and Franklin [33] in the 1750s. However such micro-motors were difficult to fabricate in small scales. Employing induced-charge electrokinetics is a promising method to develop a practical micro-motor.

An ICEK micro-motor which is comprised of a triangular heterogeneous particle in a micro-chamber is shown in Fig.5. This ICEK micro-motor is able to rotate nonstop as long as DC electric field is applied. The key point in generating and controlling the continuous rotation of this micro-motor is the particular design of its geometry. This triangular heterogeneous particle (THP) has an electrically non-conducting body and three electrically conducting corners. The configuration of the THP conducting and non-conducting sections must be such that the applied to the particle are unbalanced all the time.

CONCLUSIONS

During the last decades, microfluidics has been extensively used in different fields such as biomedical, engineering, and chemical. Depending on the nature of the application one can simply design and prototype a microfluidic device which is controllable, inexpensive and accurate. Controlling the zeta potential of the surfaces in contact with electrolytes is an easy a common methods of predicting the resulting electrokinetic effects in the system. Induced charge electrokinetics has a great potential to be used for variety of scientific applications such as LOC devices.

A micro-mixer, micro-valve and micro-motor has been introduced and described in this paper, these can be considered as good candidates to be used in current microfluidics devices. Also this manuscript shows that using the microfluidic techniques, one is capable of concentrating the species which are suspended in a very dilute solution.

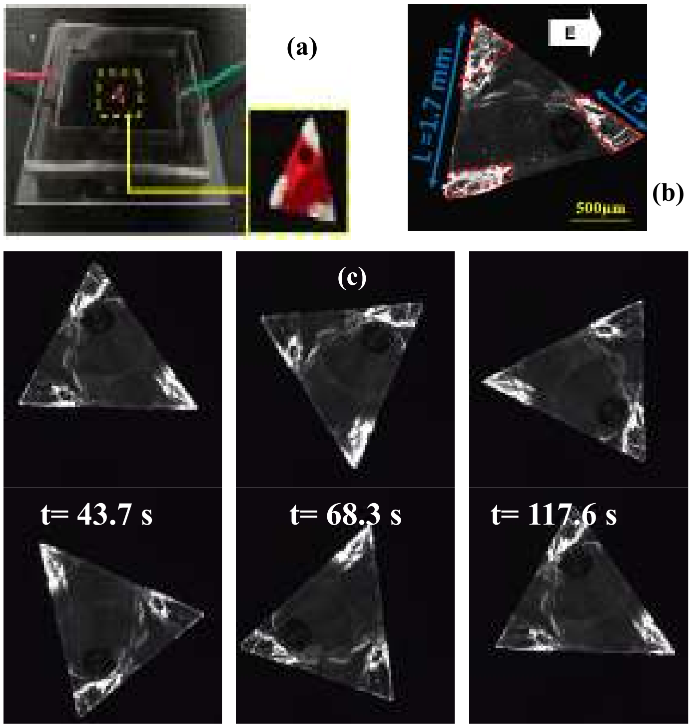

FIGURE 6 (A) A TRIANGULAR HETEROGENEOUS PARTICLE IS SUSPENDED IN DI WATER IN THE CHAMBER WITH TWO ELECTRODES. (B) THE DIMENSIONS OF THE TRIANGULAR HETEROGENEOUS PARTICLE. (C) THE HETEROGENEOUS TRIANGULAR PARTICLE ROTATES A FULL TURN. L=1.7MM, C1=0.57MM, DC ELECTRIC FIELD E=80V/CM IS APPLIED FROM LEFT TO RIGHT

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