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REVIEW

Advances of Particles/Cells Magnetic Manipulation in Microfluidic Chips

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Abstract: Magnetic manipulation of particles/cells in microfluidic chips is a promising research field. This review stated the operation mechanism and the primary means of manipulation, including separation, concentration, capture, arrangement, and assembly. Especially, the concept of particles/cells separation with different criteria, such as sizes, shapes, and magnetic properties was emphasized. Besides, the effects of the channel geometry, the intensity and distribution of the magnetic field, and the types of magnetic liquid (paramagnetic salt solutions and ferrofluids) on the performance of the magnetic manipulation were compared. In the end, the perspective on the prospect of magnetic manipulation about particles/cells in a microfluidic chip was depicted.

Key Words: Microfluidic chips; Magnetic field; Particles/cells; Ferrofluids; Manipulation; Review

1 Introduction

Since the poor understanding of the cancer pathogenesis and cancer cell metastasis, as much as 90% of cancer-associated mortality happened[1]. Medically, it will enhance the therapeutic effect of cancer patients by building perspective on the cancer metastasis mechanism and pursuing the appropriate method to stop or remove it. Currently, numerous techniques and means have been used to isolate and analyze rare circulating tumor cells (CTCs) from the blood. Through the non-invasive screening of CTCs and biomarker detection, the status of the tumor can be explored[2]. As the magnetism is the inherent property of matter, the difference in susceptibility induces magnetic force under the external magnetic field, which means micro-scale particles or cells can be manipulated magnetically. For instance, the target cells can be separated from the heterogeneous mixtures under magnetic field[3].

In recent years, more and more attention has been paid to the microfluidic manipulation technique due to its potential applications in chemistry and biomedicine. Microfluidics was already used in cell separation[4], cancer diagnosis[5], delivery and screening of therapeutic drugs[6–8], sample preparation[9], water quality control and environmental monitoring[10,11]. In comparison with the traditional techniques, the miniaturization of microfluidic manipulations has the advantages such as less sample consumption, low cost, comparatively fast reaction times and less environmental pollution[12,13].

The primary means of manipulation in microfluidic chips include separation, capture, and focusing. The traditional methods, including panning[14] and hydrodynamic manipulation[15], need sophisticated preparation process and are costly, and easy to lose the marked cells. The active manipulation techniques exploit various external forces such as optical, dielectrophoretic, acoustic, and magnetic forces. For instance, optical force[16] can capture a single particle/cell, but it needs a high optical requirement and can generate Joule heat. Dielectrophoresis can achieve high cell throughput while its dissolved ions and surface potential may damage the cells[17]. The acoustic technique also has its limitation[18] due to its lower resolution. In comparison, magnetic manipulation has some advantages[19] including easily controllable magnetic fields, no additional heat (permanent magnet), and no expensive external system as a supplement.

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The non-uniform magnetic field can induce the effective magnetic dipole moment of the non-magnetic materials, which suspend in the magnetic liquids (ferrofluids, paramagnetic salt solutions), resulting in a negative magnetophoresis effect. The ferrofluids is a stable colloidal suspension[20] containing the single magnetic domain of about 10 nm in diameter. The material of the particles is usually Fe_3O_4, which is stably dispersed in water or oil by coating a layer of surfactant. Under the continuous flow condition, the particle/cell magnetic manipulation has a higher throughput and efficiency. Many theoretical methods and analytical models are presented in the papers[21–24] to optimize the micro-device design to improve effectiveness. As we know, the fluid velocity, channel geometry, and the parameters of the magnet are the key factors of magnetic separation.

In this article, the basic principle and primary applications of particle/cell magnetic manipulation in microfluidic chips were summarized. First, the theoretical explanation of particles/cells manipulation in a microfluidic chip, and the dominant parameters were described. Next, the current primary means of manipulation, including separation, concentration, capture, arrangement and assembly, and comparisons of these methods were discussed in detail. Finally, the advantages and prospects of this concept in future developments were pointed out.

2 Physics of particle/cell manipulation

In micro-scale, many forces control the dynamics of particles/cells. This section principally described the main forces affected the trajectory of particles/cells, and determined the dominant forces. In addition, the parameters and conditions that affected particle/cell magnetic manipulation were also discussed.

2.1 Magnetic force

In the ferrofluids or paramagnetic salt solutions, the exerted magnetic force ($\boldsymbol{F}_\mathbf{m}$) of the particles/cells by the magnetic field depends on the volume (V) of the particles/cells, the difference in the magnetic susceptibilities ($\Delta\chi$) between particles/cells (χ_P) and the suspending medium (χ_m), as well as the magnitude of the applied magnetic field ($\boldsymbol{B}$) and its gradient[25].

$$\boldsymbol{F}_\mathbf{m} = (V\Delta\chi/\mu_0)(\boldsymbol{B}\nabla)\boldsymbol{B} \quad (1)$$

where, $\Delta\chi = \chi_p - \chi_m$. When in a paramagnetic solution ($\chi_m > 0$), $\Delta\chi < 0$, diamagnetic particles/cells ($\chi_p < 0$) experiences a force in the direction of weaker magnetic field; when in a diamagnetic solution ($\chi_m < 0$), $\Delta\chi > 0$, paramagnetic particles/cells ($\chi_p > 0$) experiences a force in the direction of magnetic source.

2.2 Viscous resistance

In the case of micro-flow, the Reynolds number is usually much smaller than 1, belonging to the laminar flow. The resistance of the spherical particles in the liquid can often be expressed as following[26]:

$$\boldsymbol{F}_\mathbf{d} = -3\pi\eta D_p(\boldsymbol{U}_\mathbf{p} - \boldsymbol{U}_\mathbf{f})f_D \quad (2)$$

where, η is the viscosity of the fluid, $\boldsymbol{U}_\mathbf{f}$ and $\boldsymbol{U}_\mathbf{P}$ are the velocities of the fluid and particle/cell, respectively, and f_D is hydrodynamic drag coefficient.

2.3 Gravity and buoyancy

The resultant force of gravity and buoyancy of spherical particles/cells is expressed by the following equation[27]:

$$F_n = \pi D_p^3(\rho_p - \rho_f)g/6 \quad (3)$$

where, g is the gravitational acceleration, ρ_p and ρ_f are the density of the particles/cells and the suspending solution, respectively. Since the density of the particles/cells and the media solution is very close, the resultant force F_n is usually one order of magnitude lower than the magnetic force or viscous resistance.

2.4 Other forces

In a paramagnetic salt solution or a ferrofluid, since the volume concentration of particles/cells is much smaller than 1, the interaction between particles and between particles and fluid can be ignored[28]. When the diameter of the particle D_P is small enough, the Brownian motion would have an effect on the movement of particles in the micro-scale. To this end, Gerber *et al*[29] use the following equation to evaluate the critical diameter of the particles:

$$|F|D_p \leq KT \quad (4)$$

where, $|F|$ is the magnitude of the total force acting on the particle/cell, K is the Boltzmann constant, T the temperature.

In a microchannel, the Reynolds number is usually small. Therefore, compared to inertia, the viscous effect has a more significant influence. Furthermore, the particles/cells are greater than the critical diameter calculated by equation (4). Thus, only the magnetic force and viscous resistance are considered.

3 Particle/cell separation

3.1 Size-based separation

The separation of particles and cells is critical in chemistry and biology. When two kinds of particles/cells with different sizes are magnetically separated, there is no need to label the magnetic particles, which can be operated according to their size, quickly and easily. Particles and cells with different sizes can be separated by dimensional difference as long as they have the same magnetic properties. Equation (1) shows that the magnetic force acting on the particles/cells is proportional to their volume under magnetic field. And the magnetic force