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Review paper

A comprehensive overview of micromixers and micropumps in biomechanical applications

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Abstract

In recent years, microfluidic devices have had various applications, such as in the biological field. Hence, it is essential to study fluid flow governing equations to realize the ability to better control fluids in different flow regimes according to microfluidic devices. Also, the study of the inducing source, fabrication technique, and numerical procedure of fluid flow simulation are necessary for flow solution and are used to select proper devices. Here, the mentioned cases have been studied. Also, numerical methods of fluid flow study for various types of fluid, their comparison, and the pros and cons of each of them have been briefly expressed that may be used for their development. Then, the extensive biological application of micromixers and micropumps has been investigated. It is expected that this paper will be of attention to scholars or practitioners in the micromixer and micropump biomedical technology field and those who enter this context for the first time and may also highlight what will assist in future development.

1. Introduction

The science and technology that manipulate fluids in the range of 10-18 to 9-10 liters in microchannel are called microfluidics [1].
Microfluidics research dates back to the early 1990s. Microdevices' behavior differs from objects with conventional dimensions that are used daily. For instance, in small systems, inertial forces are minimal, and surface effects become important. When devices become small, forces such as electrostatic, friction, and viscous effects have more influence because of the surrounding fluid [2].
Recently, microfluidic devices with such diverse functions in a wide range have rapidly developed since advances in the technologies of micro-electro-mechanical systems (MEMS) have occurred [3-8]. In recent years, microfluidics has had many uses in many fields such as life science, environment, analytical chemistry, etc. Usually, integrated systems with multiple components are applied in microfluidic systems to handle fluid on the micro and nanoscale [9].
Also, microfluidic systems have had an essential effect on the biomedical diagnostics field and are widely used in drug delivery and biomedical research industries [10].
Fig. 1 shows the size characteristics of microfluidic devices. The principal differences in fluid mechanics between microscales and macroscales can be categorized into:
• Effects of the non-continuum,
• Effect of surface domination,

• Effect of low Reynolds number,
• Effect of multiscale and multiphysics [2].

The lower volume utilization of samples, chemicals, or reagents in microfluidics reduces the cost of the applications. Due to its compact size, most of the operations are performed at the same time, shortening the experiment time. Microfluidics present excellent data quality and significant control of the parameters, which enables automation of the process while preserving efficiency. They are capable of using minor samples to process and analyze. The incorporated automation in the microfluidic chip makes it possible to generate multi-step reactions which need a low level of expertise [11].

The industrial success of MEMS has two reasons. The sensitivity and response of sensors are improved, and they are able to integrate detection, analyze data, and process signals on a chip [12].

- *Microfluidic device*

Microfluidic devices utilize the gas and liquid's physical and chemical properties of gases and liquids at a very small scale.

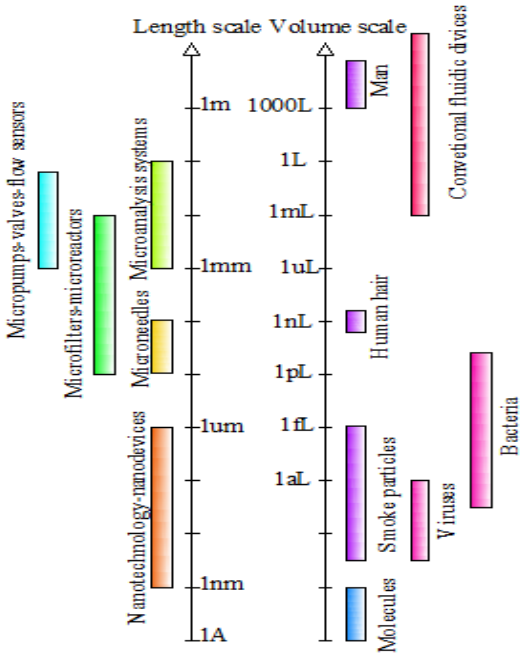

Fig. 1. Microfluidic devices size characteristic [1].

There are many advantages for microfluidic devices over systems of conventional sizes. In this section, two of the most widely used devices have been introduced. The types of micromixers and micropumps are classified in Fig. 2.

1.1. Micromixer

A micromixer is a device for fluid mixing, based on mechanical microparts. Micromixers are crucial components in micro biomedical systems [13]. Micromixers create a closer contact between the molecules of the reagent to interact in biological and chemical reactions [14, 15]. Lately, the advances of diverse micromixers have led to the kinetics investigation of biochemical reactions [15]. In a micromixer, fluid is more controllable, and its harness is more straightforward in contrast with conventional technologies of mixing. The significant advantages of micromixers are that they consume small samples and have less mixing time [16]. Their production is also simpler and inexpensive, and they can integrate easily with various optical spectroscopy techniques [14].

The use of a micromixer caused experimental observation of events like transient states in the folding of DNA or protein, which were obscured before [17-19]. In the past decade, advances in the design of micromixers have been made to understand the biochemical reaction's mechanism and improve mixing, slow time, and consumption of sample consumption [17, 19, 20].

Generally, micromixers are divided into two types based on mixing principles: passive and active [21]. An external source is utilized in active micromixers like acoustic, magnetic, electrical, or optical energy that increases the mixing [22-25].

By contrast, the fabrication of passive micromixers is relatively simple and their integration with other components to achieve complex tasks is uncomplicated. Therefore, the use of the passive type of micromixers is relatively more common [28].

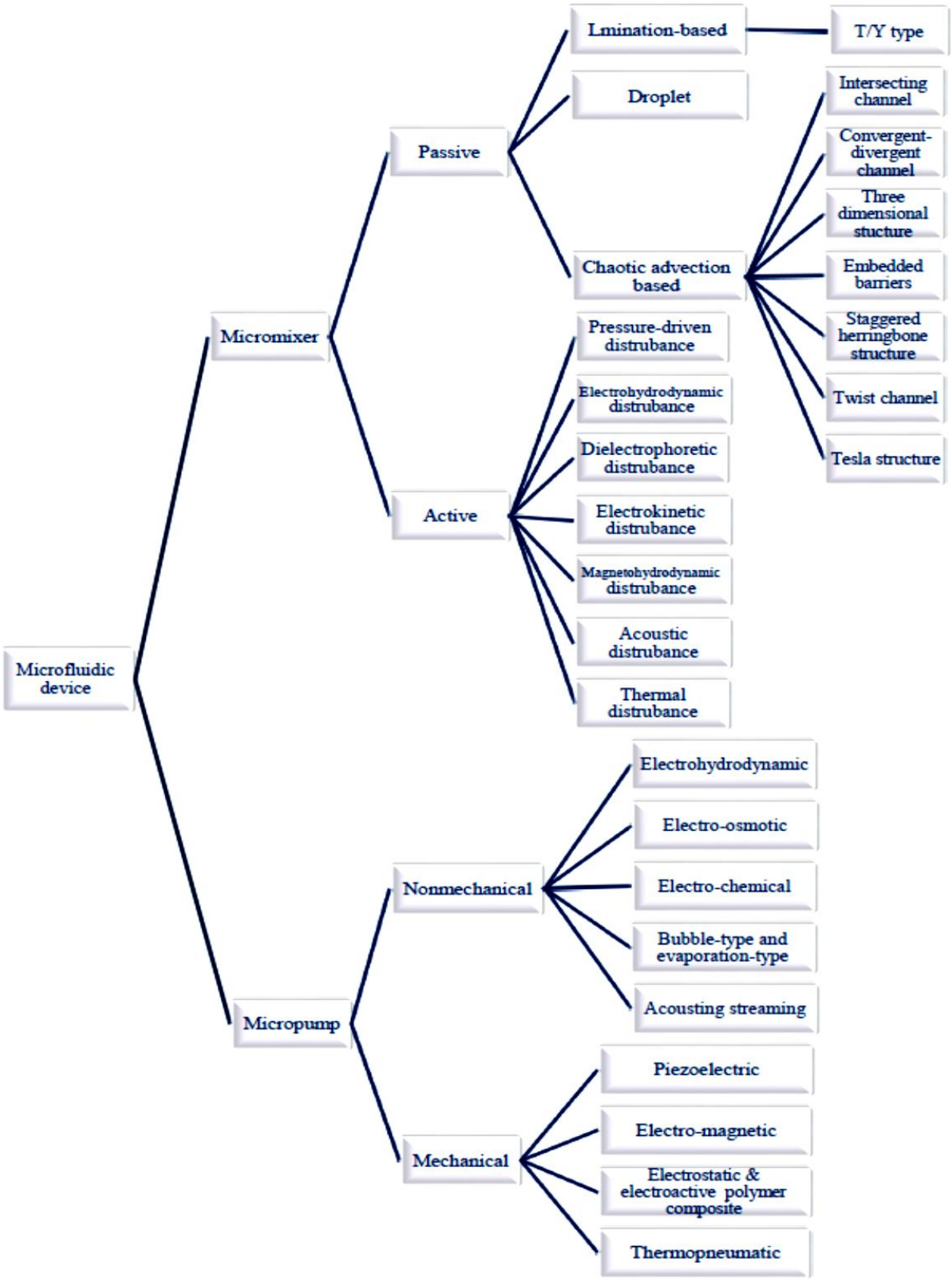

Fig. 2. Chart of classification types of micromixers and micropumps.

In microchannels, very low Reynolds number regimes are produced, which derive laminar flow; therefore, mixing of species happens because of diffusion, which is inherently a slow process. As a consequence, high-efficiency microfluidic mixing schemes are needed to promote biomedical microsystems throughput and to develop micro-total-analysis systems (μTAS) [29-31] and lab-on-a-chip (LOC) devices [32, 33].

Generally, methods of mixing are based on chaotic advection and turbulence generation that causes irregular variation of fluid motion. Hence, pressure and velocity quantities change randomly in time and space.

In vivo, many biochemical reactions occur in liquids with high viscosity [34]. As the solution's viscosity increases, the Reynolds number decreases, making the laminar flow barely disrupted. In a high-viscosity solution, the diffusion coefficient is less, leading to a reduction in the velocity of molecule diffusion and an increase in the mixing time. To achieve the effective mixing of samples with high viscosity in vitro to imitate the in vivo situation is one of the challenging problems.

Several types of chaotic convection mixers were designed in order to mix solutions with high viscosity [28]. In addition to chaotic advection, molecular diffusion has an important impact on mass transfer in passive types of micromixers. In strictly laminar flow, the mixing process happens because of the concentration difference between layers by molecular diffusion. As a result, if the fluid layer is greater than the characteristic diffusion length, achieving to an efficient and fast mixing performance is difficult. Thus, in microchannel design, it is needed that different fluid layers have more contact surface area, which leads to a reduction in the path of diffusion. Another way is related to the design of the microchannel structure so that the species are folded several times when they flow along the channel. This approach causes an enhancement in the contact region between the species flows and lengthening of species contact [35 and 36].

Hence, an increase in the efficiency of 2D micromixers in terms of mixing length, time, and pressure drop is possible through efficient structure design.

The important parameters in an efficient passive micromixer design are fluid dynamics, mixing skills, and the facility of fabrication techniques in order to integrate with other microfluidic components.

In order to access rapid and efficient mixing, researchers have attempted to carefully resolve geometrical limitations in the microchannel design or apply an external energy source to reduce the mixing pathway or extend the contact region [37]. As mentioned, the efficiency and flow rate of mixing are the key dominant factors in describing mixing in microdevices [38]. Fig. 3 depicts determining blood type using a lab-on-chip concept.

1.2. Micropump

A micropump is used to control and manipulate small fluid volumes. The operation of micropumps provides the required energy to drive fluid through microfluidic systems.

Micropumps have developed from the beginning until now and have such powerful benefits nowadays, consisting of miniature size and low weight, low cost, good transportability, various flow rates, low power usage, and they can integrate with other microfluidic devices. In μTAS, numerous applied devices on one platform are integrated and prepare the tools to carry out perfect biological assays in a rapid, low-cost, and very repeatable state [39-46].

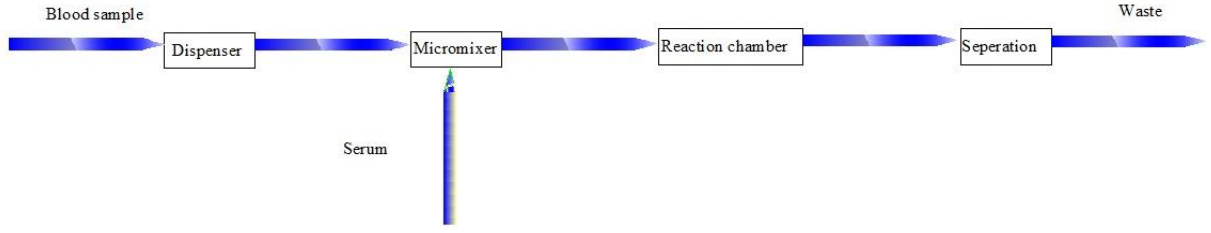

Fig. 3. Blood typing by a lab-on-a-chip.

In biomedical, biological, and environmental applications that need reagents and sample volumes so little, micropumps have a significant role [45]. They are one of the strongest assets for applications of biomedical engineering. Ideally, micropumps should be able to precisely adjust the flow rate and injection volume and concurrently achieve low power usage, biologically secure activation, and the slightest backflow pressure [14].

2. Fluid flow and heat transfer equations

Two important different ways are used for fluid flow modeling: 1. a collection of individuals, interacting molecules; 2. a continuum in which properties are defined to be continuously defined in the whole space. Gases and liquids can be summarized as follows:
The parameter that predicts the way gas flows when external forces act is called the Knudsen number [1]:

- Kn ≤ 0.01: continuum,
- Kn ≥ *O* (10): free molecular flow.

Knudsen numbers between 0.01 and 10 indicate that rarefied gas is classified as follows:

- Kn between 0.01 and 0.1indicates slip flow
- Kn between 0.1 and 10 indicates transition flow [2].

Unlike gases, where the Knudsen number is used as a basis for the determination how a fluid will react to external forces, for liquids, the condition is more complicated.
In most cases, the behavior of liquids, due to the tight spacing between their molecules, is in continuum form. Also, no-slip and no-temperature jump conditions are observed at the boundary.
The generic continuum analysis is applied except when particular situations exist, which are explained below:

- An argumentation is rendered based on having a population of molecules large enough to prevent significant statistical changes in point quantities. If the flow length scale of simple molecules is greater than 10 nm, the liquid is considered a continuum flow. Nevertheless, if molecules are complicated, the argumentation should be modified.
- If the shear of liquid is intense such that the shear rate is larger than twice the molecular interaction frequency, it will not act as a Newtonian fluid, and computational means are required to analyze the flow [1].

2.1. Governing equation

Continuity, momentum, and energy equations are generally the equations for the simulation of Newtonian and non-Newtonian fluids. In the mechanic of continuum approach, the Eqs. 1-3 are presented as follows, respectively [47]:

$$\partial\rho/\partial t + \nabla.\ \rho \mathrm{V} = 0 \quad (1)$$

$$\partial\rho \mathrm{V}/\partial t = -\nabla.\ (\rho \mathrm{VV}) + \rho \mathrm{f} + \nabla.\ \boldsymbol{\tau} \quad (2)$$

$$\partial\rho e/\partial t = \nabla.\ (\rho e \mathrm{V} - \boldsymbol{\tau} \mathrm{V} + \mathrm{q}) \quad (3)$$

where V shows the velocity vector, ρ is the density, f refers to the body forces, $\boldsymbol{\tau}$ shows the tensor of shear stress, e indicates the energy, prefers to the pressure, and q indicates the vector of heat-flux. The shear stress tensor is expressed differently for Newtonian and non-Newtonian fluids.
Convection-diffusion transport equation is used for concentration distribution determination [48]:

$$\partial \mathrm{c}/\partial t + \mathrm{V}.\ \nabla \mathrm{c} = \mathrm{D}\nabla^2 \quad (4)$$

where c shows the species concentration and D refers to the coefficient of diffusion.

2.2. Dimensionless parameters [49, 50]

Since the dimensions of microchannels are tens to hundreds of micrometers, the Reynolds number is usually under 100, and the flow regime is laminar. The viscous effects overcome inertial effects, and the mass transfer happens in the fluid flow direction [51].
The principle of the mixing path reduction is the base of fast mixing by hydrodynamic focusing.

$$\mathrm{t} = \mathrm{L}^2/\mathrm{D} \quad (5)$$

where L and D refer to the distance and coefficient of diffusion. A reduction in L remarkably cause the mixing time reduction [52, 53]. In order to attain a narrow sample flow, a great flow proportion between the sample flow and the sheath flow should be

achieved. The optimization of the input channel resistances and the external pressure sources causes to efficiently increasing the flow rate ratio [54]. Therefore, the mixing time reaches microseconds.
A mixing index is described to determine of mixing increment degree at every cross-section, as:

$$\sigma = \left(1 - \frac{\int_0^w |m - m_\infty| dy}{\int_0^w |m_0 - m_\infty| dy}\right) \times 100\% \quad (6)$$

where m refers to the concentration profile of species among the mixing channel's width, and m_0 and m_∞ are concentration of species in the unmixed and mixed mode, respectively [36].
In cases such as oscillate flow which is time-dependent, it is necessary to calculate the mixing index for a while. So the mixing index depends on time.

$$Dl = \frac{1}{T}\int_T \sigma dt \quad (7)$$

In Eq. 7, T is the period of sampling that is equal to one or more periods of oscillation. Increasing or decreasing the percentage of mixing rate at the channel output to the base mixing index is obtained from the following equation:

$$\eta = \frac{Dl_{st} - Dl_{out}}{Dl_{st}} \times 100 \quad (8)$$

2.3. Boundary condition

The common boundary condition is no-slip/no-jump for most microscopic fluids in the Navier-Stokes equation. In other words, the temperature and velocity of the fluid equal to the wall temperature and velocity [1].
However, for the gas flow, the BC for that governing equations are different, and slip boundary conditions are used for velocity and temperature based on the Knudsen number. The slip condition of velocity is specified by Maxwell [55];

$$u_{gas} - u_{wall} = \lambda \frac{2-\sigma_v}{\sigma_v} \frac{\partial u}{\partial y}\bigg|_{wall} + \frac{3}{4}\frac{\mu}{\rho T_{gas}} \frac{\partial T}{\partial x}\bigg|_{wall} \quad (9)$$

Also, the condition of temperature jump is determined as follows [56]:

$$T_{gas} - T_{wall} = \frac{2-\sigma_T}{\sigma_T} \frac{2k}{k+1} \frac{\lambda}{\Pr} \frac{\partial T}{\partial y}\bigg|_{wall} \quad (10)$$

where σ_v is the tangential momentum and σ_T shows the coefficients of temperature accommodation. λ is the mean free path, k shows the thermal conductivity, and Pr indicates the Prandtl number.

3. Source term in microdevices

3.1. Electromagnetic actuation

The governing equations for electromagnetic sources are expressed by Maxwell's, constitutive and current continuity equation [57]. Magnetic actuation micropumps use one of the electromagnetic mechanisms or the magnetostrictive mode. When the permanent magnets located on the opposite side of a chamber produce a transverse uniform magnetic field, a set of microwires exert a square-wave low-frequency electric current. This Lorentz force is expressed by:

$$F_i = N(I \times B)l \quad (11)$$

that N is the number of microwires, B indicates the density of magnetic flux, I show the electric current measure, and l is the microwires length. For an electromagnetic micropump, the interaction of the permanent magnets with a valuable magnetic field, which is produced by a micro-coil that has current, causes to generate diagram movement [58, 59].

3.2. Magnetohydrodynamic

Magnetohydrodynamics (MHD) relates to the electrically conducting fluid flow in magnetic and electric fields [60-64]. The governing equations on the MHD are Ohm's law, mass conservation, and momentum conservation, with assumptions of the properties such as electric, magnetic, and fluid are constant, flow is single-phase, and free charge density is negligible [65].

$$\begin{aligned} &J = \sigma(E + v \times B) \\ &\nabla . v = 0 \\ &\rho\left(\frac{\partial v}{\partial t} + v.\nabla v\right) = -\nabla p + \mu\nabla^2 v + J \times B \end{aligned} \quad (12)$$

Generally, the structure of the MHD micropump is simple, and it consists of a microchannel that is bounded by two walls of electrodes generating an electric field and two walls of opposite-polarity permanent magnets creating the magnetic field. A Lorentz force is produced by the interplay of the magnetic and electric field, and its measure is:

$$F = Y \times B \quad (13)$$

where Y shows the density of the electric current and B indicates the density of the magnetic flux. MHD micropumps are able to pump conductive liquids and aqueous-based solutions applied in conventional biological approaches. In addition, MHD micropumps are implemented by DC [66-70] or AC- operated [71-76] electric fields. The advantages of MHD-based micropumps are:

(1) High reliability due to no moving Components;
(2) Relatively simple fabrication method and having batch fabrication potential;
(3) Containing the remote or teleoperation potential using an external magnetic field;
(4) Being able to integrate with other systems or modules without any restriction on the form of the channels

In order to develop MHD micropumps, a lot of efforts have been focused. Since its simplicity reduces the risk of clogging and harm to molecular materials, it is used in biomedical applications [57].

3.3. Electrostatic and electroactive polymer composite micropumps

To apply the force or induce movement, the Columbic attraction generated by two oppositely charged bodies is important in electrostatic actuation [77-81]. The amount of force attracted depends on this sorted energy in the electrostatic field. If a voltage V is applied between two plates with area A and an air gap d between them, the electrostatic force is calculated by:

$$F = 0.5\varepsilon_0 \left(\frac{V}{d}\right)^2 A \quad (14)$$

where ε_0 is the free space permittivity.

3.4. Thermal actuation micropump

The base of thermal actuation micropumps includes thermopneumatics [82-87], shape memory alloy [88-92], or polymer mechanisms that are expandable thermally [93-97]. The pressure change for liquid is shown by:

$$\Delta P = E(\beta \Delta T - \Delta V / V) \quad (15)$$

ΔP shows the difference in pressure, E indicates the elasticity modulus, β is the coefficient of liquid thermal expansion, and ΔV/V shows the percentage of the change of volume. In these micropumps, the performance is so simple. Even if the generated pumping force is large, the diaphragm deviation will be limited because the difference between the coefficients of thermal expansion is very small [14].

3.5. Electrohydrodynamic

The fluid flow is induced through the electrostatic forces acting on dielectric liquids in electrohydrodynamic micropumps [98-108]. The fluid flow is induced by the interaction between an external electric field and this field charges in the fluid. The magnitude of electric body force density is expressed by [99]:

$$F_e = \rho_f E - 0.5E^2 \nabla \varepsilon + 0.5\nabla \left[E^2 \left(\frac{\partial \varepsilon}{\partial \rho_n} \right) \right] \rho_n \quad (16)$$

3.6. Electroosmotic

Electrokinetic phenome contains electrophoresis (EP), electroosmosis (EO), and dielectrophoresis (DEP) [109-111]. EO happens when there is an interplay between the electric double layers created on the surface of electronic conductors in contact with the electrolyte solution and the forces of the electrostatic surface [112]. Most EO micropumps use this to cause the movement of an uncharged sample liquid toward a fixed charged surface under the impact of an external electric field [113-129]. EO micropumps may be performed by one of DC or AC-operated fields.

3.7. Evaporation and bubble type micropumps

A controlled voltage input in this type of micropump causes periodic expansion, then

bubbles collapse in the microchannel, and the pumping effect is generated [130-140]. More precisely, the volume changes in the chamber via a diffuser-nozzle mechanism that determines the direction of flow, as well.

4. Numerical procedure

The numerical simulation procedure of each flow is shown in Table 1 [2, 141-148].

5. Fabrication techniques

The geometry of the microfluidic devices and the particle size of the materials are two main features of microfluidic device fabrication. Recently, Chaurasia *et al.* [149] showed that an integrated microfluidic method using oil-encapsulated calcium alginate microfibers represented the encapsulate form could be adjusted for various geometries such as spherical, ellipsoidal, etc. Their material is chosen according to the microdevices application. The materials are categorized into two types of organic like polydimethylsiloxane (PDMS) and polymethyl methacrylate (PMMA), and nonorganic include silicon, Plexiglas, and glass [150]. Polymers are used widely for micro and nanodevices due to their low cost, easy processing, and environmental compatibility [151]. Different types of microtechnologies are depicted in Fig. 4.

For microfluidics, the primary microfabrication methods are left from MEMS technology. Usually, procedures like chemical etching, complicated photolithography, surface micromachining, bulk micromachining, and metal sputtering [152, 153] are utilized for the microfluidic devices fabrication, which bases are glass or silicon wafers [154, 155].

Nowadays, engineers have developed many diverse techniques to fabricate microfluidic devices which include soft lithography [156], laser ablation [157], micro/nano imprinting [158], and micro-injection molding [159]. The basic techniques of microfabrication are shown in Fig. 5.

The development of modular microfluidic systems has caused to representation of various of these systems based on diverse fabricants of procedures and materials. Diverse ideas have appeared one after another, consisting of the fluid breadboard (FBB) [160], microfluidics assembly blocks (MABs) [161], mixed circuit board (MCB) [162], and microfluidics building blocks (MFBB) [163]. The primary stage for the modular microfluidics technique is modular dividing which requires an in-depth case study of the integrated microfluidic system.

Most micromixers are fabricated by the use of polymer laminates [164]. In this method, several bonded layers together make the microchannel. In laminate device fabrication, common materials are polycarbonate, PMMA, cyclic olefin copolymer (COC), and glass. Polymer molding is the other approach, consisting of soft lithography, injection molding, and hot embossing. Photolithography such as SU-8 is used in soft lithography to pour and cure the polymer like PDMS [165]. The steps of photolithography are shown in Fig. 6.

Microinjection molding in order to form microfluidic devices commercially uses thermoplastics. This method is filling the mold cavity with melted thermoplastic followed by cooling [166]. In the hot embossing method to shape a microfluidic device, the materials, including thermoplastics or polymers (for instance, polycarbonate, COC, PMMA, and polyethylene terephthalate), are molded, pressured, and heated [167].

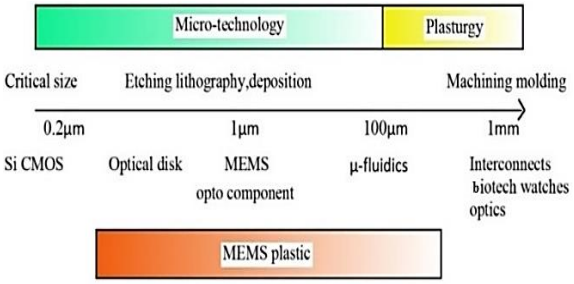

Fig. 4. Different types of microtechnologies [46].

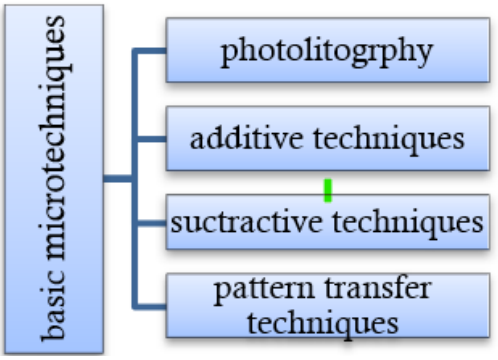

Fig. 5. Chart of basic microfabrication technique.

Table 1. Classification of numerical methods.

	Method	Pros	Cons
Continuum method	Spectral element	Suitable for a smooth solution, good at complex geometry and electro-osmotic flow, more efficient than low degree FEM	Geometry irregularities or dimensions make this method unsuitable.
	Finite element	Ability to solve different dimensions due to adaptive mesh arrangement, suitable for arbitrary geometry, Comsol and Conventor use this method.	Difficulty with topology change and large boundary deformation, computationally expensive
	Finite volume	Conservative Good at arbitrary geometry and inhomogeneous material with variable properties, CFD-ACE+ and Fluent use this method	Difficulty with multiphase systems and evolving interfaces
	Boundary element	Efficient for homogeneous linear PDEs	Difficult implementation, Difficulty with inhomogeneous material and nonlinear PDEs
	Meshless		
	Force coupling		
Atomistic gas flow simulation	DSMC		Slow converge, Large statistical noise, Too many simulated molecules, Absence of definite surface effects
	Boltzmann	Low computational cost, Simple finding the pressure magnitude from equations	Difficulty with modeling gas-liquid multiphase flows with density difference or high viscosity difference between phases, Difficulty with streams with high Mach numbers, Difficulty with curved boundary geometry
	Lattice Boltzmann	Ability to simulate interface, Good at complicated boundary conditions, Ability to solve N.S equation for compressible and incompressible mode, Ability to simulate specific thermal solutions with heat transfer	Difficulty with high Mach number flow, Dynamic restricted to adjacent nodes on Lattice, Diffuse interface
Atomistic simulation for liquids and dense gas flow	Molecular dynamic	The most accurate simulation method, Suitable for the complex multi-particle systems, Capable of computing properties Including energy, structural, dynamic, mechanical, and thermodynamic properties	Unsuitable for large length scale than 100 nm
	Lattice Boltzmann	Ability to simulate interface, Good at complicated boundary conditions, Ability to solve N.S equation for compressible and incompressible mode, Ability to simulate specific thermal solutions with heat transfer	Difficulty with high Mach number flow, Dynamic restricted to adjacent nodes on Lattice, Diffuse interface
	DP	High simulation speed and low computational cost	Inefficient

Also, the 3D printing method is used to fabricate the three-dimensional model of the microfluidic device. The materials that are utilized to build microfluidic devices by various 3D printing methods usually include acrylonitrile butadiene styrene (ABS), polycarbonate, polyamide, polystyrene, and PDMS [168].

Nanofabrication, which contains top-down [169] and bottom-up [170] techniques, are the recent procedure for microdevices fabrication. The restrictions of extreme ultraviolet lithography and electron beam lithography that are applied for microdevices fabrication at present are the cost and serial processing.

Micropumps are fabricated by use of MEMS methods on biocompatible substrates like silicon, polymer, or glass [171-177].
The primary step in the fabrication of micropumps purely relied on silicon micromachining, represented by Spencer *et al.* [178]. The drawbacks of mechanical micropump technology fabricated widely using micromachining processes based on silicon glass include high cost of material and fabrication and spent time. However, in this method, microfabrication yields better properties. The usual casting method or spin coating easily molds polymeric materials to build the various parts like the chamber body, diaphragm, and microfluidic components [179-187] In recent works, micro CNC machining [188-192], CO_2-based laser cutting, and engraving procedures [193-195] are utilized to micropumps fabrication with materials like PMMA, and PLLA. Polymer-based materials with common machining and fabrication operations have several advantages such as a reduction in the cost of material, material compatibility improvement, strength, and reduced fabrication cost. The PDMS-based micropumps [196-202] have a lot of advantages. Nonetheless, their fabricant method is generally very complicated. For instance, the bonding of several PDMS layers and casting is needed, and if the bonding stages are not carefully done, the considered microstructures built are simply compromised, and the pump operation is degraded.

6. Biological application

Microfluidic technology has resulted in the development of high-powered instruments in order to manage the complete cellular environment, leading to discoveries and this technology has diverse advantages for microbiology. Classification of the biological application of micromixers and micropumps are presented in Fig. 7.

6.1. Micromixer

Gradient generators type of micromixer has abundant biological applications. The crucial biological method of concentration gradient based micromixers includes immune response, axon guidance, cancer chemotaxis, stem cell differentiation, and angiogenesis [203, 204].
The late step of the cancer disease is metastasis in which cancer cells diffuse to other organs. Intravasation and extravasation are two major steps of metastases.
Cancer cells are carried in the circulation system (the intravasation stage) and then spread to the organ tissues from blood vessels (in the extravasation stage). Some chemoattractants like growth factors and chemokines that are chemotactic cytokines regulate these steps. The chemoattractant gradient has a significant effect on the migration of cancer cells. Under controlled situations, gradient generators can imitate the environment in tissues.
The progression of modern cancer therapy can be reached by the realization of cancer metastasis in gradient generators. Wang *et al.*, [205] to study metastasis cells of breast cancer, used a parallel lamination generator to create an EGF concentration gradient.

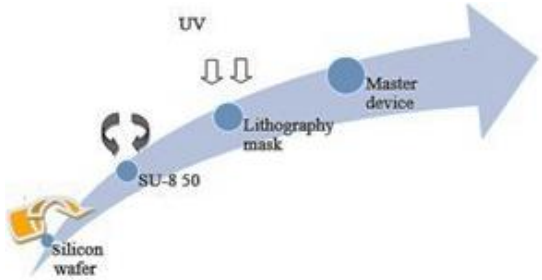

Fig. 6. Steps of photolithography.

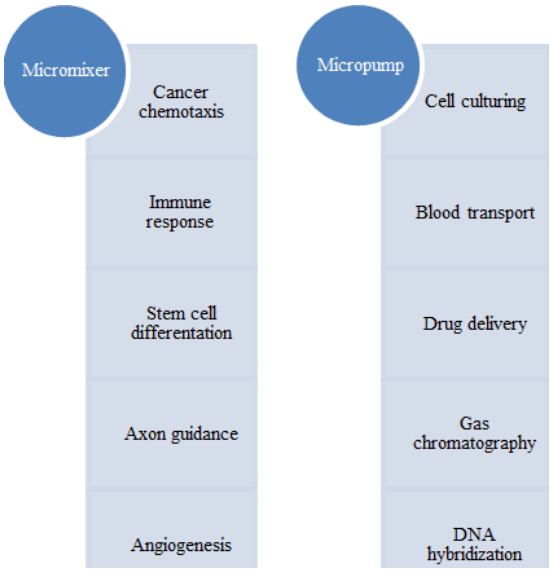

Fig. 7. Biological application of micromixer and micropump.

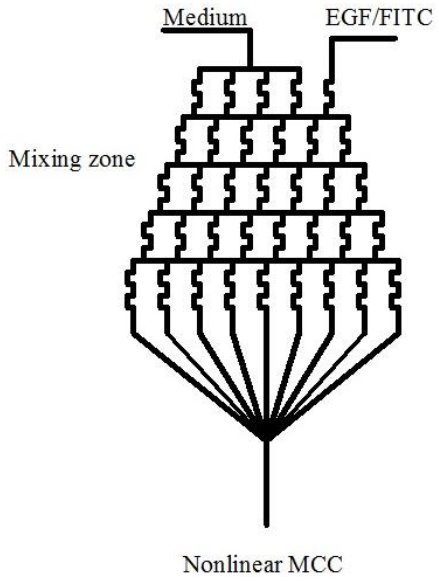

Fig. 8. Device concept of parallel lamination gradient generator.

The results represent the directional movement of cancer cells is different in a nonlinear and linear-gradient condition, and they moved more in a nonlinear gradient. Fig. 8 illustrates the device concept of a parallel lamination gradient generator.

A free diffusion generator was utilized by Abhyankar *et al.* [206] to study the metastasis of the rat mammary adenocarcinoma cells. Chemokines and their receptor impressed on the immune response. Leukocytes were recruited by chemokines to the infection site. In the blood of mammals, the most plentiful type of WBC is constituted of neutrophils or polymorphonuclear neutrophils (PMNs).

In the blood of mammals, the most plentiful type of WBC is constituted of neutrophils or polymorphonuclear neutrophils (PMNs). Neutrophils are one of the primary responders that immigrate to the site of infection during the early phase of inflammation. The migration of Neutrophils is done by the blood vessels and then interstitial tissue, following the gradient of the chemoattractant. Jeon *et al.* [207] utilized a parallel lamination generator to study human neutrophils' chemotaxis in a concentration gradient of IL-8 (chemoattractants). The results show that the neutrophil's manner relates to both the gradient and the concentration distribution form. More studies on the same platform [208] show that the average concentration of linear gradients has an extreme impact on the neutrophil's directed motility. Axon guidance is significant for nerve cell regeneration. Dertinger *et al.* [209] utilized a parallel lamination generator to study the impression of laminin gradient on the axon characteristics of rat hippocampal neurons. The orientation of axons was toward where laminin concentration was higher. Another significant factor impressing the axon guide is the mechanical stiffness of the substrate. Stem cells are those that can grow into specific types of cells in body organs and tissues. The differentiation of stem cells is controlled by several biochemical and biophysical factors [210]. Amadi *et al.* [211] studied the embryoid separation by a free-diffusion gradient generator.

Angiogenesis is the procedure in which new blood vessels grow from existing vessels. It is a biotic procedure in the growth, advancement, and healing the wounds. Nevertheless, angiogenesis also plays a key role in tumor transportation from a dormant to a malignant state [212]. Shamloo *et al.* [213] investigated the HUVECs response in a gradient of VEGF. In a free-diffusion generator, the linear gradient was created. The results indicated that not only average concentration but also gradient influence the directional migration of HUVECs.

6.1.1. Analysis application

To simplify on-chip measurement, the integration of micro coils for nuclear magnetic resonance (NMR) with the micromixer can be done (Fig. 9(a)) [214] Fluri *et al.* [215] combined T-shaped intersection with capillary electrophoresis (CE) separation to react the amino acids with the labeling reagent o-phthaldialdehyde (OPA; Fig. 9(b)). In this device, fluid flows were electrokinetically driven. Fast mixing that helps to trap meta-stable intermediates in rapid chemical or biochemical reactions with a micromixer was utilized for the freeze-quenching method.

The freeze-quenching method throws out the mixture at about –130°C from a mixer of continuous flow mixer via a small nozzle into an isopentane bath. The samples, which are frozen, consist of trapped reaction intermediates, which are able to easily check without the time limitation (Fig. 9(c)). The use

of the freeze-quenching method on a macroscale is limited due to the slow time of cryogenic fluids freezing and the longtime of mixing. The delay time is on milliseconds.

6.1.2. Purification and preconcentration

In biochemical analysis, it is crucial to detect sensitivity. The condition of the sample may impress the process's quality, like polymerase chain reactions (PCR).
Purification and preconcentration of a DNA sample are essential before PCR to promote the precision of pathogen detection. In addition, the higher concentration of sample causes higher detection sensibility, as well. Micromixers, considering the concept of filtering or trapping, can be utilized to control buffer concentration or to generate chaotic advection.

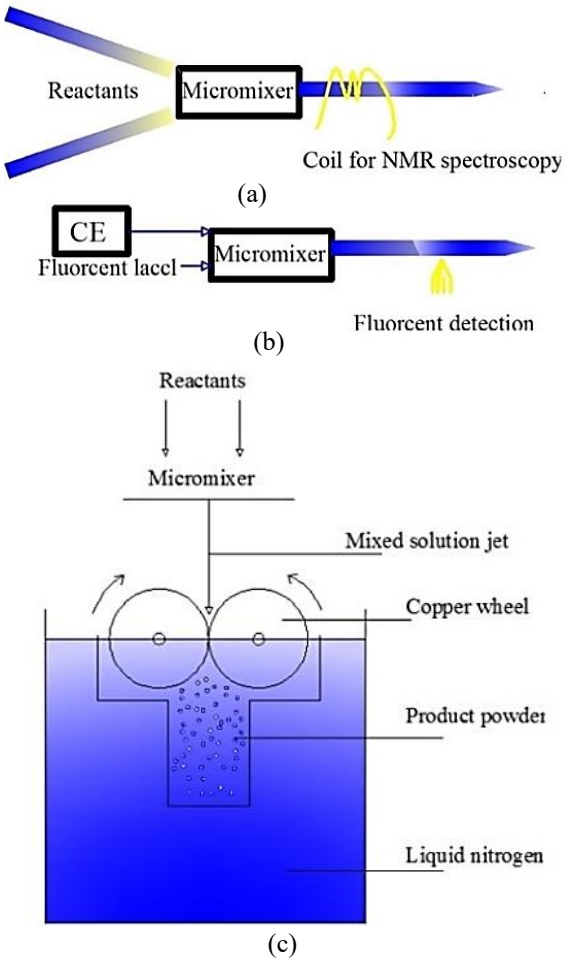

Fig. 9. Schematic of applications of micromixer in analysis; (a) NMR measurement [214], (b) CE measurement [215], and (c) freeze-quenching reactions [215].

Lee *et al.* [216] utilized a chaotic serpentine type of micromixer to purify DNA. The negative charge of DNA caused the glass surface to absorb it forcefully when the buffer is under a high salt situation. The other components of force, like protein or sugar, are sort of weak for glass absorption. Hence, the purification of DNA can be done by these collected beads. If a low-salt buffer is introduced to the packed chamber, the adsorbed DNA can subsequently be released and collected. The salt concentration stepwise variation in a buffer solution can be realized by the micromixer before flushing it through the packed chamber. They applied a micromixer to vary the concentration of $MgCl_2$. For this intention, 1:1 and 1:66 mixing ratios were controlled. Dielectrophoresis (DEP) can be used to trap, manipulate, and separate bioparticles, like viruses, bacteria, DNA molecules, and cells. Planar interdigitated electrodes (IDEs) are utilized for the nonuniform electric field generation needed for dielectrophoresis. Lee and Voldman [217] used a micromixer to bring more sample particles closer to the IDEs. Chaotic advection causes to increase in the quantity of the trapped particles on the surface. According to the mixer results, the quantity of the trapped particles is enhanced by 50% in comparison with a smooth and straight channel.

6.1.3. Biomolecular interactions

Biomolecular interactions such as DNA hybridization [218], DNA protein binding [219], and protein-protein interaction [220] often occur in living cells that are consequential in adjusting gene replication and expression and other biological activities [221]. Nucleic acid hybridization is a significant strategy at the gene level of biomedical analysis, like rapid high-throughput gene analysis [222, 223]. Liu *et al.* [224] used an acoustic micromixer to study the kinetics of DNA hybridization. The signal uniformity throughout the chip was seriously increased when the hybridization rate was 5-fold enhanced. The interaction kinetics between human telomere G-quadruplex and the single-stranded DNA binding protein (SSBP) was tracked by the dual-hydrodynamic focusing micromixer. Li *et al.* [221] showed the process

of how SSBP opens the folded structure of the G-quadruple.

Not only do micromixers play critical roles in biological and chemical utilization, but also are applied to accomplish significant operations like microfluidic switching; oxidation, nanocomplex, and adduct formation; supercritical fluid fractionation; measurement of velocity, etc. [225-231]. A rapid active mixer, which was based on the localized vaporization of a perfluorocarbon stream placed between two streams of an ultrasound transducer, has been represented by Bezagu *et al.* [226] (Fig. 10). The results showed that about 100 milliseconds after an acoustic pulse usage can be gotten a complete mixed PFC stream with the adjacent fluid streams. Also, the laminar flow was established again almost at a similar time. Therefore, the mixed and PFC phase could be simply detached at the channel outlet. Van den Brink *et al.* [229] designed a micromixer to oxidize and form an adduct of xenobiotics. That was planned especially for the mixing of liquids in the shallow channels for electrochemical flow cells. In addition, the operation concept was based on the concentration gradient orientation over the whole height of the channel. That mixer provides the ability for mixing within seconds after generation with 80% efficiency which is 8-fold higher in comparison with a T-junction mixer.

6.1.4. Micro total analysis systems or lab-on-chip

The main applications of Micro Total Analysis Systems or Lab-on-Chip (LOC) that are miniaturized devices and made on a chip include chemical or biological analysis and discovery of drug [232]. The performance of LOC devices relates remarkably to moving fluids for the performance of their operation.

Due to micropumps' capability to control and deliver diverse liquid kinds at the needed pressure, they are effectively utilized in LOC or μTAS. As the main goal, μTAS type of micropumps control the fluid flow through microchannels. LOC applications of micropumps must be able to make fewer reagent quantities or sizes of the sample and, besides accurate control and delivery of a vast measure of pressure and flow, incorporate low-cost disposable materials. An analysis system requires a fully autonomous micropump which must be able to operate without human intermediation that causes to avoid pollution. Zhang and Eitel [233], Wang *et al.* [234], and Ha *et al.* [235] have worked on LOC/μTAS applications of mechanical micropump. Some of the researches that have been done for the biological application of micromixers are represented in Table 2.

6.2. Micropump

Micropumps such as micromixers have been used for biomedical applications that will be described. Whenever cells located in a microchannel or chamber are exposed to a stream, and it causes a situational experience that is more similar to cases faced in vivo environments. The critical issue in accomplishing cell culture in microfluidic devices is developing methods to deliver the culture media to cells encased in devices that are smaller than the hand palm [236-253] Chang *et al.* [237] presented a loop-mediated isothermal amplification (LAMP)-based microfluidic system in order to the aquaculture pathogens rapid finding based on a system of normally-closed micropump, microvalve, chamber of LAMP reaction and wash unit. In this device, the magnetic beads, which were covered with capture probes, separated the target pathogen DNA. Then a LAMP process was produced to amplify the extracted DNA segments and eventually, by the use of a real-time fluorescent optical detection method the amplified productions were recognized.

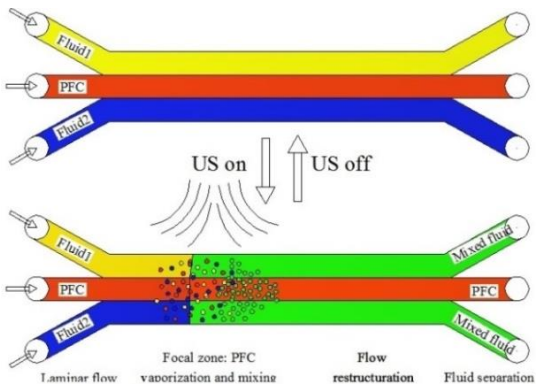

Fig. 10. Efficient mixing in microfluidic channels by vaporization of an ultrasound-induced perfluorocarbon phase.

6.2.1. Cell culturing

Microfluidic devices are marvelous instruments to culture cells because they are capable of controlling physical and chemical environments over than common culture of cells in vitro in Petri dishes or well plates.
In a pneumatic micropump, compressed air with 70 kPa pressure transports the species through the microfluidic system at 400 µl/min. The both proposed procedures attained a reduction of 10-fold in the reagent utilization over traditional methods and permitted the whole detection and isolation to be done within 65 min with the limitation of ten copies detection. A little while later, the same group introduced PCR and LAMP-based integrated microfluidic systems for culturing diverse types of cells, containing bacteria, etc. [238-243]. Pump-less types of microfluidic systems, like digital microfluidics (DMF), are new and significant techniques to manipulate liquids in microdevices. In these microfluidic systems, the pump is a microfluidic chip section, and EWOD carries out the manipulation of the liquid droplet. A DMF system has been developed to evaluate multiplexed cell-based apoptosis by the Wheeler group [244]. The results showed that it was better than conventional pipetting and aspiration techniques for preserving weak adhered apoptotic cells for analysis. By using the DMF procedure, the utilization of regent 33-fold decreases relative to common methods. Also, the lower detection limit and a premier dynamic range are attained. A similar DMF method is used to culture variant other types of cells by this group [245-249].
Ma *et al.* [251] created an integrated electrostatic sampler for bioaerosols. Shaegh *et al.* [253] represented a rapid prototyping technique for PMMA whole-thermoplastic chip fabrication, including microvalves, pumps, and bioreactors. It showed that the peristaltic micropump can do the liquid flows continuously pumping at 3.5 microliter per min for 10 days constantly.

6.2.2. Blood transport

The main transport fluid all over the body is blood, and it is involved in all bodily functions. Because it provides oxygen and nutrients in order to fight infection and play a role in getting rid of waste, is a significant human health indicator, and thus is utilized in a lot of biomedical assays. Recently, various microfluidic devices have been developed to test blood and analyze which micropump is an important element in these devices and is applied to blood transport through the system [254-263].
Jebrail *et al.* [254] suggested a DMF system that contains a module of extraction and a purification module based on DMF integrated with a bridging droplet that could extract RNA from blood lysates and purify better in microscale volumes. The results indicated that compared with conventional methods, the DMF system achieved equal quality and efficiency of RNA by consuming 12-fold fewer reagents and being more than 2-fold faster. Feeny *et al.* [255] in order to attain the time-controlled extraction of samples dried onto filters, proposed an advanced pumping system, which uses the gas permeability of PDMS for fluid transportation in a microchannel. The system was applied for the extraction of 250 micromolar to 1 millimolar dopamine from dried filter samples and the time of elicitation was almost 5 min.
Zehnle *et al.* [256, 257] proposed a procedure to pump the liquids on a rotational microfluidic disc in a radially inside direction by use of an air-filled chamber. When the disc rotates, centrifugal forces compress the air. Although perfect liquid volume transition to the disc center is not guaranteed in this technique, transfer of most volume can be done with success without the requirement for any external actuation mechanisms or dedicated fabrication steps. The results indicated the micropumping mechanism is efficient by more than 75% per pump cycle.
Song *et al.* [258] presented an integrated microfluidic device for sorting. The operation mechanism of this microfluidic device is based on size differences between non-target and target cells. This device can sort 100 target cells in 60 s. The electromagnetic pump actuation had no effect on the detection and sorting processes of RPS cells. A peristaltic micropump that delivers a whole blood sample with optimized fluid chambers, the modified discharge, and a less reverse flow is introduced by Kant *et al.* [259].

Table 2. Application of micromixer for biological analytical process [13].

First author	Ref.	Year	Micromixer type	Objective	Materials	Index (%)	Flow rate
Chen	307	2007	Filtration mixer (passive)	Cell separation, lysis, and DNA purification	Whole blood	M: ~90%	1–25 µL/min
Huh	308	2007	Actuated mixer (active)	Cell disruption	Escherichia coli	M: ~90%	1.96 Hz
Nason	309	2011	Zig-zag shaped mixer (passive)	Drug screening	SaOS-2 cell	M: 79.4%	0.3–3 µL/min
Wang	310	2012	Ribcage mixer (passive)	Measurements of protein concentration	Bovine serum albumin (BSA)	M: ~100%	0.05 mL/h
Louns-bury	311	2013	Serpentine mixer (passive)	PCR system	B globin, gelsolin genes	A: 6-fold	10 µL/min
Li	227	2013	Dual-focusing mixer (passive)	Interaction of DNA–protein	G-quadruplex, SSBP	M: 93%	35 kPa
Yang	312	2015	Vortex-type mixer (active)	C-reactive protein measurement	C-reactive protein	M: > 96% (7 Hz)	300 µL/min
Rajabi	313	2014	SHM and SAR mixer (passive)	Cell perturbation, lysis, and separation	CHO cell	CL: 100%	2000 µL/min
Femmer	314	2015	SHM mixer (passive)	Gas-liquid contact oxygenation	Red blood cell	N/R	Re = 10
Cosen-tino	315	2015	3-SERP mixer (passive)	Lysis of red blood cell	Red blood cell	M: 93%	Re = 0.1
Gao	316	2015	Acoustic mixer (passive)	Antibody-antigen binding assay	Antibody-antigen	B: >50%	125–150 Hz
Wang	317	2013	USCC mixer (passive)	Bacteria detection and quantification	Escherichia coli	M: >80%	Re > 80
Petkovic	318	2017	Rotary mixer (active)	Detection of Hendra virus	Hendra virus	N/R	Re = 0.02
Petkovic	319	2011	Serpentine 3D mixer (passive)	Detection of multiplex pathogen	3 bacteria cells, barcode DNA	CP: 100%	3.8–100 µL/h
Liu	320	2016	3D U-type mixer (passive)	Biomacromolecules folding kinetics analysis	G-quadruplex	M: >90%	0.21 µL/min
Balbino	321	2013	Vortex mixer (passive)	Produce pDNA/CL complexes	Plasmid DNA, cationic liposome	N/R	140 mm/s
Lin	322	2014	Bubble-driven mixer (active)	Bladder cancer biomarker detection	Bladder cancer	M: 90%	25–400 mL/h
Aguirre	323	2015	Trapezoid type mixer (passive)	v/v blood Incubation and cancer cell separation	MCF7 breast cancer cell	B:2%	Re = 11
Lee	324	2017	Multivortex mixer (passive)	Circulating tumor cells isolation	MCF-7 cell	R: 90.63%	400 µL/min

A: Efficiency of amplification; B: Efficiency of Binding; CL: Efficiency of cell lysis. CP: Efficiency of cell capture; D: Efficiency of depletion; M: Mixing index; R: Recovery efficiency; N/R: Not reported

Manshadi *et al.* [261] carried out numerical simulations to study and upgrade the performance and voltage demands of parallel electroosmotic micropumps to non-Newtonian fluids transport. Kumar *et al.* [263] designed a without-valve micropump with single and multiple inlet- and outlet adjustments to transport cell lines and diluted blood samples. The experiments indicate the maximum flow rate of diluted blood samples is 106 µl per min at 135 Hz.

6.2.3. Drug delivery

A specified level of concentration is required for drugs or chemical agents to achieve the desired therapeutic effect in the clinic. As a result, a lot of new techniques of microdevices for controlled delivery of drugs have been suggested, which are designed to deliver drugs to exactly measured quantities at the best time and in the best situation. Such instruments usually include polymer or silicon-built reservoirs, micropumps, the controlled-release motive force, and needles for drug delivery, dispensing, and storage [264-266]. High performance, accuracy, and reliability of drug transfer from the reservoir to the objective position cause micropumps to be a very important device in drug delivery applications [210-225]. Cobo *et al.* [267, 268] presented a wireless micropump that was capable of being implanted for persistent drug administration in cancer patients by a low-power electrolysis actuator. A static experimental trial confirmed the suggested pump feasibility for applications of anti-cancer drug delivery that showed the micropump delivered a single bolus diurnal with rate of microlitre per min for three weeks with success. In addition, an in vivo research presented the tool could precisely supply a 30 µl per day to a rodent that was moving freely, over 21 days without changing the flow rate by more than 6%. Self-powered types of micropumps can be used in various fields, and controlled drug delivery is one of them [269-273]. One method is to apply the pump to induce fluid flow in order to convective molecules release that is embedded before the pump. Sen group [269, 270] exhibited an enzyme micropump including urease enzymes and positively charged hydrogels. The obtained result by use of catalase, urease, lipase, and glucose oxidase indicated that increases in the speed of pumping occur when both concentration of substrate and reaction rate increase [271].

Unexpectedly, the results of the solutal and thermal buoyancy impact study on the micropump action based on phosphatase indicated notwithstanding that the catalyzed reactions are strongly exothermic, thermal effects had just a little impress on the observed fluid flow. These studies were performed by use of reactants series with familiar parameters of thermodynamic and kinetic [272].

Microfluidic drug delivery droplet devices traditionally utilize syringe pumps for driving the drug via the distributor catheter. Nevertheless, most new designs use an integrated micropump for system size reduction [274-278].

Okura *et al.* [274] produced a microfluidic device to generate droplets that were made of a T-junction channel geometry on a PDMS microfluidic chip, which includes two inlets and one outlet reservoir with a PZT diaphragm micropump and its controller. This device was able to produce up to 10 mL per min water flow rates by utilizing a standard wave whose voltage is 250 V, and its frequency is 60 Hz. Moreover, the creation of droplets was represented to be strongly reproducible so that the uniformity of droplet size was lower than 4%. Several other micropumps for delivering the drug have been described [279-282]. For instance, Akyazi *et al.* [223] constructed a microfluidic analytical device based on a paper that utilized an ionogel negative passive pump to adjust the flow orientation. Uguz *et al.* [282] produced a microfluidic ion pump that can deliver a drug through electrophoresis with the use of no solvent. The results indicated the device can operate at low voltage, and its capacity for drug delivery and ON/OFF ratio is high. Consequently, this micropump feasibility for in vivo drug delivery was justified.

6.2.4. DNA hybridization

DNA hybridization enables to detection of nucleic acids sensitively, specifically, and rapidly in a sample. Hence, it provides a primary test to detect and identify pathogens in clinical samples [283-285]. Chia *et al.* [286]

and Ullakko *et al.* [287]proposed to utilize their work on micropumps for the purpose of DNA hybridization and profiling. The main demand of micropump for DNA hybridization is careful DNA sample delivery with a reduction in the size of the sample or reagents in conjunction with compactness and biocompatibility. The bidirectional flow capability of the peristaltic micropump is beneficial in the biological sample's motion in the back-and-forth direction, and it is also one of the requirements of this specific application [288].

6. Conclusions

This article provides a wide overview of advances in micropumps and micromixers technologies. The review categorizes the various types of microfluidic devices and fabrication designs. The different designs of micromixers and micropumps and their operation conditions, as well as the numerical procedures, are discussed. The recent applications of microfluidics in biology are described in this paper. Certainly, there is a room for new designs and principles, and this work is expected to be important for future development.

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