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The microfabricated electrokinetic pump: a potential promising drug delivery technique

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Directly delivering liquid using direct current power was a dream for 40 years. Now, the electrokinetic pump can accomplish it. This review reports recent developments in microfabricated electrokinetic pump technologies and their applications, and also discusses the electrophoresis pump and elctroosmotic pump, as well as the materials and fabrication methods frequently used for the production of these pump devices. Electrokinetics pumps can be used to deliver pure water, pure polar organic solvents, inorganic buffer and biomacromolecules, with wide applications for the delivery of liquids. These devices have the potential to become drug delivery systems, for the precise, timed and/or targeted delivery of drugs. Future trends, limitations and possibilities are also discussed.

Keywords: electrokinetic pump, electroosmotic flow, elctroosmotic pump, electrophoresis pump, microdosing systems

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1. Introduction

Research into controlled drug delivery technologies goes back to the 1970s. In the last decade, controlled drug delivery technology increasingly attracted researchers' attention, especially in biomedical control engineering. With the rapid development of microelectromechanical systems (MEMS), there was a trend of integration between micro drug delivery and MEMS fabrication technology, and an increase in its application in medical fields [1-6]. Such systems are mainly aimed at serious chronic disease, such as diabetes, melancholia, malignant lymphoma, or acute, life-threatening illness, such as heart attack, stroke and septicaemia. The trends in new, controlled-release devices are toward the optimisation of site-specific targeting and the matching of the drug release to the circadian rhythm. In addition, drug delivery technology covers other specific needs such as: i) to obtain a slow release of water soluble drugs; ii) to improve the bioavailability of poorly water soluble drugs; iii) to deliver two or more agents in the same formulation; iv) to develop carriers that are readily eliminated from the body; v) to improve the biodistribution of drugs with a high rate of metabolism or rapid clearance; vi) to control the release of highly toxic drugs; and vii) to improve targeting to the tissues or cells [7]. In general, drugs or chemical agents have to be present at certain concentrations so that the desired therapeutic effects can be achieved. Drug concentrations below or above the designed limits might cause toxic side effects or result in ineffective therapy. Certain physical or chemical properties of doses, such as biodissolution, biocompatibility and sensitivity to pH and temperature, should be considered in drug delivery. Ideally, with the automatic dosing system, irregular/incorrect dosing or sudden death of the patient should be prevented. Based on real-time measurement from microsensors, an appropriate and effective dose will be precisely calculated by the controller and released by microactuators/mechanisms in real time. In microdosing or drug delivery control systems, the driving methodology and biocompatibility are the two key issues that interest researchers. As these devices are applied in humans,

safety and anti-infection will be the major concerns. A microdosing system or microscale drug delivery system generally consists of micropumps, microsensors, microfluid channels and the necessary related circuits. The driving devices or micropumps used to dispense drugs or therapeutic agents into the human body have been a key component that requires good design and fabrication.

Technically, micropumps are categorised into two types: mechanical and non-mechanical. The mechanical type needs a physical actuator or mechanism to perform the pumping function. Most mechanical pump consists of valves and an actuating membrane, so fatigue and reliability are the main concerns. However, non-mechanical pumps have to transform certain non-mechanical energy into kinetic momentum so that the fluid in microchannels can be driven. These micropumps normally cannot achieve a sufficient flow rate, driving pressure or fast response. Non-mechanical pumps can be further categorised into electrical, chemical, magnetic and surface-tension-driving micropumps. The basic requirements of the pump in drug delivery are:

- low driving voltage: the ideal voltage is in the range of 0 – 36 V
- a high-pressure head (at least 1.0×10^4 Pa), volumetric flow rate (from nl/min to at least several µl per minute) and lower power consumption
- a high degree of biocompatibility
- a wide, working concentration range of drugs or chemical agents
- relative insensitivity to pH
- an automatic dosing system and real-time precise measurement
- fabrication in miniaturised chip-based or implantable microchips

No drug delivery pump can meet all these requirements. Comparisons have been made to unveil the advantages and shortcomings of different pump technology designs [101,8]. As the microdosing and drug delivery systems cannot tolerate any detrimental influence from the driving force, electrostatic micropumps and piezoelectric micropumps have to be ruled out because of the high driving voltage required. Electrohydrodynamic and magnetohydrodynamic micropumps employ working fluid with a certain degree of electric conductivity. This would narrow down the application fields, particularly in biochips. Although the bubble-type and most of the non-mechanical micropumps do not need physical actuation components, their slow responses do devalue their effectiveness. Shape memory alloy micropumps suffer from a relatively low flow rate and insufficient biocompatibility. Indeed, in addition to applied voltage and the driving methodology, the other crucial issue for microdosing is the degree of biocompatibility. This is extremely important for the biological applications of implants. In comparison, the electrokinetic pump (EKP), electrophoresis pump (EPP) and the electroosmotic pump (EOP), provide a variety of fluid pumping schemes that provide a high-pressure head, adjustable flow rate and simple design. Ionic, conductive, polymer film micropumps possess the advantages of a long stroke, low driving voltage, qualified flexibility and biocompatibility [9,10]. Bimetallic micropumps have the advantages of a high flow rate and pressure head [11,12]. If the associated flexibility and biocompatibility can be further improved, they would become more competitive. In this review, the focus is on micro-fabricated EKP technologies. The related techniques, materials and fabrication methods for the production of such pump devices are also discussed.

2. The electrokinetic pump

Electrokinetics is a branch of electrohydrodynamics that describes the coupling of ion transport, fluid flow and electric fields; it is distinguished from electrohydrodynamics by the relevance of interface charge at solid–liquid interfaces. In this section, the authors describe EKPs relating to electrokinetic phenomena. There are two main types of EKPs: electrophoresis pumps and EOPs, which are all based on the electrokinetic phenomena (electrophoresis flow and electroosmotic flow [EOF]). The EPP is based on a low pressure ($0 – 1 \times 10^4$ Pa) and a micro flow rate (nl – µl/min), and is widely used in capillary electrophoresis and lab-on-a-chip systems. When an EPP made from glass capillaries operates, the capillary channel walls are naturally negatively charged at pH 2 – 10. During the electrophosesis process, the positively charged and non-charged species move in the direction of EOF, and the negatively charged species move in the opposite direction, as shown in Figure 1. The pressure generation will obviously be small because of the large diameter of the capillary channel (50 – 320 µm).

The basic theoretical considerations about the EPP can be found in any electrophoresis book. The volume flow rate (Q) of the EPP it is related to the cross-sectional area of the channel (A) by Equation 1.

$$Q = \left(\mu_E + \frac{\varepsilon\zeta}{\eta}\right) EA \quad (1)$$

In equation 1, μ_E is the electrophoretic mobility, E is the electric field strength, ε is the dielectric constant, ζ is the zeta potential, and η is the viscosity of the liquid delivered.

As the channel of the capillary gets smaller and smaller, for example from tens of microns to several microns, the EOF will gradually dominate the whole flow because it only occurs in the presence of an electrical double layer at the surface of a channel. When the channel is a nanosized channel, the magnitude of the electrophoretic mobility of ions in an electric field is so small that is often ignored – the EPP becomes an EOP, which is discussed below.

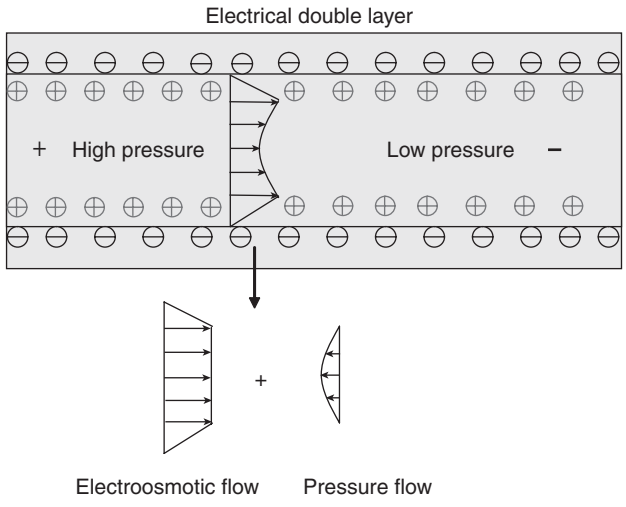

Figure 1. Principle of the electrophoresis pump. In general, the inner wall of the silica capillary carries a large number of anion SiO^- on its surface. Thus, the electrolyte that contacts the walls is protonated. If an external electric field is appropriately applied at the electrodes located at the longitudinal ends of microchannel, the fluid will be driven towards the cathode due to Coulomb force. This is referred to as an electroosmotic flow. No actual mechanical actuator is needed for this type of pump.

The EOP uses electroosmosis in charged porous media to generate pressure and flow in microdevices, which are formed by applying voltage across a porous bed, typically a monolithic porous media or a bed of packed silica particles. The EOP is essentially driven by electrokinetic forces forming an electrokinetic flow (EKP: electrophoresis flow and EOF), and is therefore also known as an EKP. The EOP is a high-pressure ($0 – 1 \times 10^7$ Pa) low flow-rate (nl/min to several hundred µl/min) technique. It works similarly to capillary electrochromatography. As a micropump technique, the EOP can avoid some crucial defects encountered in the conventional, high-pressure, piston-driven mechanical pumps, such as leakage, material fatigue and wear-out, stroke and noise. Recently, the nanochannel pump has been mainly based on electroosmosis, with functions similar to EOP, and draws more and more attention due to its easy integration into the microsystem. There are many fabrication techniques for various high-pressure EOPs, such as packed-bed EOPs [13,16], sintered porous glass [17], macroporous polymer monolith pumps [18] and parallel channel pumps [19,20]. Table 1 shows a comparison of their characteristic maximum pressure, flow rate and applied voltage.

2.1 Packed-bed column

The packed-bed column can be used to fabricate a high pressure EOP [22] (Figure 2). The packed-bed EOP packed columns are similar to those columns used in capillary electrochromatography [13-16,102]. The interstitial spaces between the particles act like multiple flow passages in parallel. The packed channel can be modeled as an array of (N) capillaries with an inner radius equal to the average pore radius of particles (a). The volume flow rate of the porous medium (Q), which is calculated for N of these capillaries, is calculated by equation 2 [13,24].

$$Q = -\frac{pA\varepsilon\zeta E}{\tau^2\eta}\left[1-\frac{2I_1(\kappa a)}{\kappa a I_0(\kappa a)}\right]-\frac{pA\Delta P a^2}{8\tau^2\eta L} \quad (2)$$

In equation 2, E is a potential gradient, τ is the tortuosity, p is porosity, ΔP is the pressure difference along the length of the capillary, and I_0 and I_1 are the zero- and first-order modified Bessel function of the first kind, respectively. When the counter flow rate inside the channel eventually counterbalances the EOF (i.e., the net flow rate is zero), the maximum pressure (ΔP_m) generated across the porous structure is obtained from Equation 3.

$$\Delta P_m = -\frac{8\varepsilon\zeta EL}{a^2}\left[1-\frac{2I_1(\kappa a)}{\kappa a I_0(\kappa a)}\right] \quad (3)$$

The maximum flow rate Q_m of the entire porous medium under the condition of no counter pressure is:

$$Q_m = -\frac{pA\varepsilon\zeta E}{\tau^2\eta}\left[1-\frac{2I_1(\kappa a)}{\kappa a I_0(\kappa a)}\right] \quad (4)$$

The relationship between the flow rate and the pressure of an EOP is:

$$\Delta P = \frac{\Delta P_m}{Q_m}Q + \Delta P_m \quad (5)$$

The thermodynamic efficiency of the EOP is η, which can be defined by Equation 6. The efficiency is the ratio of the useful pressure work (ΔPQ) to the applied electrical work (VI). The total current (I) is the sum of Joule current in the bulk liquid and the current associated with electromigration in the electrical double layer.

$$\eta = \frac{\Delta PQ}{VI} \quad (6)$$

Table 1. A comparison of typical electroosmotic or electrokinetic pumps based on the electroosmotic flow principle.

Pump types	V	Q_{max} (∝l/min)	P_{max} (MPa)	Structure*	Year	Ref.
Electrophoresis pump	1 – 500	1 – 20	0.01 – 0.002	Simple	2003	[22]
Packed-bed EOP	2000	3.6	2.0	Complex	2001	[13]
Multiple open-channel EOP with channels of 1 – 6 µm in depth, 4 – 50 mm in length	1000	0.010 – 0.40	0.55	Simple	2002	[19]
Macroporous polymer monolith packed-bed EOP	50	410	0.38	Simple	2004	[18]
Packed-bed EOP	5000	2	11	Complex	2005	[21]
Nanometre silica grains packed-bed EOP	10000	1 – 10	20	Simple	2005	[16]
Ion-exchange polymer membrane EOP	30	6	0.45	Simple	2005	[29]
Nanochannel EOP	500 (E)	0.030 – 0.100	0.6 – 1.4	Simple	2006	[20]

* Precise flow and pressure characteristics of the EOPs are achieved by controlling the electric potential across a fluid filled ,porous packed-bed or membrane. The structures mentioned here denote maneuverability to realise the corresponding pumping types into miniaturised medical device.
E: Elelectric field strength (V/cm); EOP: Electroosmotic pump; P_{max}: Maximum pressure; Q_{max}: Maxium flow rate; V: Voltage.

The physical properties of the pump, including tortuosity, porosity, effective pore diameter and zeta potential of the pumping surfaces, can be derived from the flow-pressure data in combination with measurements of resistance and wet versus dry weight. Strategies for the optimisation of EOP performance, based on physical geometry and the properties of the working fluid, have also been investigated [13,14]. Some mathematical models on EOF can help us to understand this type of pump [17,24].

2.2. Porous polymer monoliths

As the preparation of porous, polymer monoliths is simple, and their porous properties and surface chemistry are easily controlled, they are ideally suited to the fabrication of porous polymer monoliths columns or disks as the active elements of EOPs, which can avoid the fabrication of frits or filters. As the pore size and pore volume of the monolith, as well as the properties of the grafted layer such as its chemistry, thickness and crosslinking density, can be easily controlled, a variety of pumping devices can be prepared to achieve the desired flow direction, flow rate and pressure. Tripp *et al.* [18] have prepared poly(chloromethylstyrene-co-divinylbenzene) monolith EOPs, which can reach pressures as high as 0.38 MPa and electric-field-specific flow rates of up to 0.41 ml/min, both at 50 V. It is a possibility for porous, polymer monolith EOPs to be designed for chip-based systems. Imprinted polymers are now well established as materials for molecular recognition, chromatographic separation and analytical sample enrichment, but are now being increasingly considered for active biomedical applications such as drug delivery and controlled release systems [25]. The combination of the advantages of the imprinted polymers and synthetic methods for the porous polymer monoliths EOPs suggests that the polymer pumps will have properties of real value in the biomedical field, leading to a promising future for these materials, such as in drug delivery devices.

2.3. Channel electroosmotic pumps

Multiple, open-channel EOPs are one type of micropump configuration, consisting of hundreds of parallel, small-diameter microchannels or even nanosized channels, as shown in Figure 3. Channel EOPs can deliver stable fluid at flow rates and backpressures compatible with common, analytical applications on a microfluidic network in microchips (i.e., 0.05 – 1.0 µl min^{-1} and up to 100 psi), and sufficiently small to enable multiplexing of individual pumps. There are numerous advantages of channel EOPs, for example they can be easily integrated on microfluidic platforms and utilised for fluid propulsion on the chip; its fabrication using standard photolithographic and wet chemical etching technologies ensures high manufacturing reproducibility; and finally, the simplicity of the design ensures robustness, reliability, and trouble-free operation. Channel EOPs are essentially parallel, multiple EPPs. When the dimension of the channels is changed to the nanometre range, it can be used as a high-pressure pump, with the same functions as those of packed-bed EOP. The nanochannel pump occupies an area of only a few square millimetres and can be easily interfaced with other functional elements of a micro total analysis system [20,26,27].

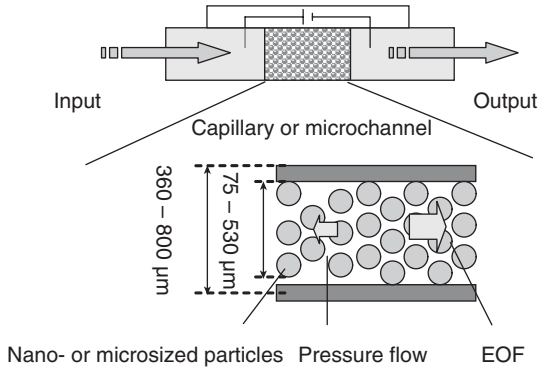

Figure 2. A schematic of a high-pressure, packed-bed EOP setup and expanded view of local position of the packed-bed column. Voltage applied across a capillary packed with silica microparticles leads to flow and pressure generation. The voltage gradient induces EOF from left to right; the pressure gradient induces Pouiseille flow from right to left. Total flow is a linear superposition of EOF and pressure-driven Poiseuille flow.
EOF: Electrophoresis flow and electroosmotic flow; EOP: Electroosmotic pump.

Channel EOPs show the potential to be easily fabricated and integrated in chip-based systems. The unique feature of integrated EOPs is their ability to pump various solutions, regardless of their intrinsic characteristics, such as pH or ionic strength, with the exception of viscosity. Typical flow rates achieved are in the nanolitre per second range, depending on the number of microchannels connected in parallel and the voltage applied. Lazar and Karger [19] have described a fully integrated, miniaturised pumping system for the generation of pressure-driven flow in microfluidic platforms, as well as theoretical considerations. Pumps with microchannels of 1 – 6 µm in depth, 4 – 50 mm in length and an overall area of a few square millimetres were constructed. Flow rates of 10 – 400 nl/min were generated in electric-field-free regions in a stable, reproducible and controllable manner. Pressure of up to 80 psi was produced. The micropump was used to deliver peptide samples for electrospray ionization-mass spectrometric (ESI-MS) detection.

When electrokinetic pumping channels are in the nanometre range or the cross-section and height are in the sub-micrometre range, it can be referred to as a nanochannel EKP. These techniques are being investigated using on-chip systems that can be used as high pressure pumps. Wang *et al.* [201] fabricated a nanochannel-based pump delivering liquid drugs. Lazar *et al.* [20] has described a microfluidic liquid chromatography system for proteomic investigations. They used a multichannel EOP to provide the necessary functionality for eluent propulsion and sample valving. EOPs are typically reported to have thermodynamic efficiencies of only a few percent or less. But, Min *et al.* [29] showed that efficiency as high as 15% may be attainable when using uniform submicron-depth microchannels in

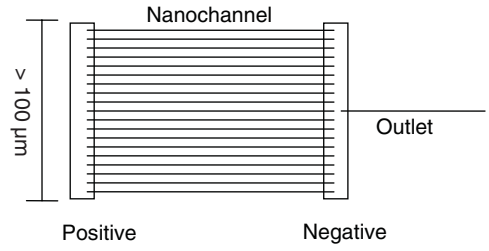

Figure 3. A schematic view of a channel pump equipped with 19 capillaries connected in parallel. The small pump is a nanochannel pump that can be easy fabricated on-chip.

substrates with moderately high zeta potentials, as well as when using electrolytes with low specific conductivity. This explains why nanochannel pumps have relatively high efficiencies.

2.4. Membrane-based EOPs

EOF occurs in a wide variety of membrane systems, and is always in the direction of counterion flow. Membrane-based EOPs are one type of non-mechanical pumping of liquids, using a membrane to achieve special function. Brask *et al.* [29] had fabricated and tested an inline frit-based EOP with ion exchange membranes. The pump is more stable due to a new flow component that ensures a controlled width of the diffusion layer close to the ion exchange membranes. The pump casing is constructed of polymers, and the electroosmotically active part, the frit, is made of nanoporous silica. The pressure capability of the pump is $Ep_m/EV = 0.15$ bar V^{-1}. The flow rate to current ratio is $Q_m/I = 6$ µl min^{-1} mA^{-1}. This translates to $Ep_m = 4.5$ bar and $Q_m = 6$ µl min^{-1} at EV = 30 V. The pump has been tested with four different buffer concentrations. Zeng *et al.* [30] have fabricated a nanoscale, polymer-silica hybrid nanochannel array with an average channel size of 50 nm, by electrokinetically inducing a silicification reaction within a polymer template.

Some nanoporous membrane pumps may help in the conception of novel membrane-based EOPs. Desai *et al.* [31] have described an approach to create precise, nanoporous mmbranes for cellular delivery based on micro- and nano-technology. Membranes can be microfabricated to present uniform and well-controlled pore sises as small as 7 nm, with tailored surface chemistries and precise microarchitecture. Such a design may overcome some of the limitations associated with conventional encapsulation and delivery technologies, including chemical instabilities, material degradation or fracture, and broad membrane pore sises. These platforms can be interfaced with living cells to allow for biomolecular separation and immunoisolation. Applications of these nanoporous membranes range from cellular delivery and cell-based biosensing to *in vitro* cell-based assays.

2.5. Related techniques for achieving drug delivery

When microfabrication EOP technologies are used to control drug delivery, certain physicochemical properties of the delivered doses, such as biodissolution, biocompatibility, pH sensitivity, driving voltages and temperature should be considered. In the following four key points, the authors discuss the driving voltage of the EOP, the drug concentration, the pH value and the degree of biocompatibility.

One major drawback in the conventional design of EOPs is the use of a high voltage to drive the pump. The driving voltages of the present EOPs are generally high, and cannot be used to deliver drugs to the human body. The ideal voltages of the micropumps have to be limited to ~ 5 – 12 V. The desired EOF pumps should be powered by a battery and, hence, be portable. Takamura *et al.* [32] have reported a low-voltage cascade EOP and made an interesting contribution to the field. Brask *et al.* [33] have reported the theoretical analysis of this kind of pump. Chen *et al.* [21] have reported the design, fabrication and theoretical characterisation of 1- to 3-stage EOPs. The principle of the multi-stage EOPs shows us an important direction of using multi-stage EOPs in a chip as a microfluidic component.

In general, drugs or chemical agents have to maintain certain concentrations so that the desired therapeutic effect can be achieved. A drug concentration below or above the designed limits might cause toxic side effects or render the therapy ineffective. When a high drug concentration is delivered with an EOP, Joule heating has to be considered. EOPs are normally used to deliver $1 – 10 \times 10^{-3}$ mol/l inorganic buffer, which is sufficient for most drug delivery purposes; the higher the drug concentration, the higher the chance of Joule heating, poor thermal efficiency and the generation of bubbles. The alternating current (AC) EOP is a solution for making bubble-free, palladium-electrode pumps [34]. The purpose of the AC EOP is to make a system with a large flow rate (~ 10 µl/min^{-1}), high pressure (~ 1 bar) and low voltage (30 V). The pump is operated in AC mode with an electroosmotic actuator in connection with a full wave rectifying valve system. A device, known as the flow field effect transistor permits high-speed unidirectional flow to be achieved with an AC drive voltage, and is consequently bubble-free. It operates by synchronously modulating the zeta potential in a 'gate' region of the channel, using a separate voltage signal. The ideal pump should not be sensitive to pH. Recently, a fritless EOP with reduced pH dependence has been fabricated on a glass microchip [35]. The chip design consists of two 500 µm channels. One channel is packed with anion exchange beads and the other is packed with cation exchange beads. The two channels produce convergent EOF streams. The pump can deliver solutions over an extended pH range of 2 – 12, which is a significant advantage over previously fabricated EOPs, which typically have a more limited pH range. The pump has the c pability of pumping nonconductive and highly conductive liquids to microreactors by the use of negative pressure applied to a reservoir containing the fluid. It is expected that the pump will be used in future microfluidic systems in applications such as reagent delivery, sample infusion for ESI-MS, flow injection analysis and separations. Using the additives to improve the performance of EKPs has proved to be an effective method [36].

Another key issue in drug microdosage delivery is biocompatibility of the pump materials. Even with special surface treatment [37-39], the MEMS devices can still provoke an immune response. EOPs operate using a very simple mechanism: EOF is induced down a porous media (very narrow microfluidic channel, packed-bed, polymer monoliths and porous membranes, among others), developing pressure until the pressure-driven back flow-rate is equal and opposite to the EOF rate. EKPs can be easily made into MEMS-based microdosing/drug delivery devices. These devices can be either implanted or just placed under the skin. Figure 4 is a conceptual illustration of MEMS-based EKP device for injection. The device is adapted for transdermal injection or implantation, and is composed of a housing that defines a reservoir in which the drug is contained. It also contains a key porous medium that affects movement of the drug out of the reservoir through the microchannel of the needle and to a delivery site, after which the drug is carried via the systemic circulation to a site of action. The device may have either a fixed or adjustable delivery rate by regulating the driven voltage, and is refillable. In the device, all the related parts that the drug contacts, such as the reservoir, porous media, needle and sometimes the electrodes, should be made from biocompatible materials. There are a wide range of materials to choose from. Table 2 is a summary of bio-MEMS materials classified by their applications and their main characteristics. Over time, a degraded or bioincompatible medical device will become malfunctional. Hence, more rigorous biocompatibility and biostability requirements have to be fulfilled. A measure for biocompatibility and foreign-body giant cell density can be used to evaluate the feasibility of designed devices and materials. Moreover, it is necessary to take into consideration if the materials will be used in a device for acute or chronic treatment. Devices for chronic use and implantable devices need to be more biocompatible. In addition to compatibility, toxicity is a concern. The toxicity of the material should be investigated at the very beginning of selecting a specific material. Another concern is to reduce the mechanical stress induced by the micropumps dynamics. Recently, polymer-MEMS have become more and more popular, mainly because they have a very low stiffness and inherently provide adequate flexibility. At present, polymer materials, such as polymethyl methacrylate, polydimethylsiloxane, SU-8 photo resist or parylene C, have proven to possess superior biocompatibility and flexibility properties. They have the potential to become the materials of choice in biomedical MEMS devices.

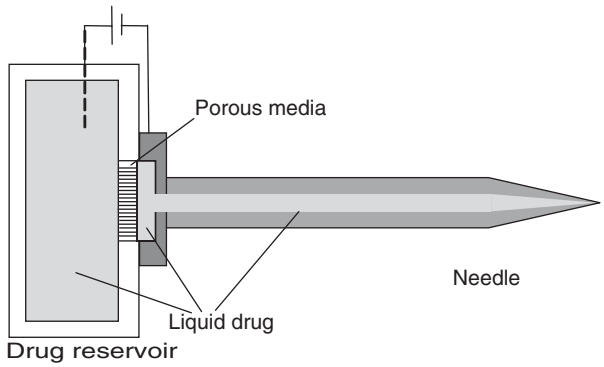

Figure 4. A conceptual illustration of a MEMS-based electrokinetic pump.
MEMS: Microelectromechanical systems.

3. Conclusions

High pressure, low volumetric flow, pulsation-free and polar-fluid delivery are the characteristics of EOPs. Chip-based microfluidic devices for micro total analytical systems have been studied extensively since the early 1990s. These systems offer the potential of assays with increased sensitivity and resolution, reduction of sample volume, and the integration of multiple laboratory processes and functions on a single platform. Many of these devices use liquid-phase electrokinetic phenomena to pump, transport, separate, concentrate and mix samples. The ability to use electrokinetic effects to control fluid flow in a valveless microchip system has proven to be very powerful for analytical applications in aqueous solvents. Its extension to manipulating the flow of organic solvents for the purposes of on-chip organic synthesis has been proven equally useful in a microfabricated glass chip [40]. So far, polar organic solvents such as methanol, acetonitrile, and aqueous solvents such as deionised water, phosphate sodium buffer, borate buffer and their mixtures [18], have all been used as pumping liquids.

With the rapid development in this area, EKP techniques, including EPPs and EOPs, will become a promising liquid micro and/or nano fluidic delivery technique for wide applications, with drug delivery being one of them.

4. Expert opinion

The nature of any type of EKP, EOP and EPP is dependent on the EKF. The EKF is the bulk fluid flow that occurs when a voltage difference is imposed across a wide variety of charged materials (capillary column, packed-bed, porous polymer monoliths, membranes and nanochannels). This flow is always in the same direction as the flow of counterions and may assist or hinder liquid drug transport. As well as small molecule liquids, EKP can even be used to drive macrobiomolecules and can, therefore, potentially be used to deliver biomolecular drugs [41]. For example, Jin *et al.* [42] have presented an approach that uses EOF to electrokinetically pump proteins through a proteolytic system. Jin *et al.* [43] have reported the use of electroosmotic and/or electrophoretic pumping to drive the cell or submicrometre particles though a network of capillary channels of a microfluidic glass chip system. The results of this study showed that transport of a variety of biological cells using direct current electrokinetic effects in a chip based capillary format was feasible. Siwy *et al.* [44] have shown that a synthetic asymmetric nanopore acts as an ion nanopump, transporting potassium ions against their concentration gradient. The limitations of the EKP are obvious. EKP can only be used for delivering a fluid with electrical conductivity and not non-polar liquids. However, this is not a serious problem because most drugs are polar and water-soluble.

Electrically driven techniques, such as electrically responsive drug delivery [45,46] and constant current AC iontophoresis [47,48], have gradually become promising liquid drug delivery techniques. These techniques can help us to find more suitable ways and/or visions to convert the EKPs into medical devices, as the majority are using EOF principle. Iontophoresis is a well-known, transdermal drug delivery technology that is enhanced by three mechanisms: i) the ion-electric field interaction provides an additional force which drives ions through the skin; ii) flow of electric current increases the permeability of skin; and iii) electroosmosis produces bulk motion of the solvent itself that carries ions or neutral species with the solvent stream. As both human and animal skins are negatively charged above pH 4, counterions are positive ions and EOF occurs from anode to cathode. The relative importance of EOF is obvious and has been reviewed by Pikal [49]. A considerable research effort has gone into exploring the feasibility of iontophoresis as a treatment platform for transporting different drug molecules with diverse physicochemical properties. However, there are no transdermal iontophoretic patches on the market. There are two reasons for this. First, the technology needs time to mature, although with the recent advances in the field of microelectronics, the feasibility of developing miniaturised delivery systems has significantly increased. Second, although iontophoretic studies were conducted on many different molecules, there was a lack of judicious selection involved in the identification of the therapeutic area and/or drug molecule [50]. In terms of pharmacodynamics, iontophoresis must provide a clear therapeutic benefit over the existing route, either in providing an improvement in efficacy or an improvement in the adverse events profile. The improved onset time of iontophoresis would offer obvious advantages over passive formulations. Topical application is much better than taking large oral doses of a drug and relying on systemic distribution to achieve a therapeutic level in the skin. The microfabrication technologies for drug delivery implants incorporate structures in the nanometre dimension [51]. These systems would involve drug delivery systems with nanopores,

Table 2. Biocompatibility materials for microelectromechanical systems-based pump.

Materials	Biocompatibility	Characteristic	Application
PDDA	Good	Porous material	Reduce toxicity of nano particle
PDMS	Good	Ultra-thin active layer	Electroosmotic membrane (soft lithography)
PMMA	Good	Simply fabrication (hot embossing)	Microfluidic structure
TiN alloy	Good	Shape memory effect	Actuator
Au	Good	Simply fabrication (low resistivity)	Electrode connection
Al2O3	Very good	Brittle	Microfluidic structure
Pt	Good	Simply fabrication (low resistivity)	Temperature sensor heater
Ti	Good	Simply fabrication	Heater
Glass/quartz	Good	Porous material	Electroosmotic membrane

Au: Gold; Al2O3: Aluminium oxide; PDDA: Poly(dimethyldiallylammonium); PDMS: Polydimethylsiloxane; PMMA: Polymethyl methacrylate; Pt: Platinum; Ti: Titanium; TiN: Titanium nitride.

nanochannels and/or nanoreservoirs fabricated from silicon and coupled with electronic sensing and actuator systems, for the precise, timed and/or targeted delivery of drugs [52].

EKP is a non-mechanical micro pump that needs to convert non-mechanical energy into kinetic momentum. In general, non-mechanical pumps do not need physical actuation components, so the design and fabrication of this type of pump is relatively simple. Based on measures of driving effect and performance, such as back pressure, flow rate, rising time and maximum stroke/deformation, non-mechanical pumps are inferior when compared with mechanical micropumps, but these do not preclude them from becoming an important pumping technique, due to their simple structure, small sise, flexible configuration and ease of use. The various types of EKPs, as well as their features described here, should provide insight into designing effective drug delivery systems for accurate (transdermal, implantable) drug delivery. The main features of the system can be summarised as following:

- small or miniaturised depending on the capacity of the reservoir for short-term and long-term (acute and chronic) medication, and the controlling system
- lightweight, depending on the materials
- inexpensive and well-suited to single-use configurations
- no moving parts and very simple
- easy integration into an independent device or to another device
- completely programmable for dosage levels.
- can be powered by a watch battery (1 – 36 V), low electrical current (nA – μA), and lower power requirement (nW – μW)
- accurate drug delivery with a flow rate at the nanolitres to microlitres per minute level, and a pressure at 0.1 to several psi.

In recent years, microfabrication EKP technologies are attracting great interest, as the miniaturisation of pump systems offers practical advantages over classical, bench-top pump systems. There has been great progress in the development of micro EKPs for use in medical device purposes. The efforts of researchers and companies [103,104] give us a vision for turning this kind of pump design into medical devices, in terms of size and access to drug reservoirs, as well as controlling system. Eksigent Technologies designs EKPump™ devices for drug delivery and other medical device applications, such as sample collection for diagnostics, apparatus cooling or catheter-based procedures [103]. The EKPump drug delivery devices are miniature, fully programmable and implantable EKPs used for research in mice, rats and other laboratory animals. These pumps are the ultimate devices for the portable delivery of biologicals and other concentrated drug compound solutions for preclinical testing, for determining a drug's toxic effects and its absorption, distribution, metabolism and excretion properties, and for pharmacokinetic applications. Precise flow characteristics are achieved by controlling the electrical potential across a fluid-filled porous membrane. EKPumps dispense solutions at rates as low as 1 nl/min at ± 5% accuracy. This allows highly concentrated doses and/or longer run times in a similar form factor. There are low, medium and high capacity pumps available, which can last 1 week, 1 month and 3 months, respectively. The operating pressure (0.2 – 2.0 psi), flow rates (from 4 nl/min nanoflow to 0.7 ml/min microflow) and voltage (3 – 24 V medical use) of the pump can be tailored to meet specific needs [104].

Microfabricated EKPs and their related techniques are emerging drug delivery technologies, from the initial concept to potential therapeutic application and the final relevance in clinical use, and is a long way to go before realising their potential. The available EKPs have some main problems, such as bubble generation due to electrolysis and pressure-driven flow dominance over EOF. Approaches

based on new materials, electrode placement and electrical drive schemes are being developed to solve these problems. For example, a liquid bridge configuration developed to allow the application of DC voltages to drive porous polymer EKPs can solve any bubble generation problems. EKPs can be used to deliver liquids at a flow rate of several nanolitres per minute with a maximum pressure head that is relatively high at very low DC voltages, where the conventional bench-top instrumentation is not always operational. With the development of special materials for some of the pumps, and the microfabrication techniques, effective drug delivery technologies based on the electro-osmotic principle will become increasingly important devices for special drug delivery purposes. For example, a key difficulty in the use of cochlear implants is that they can only be inserted at a limited distance into the cochlea, due to its helical shape and insertion trauma from contact with the scala tympani wall. An EKP with relatively high pressures, but low flowrates (5 – 10 nl/s), is needed for this device as a pressure source for the actuation of the insertion tool [53]. We are sure that the microfabricated EKP and its related techniques will be valuable drug delivery tools in the near future, both for scientific research and medical uses.

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