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Polymeric microdevices for transdermal and subcutaneous drug delivery☆

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Abstract

Low cost manufacturing of polymeric microdevices for transdermal and subcutaneous drug delivery is slated to have a major impact on next generation devices for administration of biopharmaceuticals and other emerging new formulations. These devices range in complexity from simple microneedle arrays to more complicated systems incorporating micropumps, micro-reservoirs, on-board sensors, and electronic intelligence. In this paper, we review devices currently in the market and those in the earlier stages of research and development. We also present two examples of the research in our laboratory towards using phase change liquids in polymeric structures to create disposable micropumps and the development of an elastomeric reservoir for MEMS-based transdermal drug delivery systems.

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1. Introduction and background

Transdermal delivery of drugs and other pharmaceutical agents has a long and celebrated history (for two recent reviews see [1,2]). Although no recorded account exists, it is possible to speculate that some small lipophilic chemicals entered the bodies of our cave-dwelling ancestors through ritualistic painting of body parts using natural products. The modern era in transdermal delivery can be traced back to 1979 when scopolamine patches were approved by the FDA. This was soon followed by a flurry of activity and commercialization of numerous patches delivering a variety of small lipophilic drugs (nitroglycerine, nicotine, fentanyl, etc.). However, the impermeability of skin for larger molecules presented a formidable barrier towards further development of transdermal patches. For many years the efforts in this area were concentrated on enhancing skin permeability through various chemical (e.g., peptide enhancers, liposome) and physical...
(ultrasound, thermal ablation, electroporation, laser micro-drilling through epidermis) methods. This area still garners a big share of research in academia and industry with iontophoretic method being used with limited success to deliver small (<10 kDa) ionizable molecules (e.g., anesthetics and corticosteroids) [3,4].

More recently, microneedle arrays fabricated from various metallic and polymeric materials have been the focus of attention [5]. These microdevices promise to reduce the pain associated with hypodermic needle injections by only penetrating the very top layer of skin, thus conveniently delivering larger molecules across the skin barrier. Despite initial enthusiasm, microneedle arrays have not been able to penetrate the market or find use in clinical settings. This has been mainly due to the fact that the diffusion alone is not capable of transporting enough drug across the skin through numerous microscale conduits generated by microneedle arrays. One still needs a micropump with adequate back-pressure to force the drug into the skin. Development of a low cost micropump with desirable performance for this application is not a trivial task (see Section 4). Recent efforts in delivering vaccines through biodegradable microneedle arrays have rekindled interest in this area [6,7] by presenting a unique application in which they can play an important role in spite of their aforementioned shortcomings.

Another area with more commercial success stories is the subcutaneous insulin delivery using small infusion sets. Minimed (www.minimed.com) and Omnipod (www.myomnipod.com) systems both use stepper motors to deliver basal and bolus insulin across the skin using a small subcutaneous catheter. Although not transdermal in a classical sense, these systems offer patients’ comfort, mobility, and a better glucose control than hypodermic injections. It is believed that such systems will continue to expand their market by tapping into explosive growth in microsystem miniaturization and hybrid integration techniques.

Achieving adequate clinical performance at low cost is one of the main drivers behind next generation transdermal and subcutaneous drug delivery systems. Microscale components such as needles, pumps, and drug reservoirs made from polymeric material can contribute to the commercial success of such systems by providing low cost disposable platforms. In addition, many high performance applications in which accurate dosage management is required, integration of sensors and some limited electronic intelligence with the aforementioned components is highly desirable. In this article, we will review some recent efforts in the area of polymeric microdevices for transdermal and subcutaneous drug delivery. In Section 2, we review microscale polymeric fabrication methods followed by a discussion on polymeric and biodegradable microneedle arrays in Section 3. Section 4 focuses on micropumps for transdermal and subcutaneous drug delivery. In Section 5, we discuss an elastomeric reservoir for MEMS-based transdermal drug delivery. Finally we conclude (Section 6) by summarizing our discussion and suggesting further research venues.

2. Microscale fabrication with polymeric materials

In addition to scaled-down versions of macro-scale polymeric device manufacturing (injection molding, hot embossing, etc.) methods, the development of next-generation polymeric drug delivery devices will employ various MEMS microfabrication techniques. These can be classified into three main categories, based on the method by which the polymeric material is processed: photolithography in which the desired structures are defined and constructed by the polymerization of a substance; replica molding, in which a polymer is cast onto or injected into a hard master mold that was fabricated using standard MEMS microfabrication techniques; and polymer micromachining in which a slab of the material is modified by micromilling or ablation to achieve the desired structure [8].

2.1. Direct photolithography

Photolithographic definition of polymeric structures is often employed in the fabrication of thin films that are typically used as membranes in biomedical microdevices. This technique involves the chemical modification of a thin layer of a liquid material by exposure to light, as is commonly done with sacrificial photoresists in traditional microfabrication. The main difference here is that the material used must eventually be released from the substrate for further processing. This is usually accomplished by using a substrate with low surface energy or by pre-treating the surface with a suitable chemical agent that will minimize the adhesion of the resist to the substrate. The resist is then deposited on the substrate surface, typically by spin coating or spraying, and it is patterned by exposure to light of an appropriate wavelength. The patterns are then developed in a developer solution, and the polymeric films are removed from the substrate for processing. Structures fabricated in this fashion serve as components that can then be assembled with the use of various adhesives [9] to form low-cost, polymeric microdevices. This fabrication technique emphasizes the use of photo-definable polymers such as SU-8 [10], PMMA [11], and thin PDMS films [12] as structural materials that can be easily patterned. This technique allows for the fabrication of device components such as valves and membranes for drug delivery micropumps [13]. Fig. 1 shows a microscale check valve fabricated from SU-8 photo-definable polymer.

2.2. Replica molding

Polymeric micro-patterns and micro-structures are also commonly formed by various molding and embossing techniques, in which a master mold is used to make polymeric replicas of the master design. Fig. 2 [14]. In this technique, a master mold is first created out of a hard material (e.g., silicon, titanium) using standard MEMS fabrication techniques. The surface of the mold can then be chemically treated as needed to ensure low adhesion to the polymeric material to be used. Next, a pre-polymer solution is deposited on to the mold and allowed to solidify either by crosslinking, curing, or cooling, depending on the technique used. The polymeric structure is then removed, and the mold can be used again repeatedly for multiple polymeric replicas. Micromolding is one such procedure, in which the master mold is typically a pattern defined on a silicon wafer. This procedure, commonly known as “soft lithography” [15] is often used to make micropattern replicas on soft materials such as PDMS. In this case, the prepolymer is simply poured onto the master mold (if necessary, under vacuum to prevent air gaps in high aspect ratio molds) and allowed to crosslink. The crosslinked polymer can then be peeled off and used to manufacture microdevices. In the case of PDMS, bonding to PDMS, glass, or bi-axially oriented polyethylene terephthalate (boPET) [16] can be achieved by plasma-induced surface activation in order to make channels or reservoirs for drug delivery devices.

Micro-injection-molding molds a thermoplastic polymer using a miniaturized version of conventional injection-molding, Fig. 3 (left panel). A closed master mold is fabricated out of a high melting point, thermally conductive material (silicon or metal), and it is heated to a temperature greater than the glass transition temperature of the thermoplastic. The thermoplastic is then heated separately to above its glass transition temperature, and it is injected into the mold. The mold (and hence, the polymer) is then cooled to below the glass transition temperature of the polymer, allowing the polymer form to set and to be removed from the mold. Bonding to other materials is then achieved by the use of various adhesives. A low temperature variation of injection molding is reactive injection molding. Rather than melting and cooling a thermoplastic, this method relies on the chemical reaction between two liquid polymers, a base polymer and a hardening agent, that are injected into the master mold simultaneously and solidify over time inside the mold. The structures
are then removed from the mold and post-processed with other polymers.

As a faster alternative to micro-molding, hot embossing can be used when replicating patterns on a thermoplastic such as PMMA, polycyclic olefin, polycarbonate, or styrenic thermoplastic elastomers [17], Fig. 3 (right panel). For this technique, a mold is fabricated on two plates of thermally conductive, thermally resistant material (silicon, or metal) using standard fabrication techniques. Next a thermoplastic polymer is placed between the two plates, which are heated to the polymer’s softening temperature and pressed against the film. The pressure and heat allow the film to flow slightly into the patterns on the plates. The polymer can then be removed by cooling it down and can be processed with other polymers. The low temperature, and hence, low reflow of the material, makes it ideal for fabricating small 3D structures on thin polymeric films [18].

2.3. Micromachining

Another technique for microfabricating polymeric structures is the direct micromachining of polymer substrates by the application of micromilling, plasma etching, or laser-assisted material ablation. Micromilling follows the trend of adapting conventional technologies to the microscale. This technique uses a micro end mill to carve out channels and reservoirs in thermoplastic or thermoset polymers [19]. Fig. 4 shows a micro-scale milling tip that can be used to machine polymeric micro-parts. Polymeric microstructures can also be patterned by plasma etching. This procedure typically uses materials such as polyimide or parylene. The materials are deposited on a substrate (pre-treated for low adhesion if necessary), typically via spin coating or chemical vapor deposition. The films are cured completely and subsequently masked with a patterned layer of photoresist or a hard mask material. Upon exposure to plasma, the unmasked organic polymeric film is etched away, and the patterned polymeric structures can be removed from the substrate [20]. Finally, laser micromachining can also be used to define highly precise patterns on polymeric films. For this method, a polymeric film is first cast onto a low adhesion surface, cured completely, and removed. The film can then be ablated by exposure to a laser beam (e.g. CO2 laser) that traces a predefined pattern along the film [21].

3. Polymeric and biodegradable microneedle arrays

As mentioned in the introduction, microneedle arrays offer a painless route to transport hydrophilic and ionizable large molecules across the skin [22,23]. Initial efforts in this area utilized silicon as the structural material. This however presented the difficulty associated...
with fragility of silicon arrays [24–27]. Subsequently, various metals such as nickel and titanium were explored by various groups in academia and industry [28–30]. Both silicon and metallic microneedles require expensive starting materials and fabrication processes. Polymeric microneedles fabricated through micro-molding techniques offer an alternative with lower large scale manufacturing cost and disposability [31–37]. Although initially attracting considerable attention, microneedles met limited success in adoption by industry. The main reason behind this had to do with difficulty in fabricating hollow microneedles and lack of a suitable microscale pump to get enough drugs across the skin (the pores created by microneedles can only transport limited dosage through simple diffusion).

More recently, biodegradable microneedles for delivering vaccines have been the focus of intense investigation. The drug formulation, which during the fabrication process is encapsulated in the structural material of the needles, their backing material, or both, diffuses during the dissolution of the array after insertion into the skin. The dissolution process can take from 1 to 5 min allowing for a single effective administration [6,37,38]. The fabrication process for a biodegradable microneedles is shown in Fig. 5 (from [36]). The master structure is first created, by forming conical SU-8 structures on silicon, using an integrated lens technique [39]. Then PDMS is poured on the master structure to form the microneedle mold with conical-shaped indentations. The structural material of the microneedles, which is mixed with the drug formulation, can be subsequently poured into the PDMS mold and vacuum-cured. Finally, the biodegradable microneedles can be detached from the PDMS.

The structural material of biodegradable microneedles should be biocompatible and have the required mechanical stiffness for insertion into the skin. The fracture force for a needle should be larger than the insertion force required for penetrating the stratum corneum. This means that the needles must be strong enough to
penetrate the skin with breaking or deforming, reach the desired depth, and deliver the loaded dosage in a reasonable time scale. In addition, the choice of the material defines the fabrication method, shelf-life, dissolution rate, and the applicable drug formulations. A variety of materials have been used; however, few have been tested in vivo. These include poly-1-lactic acid (L-PLA), poly-glycolic acid (PGA), poly-lactic-co-glycolic acid (PLGA) [39], carboxymethylcellulose (CMC), amylopectin formulations, bovine serum albumin (BSA) mixed with CMC [37], maltose [35,38], and polyvinylpyrrolidone (PVP) [6,36]. Table 1 summarizes some important properties of biodegradable materials used in micronneedle arrays. Fig. 6 shows bright-field and scanning electron microscopy pictures of the cited microneedles.

4. Micropumps for transdermal and subcutaneous drug delivery

Among the various micro-scale devices and systems developed to improve transdermal and subcutaneous drug delivery [40], micropumps play a critical role by providing an active pressure source to counteract the opposing dermal pressure. There has been intense research and development targeting towards developing micropumps for various microfluidic and drug delivery applications [41]. However, many of these devices do not meet the stringent requirements for transdermal drug delivery. These requirements include small dimensions, low cost, low power consumption, high backpressure, adequate flow rate, and high accuracy in applications in which precise dosage metering is required (e.g., insulin delivery). Although the academic community has produced numerous micropumps made of various materials and employing many actuation techniques, only a few have been commercialized. In the search for a low cost solution, research and development in the area of polymeric micropumps continue to grow.

4.1. Basic requirements for a micropump-driven transdermal drug delivery systems

As discussed previously, most transdermal and subcutaneous drug delivery systems (except the ones that rely on simple diffusion) require a micropump to allow for adequate dosage administration across the skin. In this section, we will describe the basic requirements for a transdermal drug delivery micropump. Among the most over-looked requirements is the drug-compatibility of the micropump. Any material that comes in contact with a drug solution must be drug-compatible, i.e., it should prevent drug from leaching out or being adsorbed on the surfaces. In addition, it should not promote drug precipitation inside the pump or tubes connecting the pump to the reservoir and outlet conduit. In this regard, of particular preference are nonporous materials that minimize both the potential contamination of the drug by the inward diffusion of external chemicals, as well as the possible loss of drug volume due to its diffusion into the polymer matrix. Another material aspect is biocompatibility, which deals with the fact that such micropumps might come in contact with the skin for a long period of time. Hence, it is also important to ensure that the packaging of such devices be biocompatible in the sense that they do not irritate the skin or cause any allergic reaction to the patient. So far, a few types of polymers have been evaluated and adopted by industry for such applications. These include silicone, ethylene vinyl acetate (EVA), polyurethane (PU), and polymethylmethacrylate (PMMA) [42].

Another crucial requirement for transdermal micropumps is the dosage accuracy and precision. This is particularly important in applications in which the drug is very potent and needs to be metered with a high degree of accuracy (e.g., insulin). Conventional hypodermic syringes may accurately deliver drug doses for volumes greater than 50 μl [43], but better accuracy is often needed (especially with infants). Young children with type I diabetes may need bolus insulin doses as low as 10 μl, an amount so small that even miniscule dosing errors can cause significant fluctuations in blood glucose level [44]. Hence for low doses, where manual syringes and pen-injectors exhibit an unacceptable degree of error, microsystems with accurate (<1%) flow control are an invaluable solution. Accurate dosage delivery can be accomplished at the micropump level or by using on-board flow

Table 1

<table>
<thead>
<tr>
<th>Material</th>
<th>Preparation temperature</th>
<th>Length (L), width (W), tip radius (R)</th>
<th>Insertion and fracture force (IF, FF)</th>
<th>Dissolution rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-PLA</td>
<td>145 °C (−70 kPa)</td>
<td>L = 1000 μm, W = 250 μm, R = 20–80 μm</td>
<td>IF = 0.04–0.6 N, FF = N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>PLGA</td>
<td>180 °C (−70 kPa)</td>
<td>L = 700 μm, W = 200 μm, R = 25 μm</td>
<td>IF = 0.06 N, FF = 0.20 N/needle</td>
<td>N/A</td>
</tr>
<tr>
<td>Maltose</td>
<td>140 °C</td>
<td>L = 500 μm, R = 5 μm (28 needles)</td>
<td>IF = N/A, FF = N/A</td>
<td>100% in 1 h (pig cadaver skin)</td>
</tr>
<tr>
<td>CMC</td>
<td>• 60–70 °C (1 atm)</td>
<td>L = 600 μm, W = 300 μm (27 needles)</td>
<td>IF = 1.5 N, FF = 0.1 N/needle</td>
<td>100% in 1 h (pig cadaver skin)</td>
</tr>
<tr>
<td>• RT</td>
<td>(−50 kPa)</td>
<td>L = 650 μm, R = 10 μm (9 × 10 array)</td>
<td>IF = 0.058 N/needle, FF = 0.13 ± 0.03 N/needle</td>
<td>83% in 15 min (mouse), 89% in 5 min (porcine skin)</td>
</tr>
</tbody>
</table>

Fig. 5. Fabrication process for biodegradable polymeric micron needles, see the text for details [36].
sensors and an output valve. The former approach, due to its simplicity, has been more popular in commercial subcutaneous drug delivery systems such as Minimed and OmniPod insulin pumps.

Micropumps for transdermal drug delivery must additionally satisfy low power consumption and high backpressure requirements. The power requirement is directly related to device lifetime. Since most such systems are battery operated, it is desirable to maximize the lifetime by adopting a low-power consumption micropump. Transdermal drug micropumps must also be able to handle large back-pressures. These micropumps move liquid drug from a storage reservoir through microchannels into the skin. Although many micropump designs may be able to handle microchannel fluid flow encountered in microfluidic platforms, the skin poses an additional physical barrier. Transdermal delivery typically requires a drug to be pumped through one or more microneedles, thus requiring the micropump to work against a nonzero backpressure of about 2 kPa \[26,45,46\], in addition to any encountered subcutaneous pressure \[47\].

4.2. Commercial micropump driven drug delivery systems

A few drug delivery systems using miniature pumps have been successfully commercialized. Although none are polymeric, they have set the operating standard for future micropump-equipped systems for transdermal delivery. The current systems are battery powered (AA, AAA, or coin cells) and use an on-board drug reservoir connected to a micropump which in turn delivers the drug across the skin via a small needle-ended tubing or cannula attached to the output. These commercial products include the various insulin delivery systems such as Insulet OmniPod, Medtronic MiniMed, Animas OneTouch Ping, Sooil Dana Diabecare, and Roche Accu-Chek Spirit. Weighing no more than 4 and as low as 1.2 oz, these systems are designed for portability, comfort, and simple user interface. The micropumps used in these systems are varied but mostly rely on stepper motor actuated schemes. A good example is the OmniPod micropump which uses a shape memory alloy actuated mechanism for precise and relatively inexpensive delivery of the stored insulin, Fig. 7. The OmniPod micropump is able to precisely deliver small bolus doses as little as 0.5 μL and can operate continuously for about 72 h to deliver a total of up to 2000 μL of stored insulin.

4.3. Polymeric micropumps

In contrast to commercialized micropump actuated drug delivery systems, the polymeric devices currently in the research phase are much less expensive, but they tend to lack the required accuracy. The biocompatibility and simple low-cost fabrication of polymeric microstructures have been the driving force behind the development

![Fig. 6. SEM and bright-field microscopy pictures of biodegradable microneedles: (a) CMC \[37\], (b) solid maltose \[35\], (c) solid maltose \[38\], (d) PLA \[39\], (e) PLGA \[39\], and (f) PVP \[6\].](image)

![Fig. 7. Opened Insulet OmniPod insulin delivery system showing drug reservoir, shape memory alloy actuator, batteries, and associated electronics.](image)
of many polymeric micropumps. Research and development in this area that have exhibited promising results are paving the way for the eventual commercialization of the ultra-low-cost micropumps for transdermal drug delivery. Research in academia has mostly focused on the use of commonly available, low cost, biocompatible polymers for fabrication. These include a variety of elastomeric, thermoplastic, and thermoset materials that can be formed into desired microstructures by techniques such as those described in Section 2.

The majority of micropumps developed in academia make use of PDMS as a structural material. This is due to its biocompatibility, low cost, and fast prototyping capabilities. However, emerging research has shown the advantages of using other suitable materials such as PMMA, polycarbonate, and polyurethane. These materials have the advantage of being stronger and more rigid while still easily processable with techniques such as laser-assisted ablation, micoinjection molding, and hot embossing. Novel alternatives to PDMS such as thermoplastic elastomers [17] are also gaining attention for their fast prototyping and low porosity.

Apart from material selection, actuation technique also plays an important role in determining the micropump operational characteristics (e.g., power consumption, flow rate, and back pressure). In the following subsections, we will briefly describe several important drive mechanisms used in microfabricated pumps. Table 2 summarizes various micropumps with their associated performance characteristics.

### 4.3.1. Thermopneumatic and phase change micropumps

Thermopneumatic micropumps rely on the heating and cooling of a thermally expandable medium to create a displacement volume in a drug reservoir and pump out the displaced drug. The micropump typically consists of a drug/pumping chamber separated from a working medium by a deflectable membrane (usually a thin elastomeric film). If accurate dosing is required a check valve is also included. The heat source for actuation is typically an integrated heating element. Pumping is initiated by a rise in temperature of the working medium which in turn expands causing a deflection of the thin membrane into the drug chamber. The deflection displaces the fluid in the pumping chamber until the temperature drops. Micropump operation consists of one or more of these cycles. Thermopneumatic pumps can create high back pressures at moderate to low flow rates. Continuously operating thermopneumatic micropumps typically rely on a resistive heater that is controlled by an external electrical signal. This increases the power consumption since heating is an energy intensive transduction mechanism.

Recently, we reported on a micropump that was designed for a single cycle operation (injecting a bolus) and could be actuated simply with skin contact [48]. This micropump relies on the evaporation and condensation (phase-change) of a low-boiling point liquid that is stored in the working medium chamber. The device consists of four stacked layers of PDMS on a silicon substrate, all bonded together via plasma-assisted surface activation. The silicon substrate provides a thermally conductive interface for heating and cooling the working liquid, causing evaporation and condensation, respectively.

Fig. 8 illustrates the structure of the device, showing the drug reservoir, phase-change liquid chamber, and a microneedle array. Fig. 9 shows the cross section of the device. Once a microneedle array or a microfluidic port is inserted, a mere two degree rise in the temperature of the working liquid due to soft skin contact increases the vapor/liquid ratio of the fluorocarbon in the working chamber, thus causing a pressure rise that deflects a thin PDMS membrane to displace a stored drug, Fig. 10. A commercially-available fluorocarbon (3M FC-3284) was selected as the working fluid due to its high vapor pressure of 35 kPa at 25 °C and performance, compared to other solvents, Fig. 11.

The skin-contact-actuated micropump was characterized based on its maximum flow rate and back pressure when actuated by touching a finger to the silicon substrate. A pressure-controlled tubing at the outlet allowed for the characterization of back pressure, and the results are shown in Fig. 12. As a proof of concept, chicken tissue was used to test the injection capability of the micropump. A single needle from a hypodermic syringe was attached to the PDMS cap. The drug chamber was filled with Evans Blue dye (Sigma-Aldrich, Saint Louis, MO) and the needle penetrated the chicken tissue to a depth of 3 mm. Dye diffusion into the tissue was observed 112 s after the insertion of the needle (Fig. 13). The characteristics of the device,
such as its flow rate (28.8 μL/min) and high back pressure (approx. 28.9 kPa), illustrate its utility as a drug dispenser or pump for transdermal drug delivery.

A second-generation device developed in our lab adds the important functionality of maintaining the pressure within the drug chamber when the heat source is removed, thus enabling sequential drug delivery (e.g., user initiated administration of pain killers over a period of time) [16]. This is achieved through the employment of a stop valve and two intermediate air chambers coupled to the working liquid and drug reservoirs, Fig. 14. In order to incorporate a stopping valve, a novel fabrication method was developed in order to achieve an irreversible bonding of a laser-patterned transparency film (3M PP2500) to PDMS by plasma-induced surface activation. Fig. 15 shows the cross section of the device in one operation cycle. The drug reservoir was filled with dyed DI-water, and 20 μL of 3M FC-3284 (50°C boiling point and 36 kPa vapor pressure at 25°C) was injected in the phase-change-liquid chamber. The remaining two chambers were left filled with air, as their purpose is simply to maintain the pressure difference required for appropriate actuation of the flap valve. The device operation starts upon skin contact with the silicon substrate, which initiates the process by evaporating the phase-change liquid, thus pumping the drug out of the reservoir. Once the skin contact with the device is removed, the phase-change-vapor condensates, and, simultaneously, the flap-valve closes, preventing reverse flow of the drug. Upon repeated cycles, more drug is pumped in a sequential manner. Fig. 16 shows a sequential pumping profile comprising of four cycles with an initial flow rate of 36.1 μL/min. Solid and broken arrows indicate the time when the skin is brought into contact with the device and when the contact is removed (one cycle), respectively.

For thermopneumatic pumps, the working medium that expands and contracts with varying temperature can be a gas, liquid, or solid. In the case of a gaseous working medium, as in [49], the expansion in the working chamber is caused by an increase in pressure due to a rise in temperature, as per Charles’ Law. Solid working media such as paraffin wax also exhibit a volumetric expansion and contraction in response to temperature, and a micropump based on this operating principle is presented by [50]. Thermopneumatic micropumps have the ability to produce high pressures to counteract the transdermal backpressure of the skin barrier. The prototypes described above report backpressures ranging from about 28 kPa to close to 1 MPa.

Another group of phase-change actuated micropumps is based on bubble generation via electrolysis. Although not thermopneumatic, they share many of the features and characteristics of such pumps. One example is the parylene bellows electrochemical actuator presented by Li et al. [51] for intraocular drug delivery. The device consists of a drug chamber separated from an electrolysis chamber by a layer of parylene. The electrolysis chamber houses an array of platinum electrodes in an electrolytic solution. An electric field across the electrodes triggers electrolysis of the solution, inducing gas generation inside the chamber. The ensuing rise in pressure deflects the parylene bellows layer, which in turn displaces drug out of the reservoir. The bellows design of the parylene membrane enables large deflection resulting in a flow rate of about 3.4 μL/min.
4.3.2. Electromagnetic micropumps

Electromagnetic micropumps rely on an externally generated magnetic field to actuate the membrane of a pumping chamber. The membrane is usually fabricated out of a polymeric material and a small magnet or ferromagnetic material is attached to it. In order to reduce the cost, other components of the micropump are also typically made out of polymers. This is the case with the micropump described by Zhou et al. [52] (illustrated in Fig. 17), which consists of a chamber, a membrane, and two diffuser/nozzle valves, entirely fabricated on PDMS. A thin magnet is embedded in the actuation membrane, allowing the pump to be actuated by a local, externally generated fluctuating magnetic field. Kim et al. [53] have also reported on a micropump of similar structural design, but fabricated out of acrylic (for the housing) and Kapton tape (to define the diffuser/nozzle valves and associated channels). In their design, shown in Fig. 18, a magnetically controlled plunger rod is attached to the membrane and an external magnetic field drives the actuation at a frequency of 180 Hz. Electromagnetic micropumps can achieve high flow rates with acceptable back pressures (if check valves are correctly designed and fabricated). However, they are typically power hungry and require a permanent magnet in their construction in order to achieve adequate displacements.

4.3.3. Piezoelectric micropumps

Piezoelectric micropumps consist of a pumping chamber connected to two passive valves and a piezo-actuated membrane. The application of an alternating voltage across the piezo-material (usually PZT) in the transverse direction causes the radial deformation and axial deflection of the membrane, thus changing the volume of the pumping chamber.
These micropumps generate a large amount of force; however, a high voltage power supply is required for their actuation. In polymeric versions of these pumps, a biocompatible polymer forms the structural base of the pump with the piezo-element mounted on top of the membrane. The chamber and valves are typically fabricated out of PDMS [54], PMMA [13], SU-8 or other suitable polymers that are processed with techniques such as those described in Section 2. The actuating membrane is in some cases a thin elastomeric film with a piezo-disk attached to its surface with a suitable adhesive; in other cases, the membrane is the piezo disk itself. The device presented by Truong et al., for instance, relies on the latter design [13]. The design, illustrated in Fig. 19, is simple to fabricate: the flap valves require only one photomask for lithographical definition of SU-8 and the remaining components are patterned by laser cutting. Simpler designs using diffuser/nozzle valves have also been reported. Piezoelectric micropumps can achieve moderate flow rates with high back pressures (if check valves are correctly designed and fabricated). However, they can be power hungry (if high actuation frequency and large disks are employed) and require a high voltage DC–DC converter to create the large actuation voltage.

Fig. 15. Multi-cycle thermopneumatic micropump for sequential dosage delivery. The device uses body heat from skin contact as the actuation source [16].

Fig. 16. Sequential delivery profile for the phase change actuated thermopneumatic micropump, showing application (solid arrows) and removal (dotted arrows) of skin contact [16].

Fig. 17. All-PDMS micropump featuring PDMS membrane with an embedded magnet for electromagnetic actuation [52].
5. Microfabricated reservoirs for transdermal and subcutaneous drug delivery

An often overlooked component of the transdermal and subcutaneous drug delivery systems is the drug reservoir. The reservoir capacity depends on the required dose and drug potency. Furthermore, the drug chamber should not contain any dead space, i.e. air or foreign compounds, in order to maximize the availability of the stored drug formulation. Lastly, filling, sealing and packaging should be designed to be performed in an automated manner. The abovementioned requirements imply that solid, monolithic reservoir chambers are not suitable for many transdermal applications. Plastic, silicon, glass or metallic (i.e. titanium) chambers which are commonly used in microfluidic devices impose an obstacle on the reservoir mechanical compliance, limit the coupling methods to the pumping module, and complicate the filling process. In addition, in some cases, the drug reservoir is attached to the rest of the system and the whole device has to be disposed after use. For these reasons, implementation of elastomeric reservoirs is increasingly pursued [48,55,56]. A particularly attractive material is PDMS which allows for batch fabrication and can be filled using high-gauge needles without forming leak tracks.

Our lab recently reported on the fabrication of an elastomeric reservoir for MEMS-based transdermal drug delivery systems [57]. In this work, the reservoir was designed to serve as a single-use module which can be attached to the microneedle delivery system and the pump (if needed). The module consisted of a PDMS chamber which was mounted on a circular silicon substrate. The substrate had a septum which was used for the insertion of the drug in the chamber and was subsequently used for microfluidic coupling to the microneedles. The induced deflection of the chamber wall due to the drug insertion was limited by an acrylic cap with an etched cavity which determined the maximum volume capacity of the chamber and protected it from plastic deformation and fracture. A vent hole was etched on the back side of the cap, in order to allow air to be displaced, eliminating backpressure. Fig. 20 shows a schematic of the reservoir and its filling/sealing procedure. Fig. 21 shows micro-reservoirs filled with DI water without cap and with cap and polyimide seal.

Two important performance parameters for the reservoirs are the fluid retention rate and extraction percentage. The retention rate is essential for the examination of the long-term storage capability and can indicate whether this module can be used as a part of a commercialized system. Assuming there is no leakage from the insertion and extraction ports, the retention rate depends on the structural layers. PDMS self-sealing property provides a reasonable seal although more protection is required for longer shelf-lives since PDMS is permeable to many aqueous formulation (we used a polyimide tape for this purpose) [58,59]. The loss can be quantified by long-term gravimetric methods. In our design, in order to reduce the leakage paths, a barrier-layer with denser matrix was deposited on the PDMS. We used chemical vapor deposited Parylene-C for this
purpose. Parylene is an excellent moisture barrier and is commonly used in medical devices due to its biocompatibility [60]. Fig. 22 shows retention rate of the micro-reservoirs stored at 4 °C, ambient temperature, and 37 °C. As can be seen, at refrigerated conditions, the liquid retention is extremely good (almost complete) while at room temperature 90% of liquid was retained for up to 500 h. Fluid extraction performance of the deformable reservoir was also evaluated. The average extraction percentage attained was 96.1% as opposed to 86.6% which was achieved in the case of the reservoir with finite initial volume [55]. This was attributed to the minimal initial dead volume of the chamber, as well as to the stretching of the PDMS wall, which provides an additional extraction force.

6. Conclusions

In this paper, we reviewed some of the recent efforts in the design and fabrication of polymeric microdevices for transdermal and subcutaneous drug delivery. Although drug patches have been a successful platform used to deliver small lipophilic molecules across the skin, their limitations have instigated a considerable research effort in ways to enhance the skin permeability or totally bypassing it through various methods such as skin abrasion and laser microdrilling. Polymeric microdevices such as microneedle arrays and micropumps will play an important role in future development of low cost transdermal delivery systems. Despite considerable effort over the past

![Image](https://example.com/image1.png)

**Fig. 19.** A laminated, piezo-actuated, polymeric micropump with SU-8 flap valves and a piezo disk used as the pumping chamber membrane [13].

![Image](https://example.com/image2.png)

**Fig. 20.** Micro-reservoir structure and filling process [57].
decade in fabricating a variety of microneedles and micropumps; their penetration into market and adoption by health care industry has been sluggish. For this transition (from academia to the market) to happen, problems associated with performance, packaging, drug-compatibility, heterogeneous integration with other components, and reliability need to be addressed.

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References


Fig. 21. Micro-reservoirs filled with de-ionized water (a) without cap and (b) with cap and polyimide seals [57].

Fig. 22. Micro-reservoir retention rate at various temperatures in devices without the cap (left) and with the cap (right) [57].