Sensors and Actuators A 330 (2021) 112820

Contents lists available at ScienceDirect

Sensors and Actuators A: Physical

journal homepage: www.elsevier.com/locate/sna

Review

Microdosing for drug delivery application—A review

Agnes Beate Bußmann[a,b,*], Lorenz Maximilian Grünerbel[a,c], Claudia Patricia Durasiewicz[a,c], Thomas Alexander Thalhofer[a,d], Axel Wille[a], Martin Richter[a]

[a] Fraunhofer EMFT Research Institution for Microsystems and Solid State Technologies, Hansastrasse 27d 80636 Munich, Germany
[b] KIT, MAB - Biomolecular Separation Engineering, Fritz-Haber-Weg 2, 76131 Karlsruhe, Germany
[c] TUM, TEP - Chair of Physics of Electrotechnology, Theresienstrasse 90, 80333 Munich, Germany
[d] TUM LBE - Heinz-Nixdorf-Chair of Biomedical Electronics, TranslaTUM, Einsteinstrasse 25, 81675 Munich, Germany

ARTICLE INFO

Article history:
Received 11 December 2020
Received in revised form 8 April 2021
Accepted 4 May 2021
Available online 11 May 2021

Keywords:
Micropump
Microdosing
Microactuation
Drug delivery
Patch pumps
Medical dosing application
Microfluidic

ABSTRACT

There is an increasing amount of research on microfluidic actuators with the aim to improve drug dosing applications. Micropumps are promising as they reduce the size and energy consumption of dosing concepts and enable new therapies. Even though there are evident advantages, there are only few examples of industrial microdosing units and micropump technology has not yet found widespread application. To answer the evoked question of what limits the application of microdosing technology for drug delivery, this work provides a comprehensive insight into the subject of drug dosing. We highlight and analyse specific microfluidic challenges and requirements in medical dosing: safety relevant aspects, such as prevention of freeflow and backflow; dosing-specific requirements, such as dosing precision and stability; and system-specific aspects, such as size, weight, and power restrictions or economic aspects. Based on these requirements, we evaluate the suitability of different mechanical micropumps and actuation mechanisms for drug administration. In addition to research work, we present industrial microdosing systems that are commercially available or close to market release. We then summarize outstanding technical solutions that ensure sufficient fluidic performance, guarantee a safe use, and fulfil the specific requirements of medical microdosing.

Contents

Abbreviations: TDD, Transdermal Drug Delivery; MEMS, Micro Electro Mechanical System; SMA, Shape Memory Alloy; EAP, Electro Active Polymer; iEAP, Ionic Electro Active Polymer; IPMC, Ionic Polymer-Metal Composite; CP, Conjugated Polymers; PPy, PolyPyrrole; PPy/PCTC, PPy matrix, polycaprolactone-block-polytetrahydrofuran-block-polycaprolactone doped; PPy/Cl^-, PPy matrix, chlorine doped; PANI, Polyaniline; MSM, Magnetic Shape Memory; PDMS, PolyDiMethylSiloxane; PMMA, Poly(methyl methacrylate); IFT, Iterative Feedback Tuning; LIGA, German acronym for Lithography, Electroplating and Molding Applications; MDI, multiple daily injections; SEBS, Styrene-Ethylene/Butylene-Styrene block copolymers; EO, Ethylene Oxide.

* Corresponding author at: Fraunhofer EMFT Research Institution for Microsystems and Solid State Technologies, Hansastrasse 27d 80636 Munich, Germany.
E-mail address: Agnes.Bussmann@emft.fraunhofer.de (A.B. Bußmann).

https://doi.org/10.1016/j.sna.2021.112820

1. Introduction

Dosage of liquid drugs is ubiquitous in medical treatment. Especially for slow, regular, or constant administration, automated systems are of great advantage. A prominent example of drug dosing applications is insulin therapy. Patients suffering from diabetes need to manage their insulin requirements carefully [1]. Research shows that continuous subcutaneous insulin injection with pump systems improves the patients' health compared to multiple daily injections, e.g., with pen injectors [2,3].

To further ameliorate the treatment, patch pumps were developed [4]. They aim to increase the patients' compliance and reduce the need for disconnection, enabling a constant insulin supply, which promotes the therapeutic success. Additionally, the vertical position of the infusion set in relation to the pump causes large deviations in delivered insulin. A patch pump can limit these fluctuations as it decreases variations in hydrostatic pressure [5]. However, existing products are still large enough to be noticeable and some studies claim less accuracy for certain patch systems compared to durable pumps [6–8]. Similar to insulin therapy, medical research on cancer treatment shows that continuous drug delivery to specific tissue can achieve therapeutic effects while limiting side effects [9–11] by minimizing exposure to toxic drug levels [12]. Furthermore, adapting the treatment to the circadian rhythm can be beneficial [9,10]. It is obvious, that precise, automated, and reliable dosing would improve patients' care tremendously and enable the use of adapted medication, such as higher concentrated doses.

Microdosing is also of high importance when it comes to animal treatment or testing. Medical studies on test animals are a crucial part of pharmaceutical research [13]. However, especially in the case of small test animals (e.g., rodents), extremely small volumes must be dosed. Furthermore, dosing units fixed to or implanted in the animal should not be of excessive size or weight to minimize animal strain. Even though there are several solutions on the market [14–16], need for improvement towards smaller systems or more flexible administration is required.

Drug dosing applications are diverse, though share the need for small, precise, energy efficient, and reliable dosing units, which makes drug dosing a focus of microdosing research [17,18]. Already early publications on micropumps aim to improve drug delivery using those devices [19–22]. Within the last 45 years, work on microfluidic actuators continued and a variety of driving technologies has been developed. Many different microactuation principles have been investigated to create even smaller and more efficient microfluidic pumps [17,18,23–26].

Considering the great opportunities leading to a vast amount of research, the number of inventions, and especially the evident improvement of treatment, the question arises why microfluidic actuation is not yet common in medical products. There are only few commercially available microdosing units (see chapter 6) in human treatment as well as for animal testing purposes. Other products are planned for market launch soon. Though, for many promising techniques, industrialization is still pending and progress towards products appears slow.

This review discusses challenges in drug dosing that limit the application of microfluidic actuators in these fields and solutions research has found to this specific and demanding environment. It is not our goal to compare specific values of fluidic performance in detail, since most pumps presented in research are not fully optimized for all influencing factors, such as pump chamber or valve geometry. Rather, we intend to emphasize challenges and chances arising with the use of microfluidic actuation within a biomedical environment and to summarize approaches within various types of microactuators to solve them. Furthermore, we intend to depict the status of development and general applicability of a technology in drug dosing systems. We focus on continuous and adaptable medical dosing and therefore address displacement micropumps.

2. Challenges and requirements for drug delivery

Microdosing systems, e.g., based on micro electro mechanical system (MEMS) pump technologies, enable the delivery of smaller volumes and minimized size and weight of the system compared to current large-scale products. However, the small dimensions implicate several fields of challenges. Environmental conditions, such as variations in backpressure or temperature, have an impact

Table 1
Overview of requirements for pumps in drug dosing applications.

Requirements	General Requirements in Drug Delivery	Specific Challenges for Microdosing in Drug Delivery
Safety Aspects		
Freeflow Stop	Uncontrolled flow caused by an overpressure at the reservoir can have severe consequences for the patient. In larger scale products, the freeflow prevention can be implemented more easily.	Many microdevices show freeflow (e.g., micro diaphragm pumps). An integrated freeflow stop needs to fulfil size and weight constraints while functioning over a large pressure range.
Backflow: Leakage and Diffusion	Backflow, caused by diffusion or backpressure leading to leakage, can lead to clogging of injection sites, damage of the pump, or dosing inaccuracy.	Leak tight valves are challenging due to geometric limitations.
Bubble Tolerance	Small bubbles can always occur in dosed liquids and the dosing unit needs to be capable of transporting them without failure.	Due to increased capillary forces and the dampening effect of air, depending on the actuation mechanism, bubbles can lead to failure of micropumps [28].
Interaction with Medium and Clogging	Dosing units must not influence the dosed drug or occlude during long use periods. Aggregation during storage or use is unacceptable.	Small channels with high surface to volume ratio and sharp edges are likely to influence the dosed medium and can promote obstruction. Particles or agglomeration can impair dosing of micropumps.
Safety Measures	Medical applications require a high level of safety. Therefore, products usually include safety measures such as pressure and temperature sensors for failure detection.	The same need for failure detection applies. However, integration into the dosing unit can be challenging for the lack of space. Failure modes can differ largely depending on the actuation and therefore development of individual safety measures is necessary.
Microdosing		
Flow Range	The required flow range depends strongly on the application.	Drug dosing applications can require extremely small flow rates. Examples are the use of highly concentrated drugs, or animal trials with small rodents.
Dosing Accuracy and Precision	Requirements are not uniform. An example is diabetes therapy, where most insulin-pump suppliers judge ±5 % deviation acceptable [29].	Even if the dosed volume is small, percentage deviation should not increase. Hence, accurate measurement and control systems are required.
Dosing Stability	Changing environmental conditions should not influence the dosing accuracy significantly to allow for safe use at all times.	Depending on the actuation type, different surrounding conditions, such as backpressure and temperature, potentially have a large influence on the microdosing unit.
Dosing Flexibility	In many applications there is a need to adapt the flow rate to the patients' need (e.g., bolus and basal rate).	Depending on the actuation method, the range of applicable flow rates can be limited.
System-Specific Requirements		
Size and Weight	Limits for size and weight vary strongly with the application.	The miniaturization of the fluidic actuation unit offers the possibility to develop microsystems for size and weight critical applications such as implants, patch pumps, or dosing units for animal trials. However, even with miniaturized actuation, limitations can stay challenging.
Power Consumption	Depending on the application, power supply via a battery over a long period can be necessary.	Especially for implantable applications with limited energy supply, low power consumption or wireless supply are necessary, limiting the choice in actuation methods.
Lifetime	Lifetime requirements can vary from some minutes to many years.	There is less knowledge about the lifetime of microdosing systems compared to current macroscopic actuators.
Cost	Cost is especially critical for disposable products. For many dosing units, such as durable pumps, the actuation mechanism is reusable.	The microdosing device is often in direct contact with the dosed fluid, limiting it to mostly disposable or partly disposable use. Cost is therefore a key factor for industrialization.
Production	Reliable and cost-efficient processes are important to be competitive.	For microsystems, production strongly depends on the pump type, e.g., MEMS processes or extreme miniaturisation of macroscopic mechanical production processes.

on the pump and its microactuator. Due to smaller dimensions, surface scaled disturbances like the damping effect of bubbles, capillary forces, or particles become more influential compared to the volume scaled forces that drive the pump. Additionally, the space to include safety measures is limited. Using the advantages of microdosing and despite all additional disturbances, microscale drug delivery systems need to meet all current requirements for medical products, such as biocompatibility, flow accuracy, or lifetime [27]. Table 1 summarizes important requirements, divided in safety aspects, flow aspects of microdosing, and application specific requirements that are explained in more detail in chapters 2.1–2.3.

2.1. Safety aspects

As safety relevant aspects we describe basic requirements, which a pump has to fulfil to guarantee safe use for the patient. For clearer presentation and due to their key function, we discuss flow requirements such as precision and accuracy, which are obviously highly relevant for safety aspects also, in a separate chapter (see chapter 2.2).

The prevention of so called "freeflow" constitutes a basic safety measure within microfluidic actuation. For many pumps, an overpressure at the inlet (e.g., hydrostatic pressure or compression of a reservoir) can cause an uncontrolled fluid flow. To prevent freeflow can be specifically challenging, since countermeasures have to function at both low and high overpressure at the inlet [30,31]. Contrary to macroscopic devices with enough space for additional valves, integration can be complex and innovative solutions with minimal space requirements are needed.

Not only fluid movement in flow direction caused by an overpressure at the inlet is problematic, but also backflow and leakage, especially while the pump is turned off. Often the required flow is not constant and sometimes the pump is turned off. If the outlet pressure exceeds the reservoir pressure, body fluid can be pushed

back, impairing the drug delivery or causing clogging of the delivery unit. Therefore, as little leakage as possible is an important property of a microfluidic dosing unit. Similar to freeflow, leakage is strongly pressure dependent. Especially for passive flap vales, which usually show an initial gap [32], low pressure can cause higher leakage than higher backpressure that pushes the valves towards their valve seat. For reasons of energy efficiency and safety, a normally closed or self-blocking setup, that is, a pump that blocks the fluid path when turned off, can be beneficial. In addition to leakage, diffusion can cause unwanted drug release or movement of body fluid towards the reservoir.

To deliver the required flow securely, a dosing unit in medical applications has to be able to overcome a certain pressure level. For instance, drug delivery requires the pump to build up more pressure than the physiologic backpressure of the target tissue. This pressure is in the range of some hundred Pa to some tens kPa [33]. However, several additional effects add up to the real backpressure Δp the pump has to overcome: hydraulic pressure caused by height differences, fluidic resistance of channels, enlarged fluidic resistance due to clogging as well as capillary forces of small bubbles in the dosed liquid. For instance, the combination of a pump with microneedles for transdermal delivery requires high backpressure capacity of the pump due to the small channels [34].

Together with delivered medium, small bubbles get transported into the micropump. Those bubbles typically have a volume several orders of magnitude smaller than the lethal doses of estimated 200–300 ml [35]. However, they can be problematic for the dosing unit itself. The bubbles can be caused by incomplete priming of the drug reservoir, accumulation in corners, transmission through gas transparent tubing/bags, increase of environmental temperature causing degassing of saturated drugs, or accidental injection during a reservoir refill [36–38]. In some pumps, gas bubbles can be caused by cavitation, a condition where the fluid inside the pump chamber degasses or evaporates due to negative pressure during the pump supply mode [39]. Air is compressible and acts as a fluidic capacitance, effectively creating a fluidic low pass filter and dampening high frequency pressure pulses. Furthermore, surface tension becomes relevant in small dimensions. Bubbles therefore cause capillary pressure and possibly accumulate and block channels [40,41], as they enter narrow structures such as check valves or filter pores.

Since it is impossible to consequently avoid bubbles, the dosing unit has to be bubble tolerant, even with applied backpressure. Many microfluidic actuators do not fulfil this criterion. All micropumps that exploit a fluid property for the actuation, such as osmotic pumps, electro-hydrodynamic pumps or magneto-hydrodynamic pumps, fail if a sufficiently large bubble enters the actuation chamber, as the fluid (that is needed for actuation) is replaced by air. These actuation mechanisms are therefore not discussed in this review, even though these pumps can be used to deliver drugs successfully, when they are primed carefully and protected against bubbles during their life cycle.

Another safety relevant issue is the interaction of the pump with the transported media. In microfluidic systems, the pumped fluid often moves through the pump itself. While shear forces alone are shown to be less problematic [42], the combination of shear forces in small fluidic channels with surface interaction can cause protein denaturation [43]. Many studies show aggregation caused by solid/liquid interfaces and evaluate the influence of material as well as topography [44–46]. Additionally, a gas/liquid interface due to bubbles or cavitation can cause damage to proteins [47,48]. Furthermore, a more severe interaction than seen in large scale dosing units is imaginable due to a large surface to volume ratio. Small and sometimes sharp moving parts, such as flap valves or microgears, are in contact with the medium and can cause additional damage. Strong interaction can cause adhesion of small agglomerates within the fluidic path that lead to a partial or total occlusion. Furthermore, the interaction of the drug with the microdosing unit can impair the drug's effect [45]. Thus, it is of great interest to investigate the interaction of a microfluidic actuator with the dosed medium.

Even devices offering robust dosing stability in most environmental conditions can fail, which makes error detection indispensable. This is eminently important when the pump is used within a high-risk medical product, e.g., insulin patch pump. It is advantageous if failure detection can be included directly into, or closely to the micropump, since additional sensors to fulfil this task need additional space and production effort – decreasing the advantages of microdosing. Some examples of possible failure detection are discussed in chapter 5.

2.2. Microdosing

Dosing flexibility, dosing accuracy, dosing precision and dosing stability are key features of a microdosing unit. Malfunctioning can have severe consequences and can even cause a patient's death [49].

Dosing flexibility is the ability to adapt the flow to what is needed, e.g., for basal and bolus delivery or adjusted to current measurements (e.g., blood sugar). Therefore, the dosing unit needs to be capable of delivering fluids with variable flow rates and the possibility to program the flow is required.

Dosing accuracy describes how close the mean dosed volume is to the target volume. Large deviations between several dosing steps can still lead to accurate dosing, if the mean corresponds to the target flow. Dosing precision describes high repeatability and therefore only minimal deviations between several dosing steps. At high precision, the mean dosed volume can differ from the target volume. Drug delivery systems have to be both, accurate and precise, to guarantee safe use.

Dosing stability addresses how the mean flow rate and the standard deviation change with environmental parameters, such as temperature, backpressure, or humidity. For example, a highly variable backpressure, as can be caused by the patient's movement or occlusion of the injection site, can distort the total dosed volume. In addition to the described need for a sufficiently high blocking pressure for safety reasons (see chapter 2.1), a pressure independent dosing within the normal limits of application is highly favourable. Similar accounts for the temperature: expected deviations in surrounding temperature should not lead to a large deviation in flow creating the need for temperature independent microfluidic actuation. It is thus crucial to know and maybe observe occurring environmental conditions and adapt the microdosing unit to this range in a way that the needed flow accuracy and precision is assured at all times.

2.3. System-specific requirements

In addition to safety and flow requirements, there are many more constraints a dosing unit has to meet. Those depend strongly on the use case, the exact setup as well as the environment in which the micropump is used.

Microdosing units are often single use products, thus cost is critical. Obviously, each specific application as well as different countries and health care systems imply different cost limitations. However, estimated production costs give an interesting insight to the feasibility of a technology within a product. For larger scale devices it is a common approach to reuse the driving unit. In microdosing units the transported medium often passes through the pump itself, which makes a safe reuse of the actuator challenging. Since cost considerations are complex and only a distinct improvement of a treatment justifies a large increase in cost, it is crucial to consider inexpensive production [50].

There are various production processes used for micropumps. Some pumps are based on standard MEMS processes with low costs for high production volumes [51]. Those processes allow for precise and repeatable production of small geometries and minimize sample to sample variation. Production is very cost efficient for high numbers, however, first industrialization and the production of small numbers generate high initial costs. Furthermore, the choice in materials can be limited, restricting considerations of surface interactions, biocompatibility, or hermetic sealing slightly [52]. Other pump types scale down known macroscopic actuation mechanisms to the microscopic world and require cost and effort during production. Small mechanical parts, such as gears, have to be produced with extremely low tolerances coming down to the order of magnitude of surface roughness [53]. Without utmost precision, assembly of the parts can be challenging and smooth sliding is not guaranteed.

The required lifetime of a micropump also strongly depends on the use case. While an implant can be used for extremely long periods, a disposable for short time use does not require long lifetime. This topic has to be addressed for each pump type individually, as each actuation method and pump geometry poses different challenges. In miniaturized systems, small scale of moving parts can cause problematic wear with a larger impact on the functionality [53], e.g., the abrasion caused on gears in a microgear pump. For micro diaphragm pumps, the lifetime of the actuator, the pump diaphragm as well as the adhesive connection of both components need to be considered in addition to the fluidic path.

Even though microfluidics imply small actuation principles, size remains a great issue for many systems, since space or weight can be extremely limited. A field with extremely challenging weight and size restrictions is the pharmaceutic testing on small rodents. Not only for animal welfare, but also to minimize the influence on test results, is it crucial to have a precise, reliable dosing unit that limits animal strain [54]. Especially the weight of the device should be limited to prevent avoidable suffering. In the case of mice, the whole dosing system including electric power supply and a drug reservoir can only weigh some grams.

Size and weight restrictions demand for energy efficient dosing units. Especially with implants designed for long term use, the units' power supply is often limited to a battery. To develop small systems, the energy consumption needs to be as little as possible in order to be provided by a small battery for the time of implantation or between recharge. Not only the energy source, but also the driving electronics need to be optimized in size, signal accuracy, and energy consumption. It is evident that the accuracy of the electronic signal has to be higher than the desired dosing accuracy to not impair pump performance.

3. Experimental evaluation of microfluidic dosing accuracy

To compare various dosing system techniques, a standardized evaluation is necessary. Currently, experimental methods differ between research works, which impacts the flow results. Differences in the measuring method, as well as fluidic surroundings, e.g., tubing length and diameter, or the fluidic resistance of sensors, can significantly change performance parameters such as maximal pressure built up or maximal flow rate. Especially for extremely small flow rates, it is delicate to avoid a strong impact of the experimental setup. When comparing different micropump solutions, it is important to keep the difference in experimental evaluation in mind.

Drug dosing units have to be tested following standard procedures. The norm IEC 60601−2-24 [55] describes the assessment of dosing accuracy as well as obstruction detection of commercially available infusion systems *in vitro* and also accounts for patch pump devices based on micropumps. It proposes a gravimetric measurement and results are to be presented in a trumpet curve. Pleus et al. [56] point out that a trumpet curve is easily misunderstood, since contrary to intuitive interpretation, it does not show an evolution over time. Furthermore, only extreme values are displayed, which might not be representative for average flow variations. In addition, the long run-in period indicated in the norm (time to half empty the reservoir, though 24 h at the most) does not reflect the clinical application, where dosing accuracy matters from the start of the pump on [29,56]. And indeed, diabetes patients sometimes report variations in their glycaemic control connected to the change of their pump [57].

In the case of insulin dosing, a lot of research has been conducted towards comparable dosing investigations. Many studies evaluate the average deviation within a given observation window or the percentage of single doses within a specific range of accuracy in addition to or instead of the trumpet curve [6,8,29,57–59]. For gravimetric methods, the influence of evaporation and condensation needs to be minimized either by covering the surface in the reservoir with oil [7,29,58] or by installing an evaporation trap [60]. To avoid any influence of hydrostatic pressure, the meniscus of liquid in the reservoir and the pump's outlet need to be levelled [29]. Further, the drift before and after dosing steps has to be measured to consider drift corrected data. Additionally, the capillary immersed to the reservoir on the balance causes inaccuracy. Changing volume in the reservoir evokes a linear change in mass caused by Archimedes force [60]. With a large enough reservoir and small tubing, this effect can be minimized. Capillary effects around the needle show to have a significant influence [60], since the microscopic roughness of the tubing changes the vertical surface forces when the meniscus is rising or falling. The effect of capillary effects can be minimized by using extremely smooth glass capillaries and reduce the surface tension of the dosed liquid by adding surfactant in the reservoir [60].

Another method to evaluate small delivery volumes is the optical observation of a meniscus in a precise measuring pipette [59]. With this method, it is crucial to have a tight connection between the pump and the pipette to avoid air bubbles and volume losses. Because of the limited size and resolution of the pipettes, the dosed volume can only be evaluated in certain ranges and it might be necessary to calculate the mean and standard deviation of single doses by repetitive measurements of several doses [59].

Exact environmental temperature and its influence on dosing accuracy is often not tracked in micropump studies and authors often only state laboratory condition within a certain range. Though, for microdevices, temperature can have a crucial influence by changing the viscosity of the pumped medium, or the pump chamber height and actuator displacement in the case of diaphragm pumps. Controlled temperature would therefore be an important addition to above methods.

To assess and compare the bubble tolerance of micropumps requires equal test conditions for each experiment. Bubbles need to be of similar and especially known size. A possible experimental setup is to fill the pump with water and then inject a defined amount of air, e.g., with a syringe pump. Alternate pulling of air and water allows a desired number and size of bubbles to accumulate in the inlet tubing [61]. This setup allows to test bubble tolerance and detect the air volume a pump cannot transport anymore. It is important to note that data points can scatter broadly, since the exact position of a bubble in the chamber influences the forces needed to move it.

Accurate flow measurement is difficult even within a laboratory environment and poses a large challenge when integration into a microdevice is necessary. However, closed loop control systems can require such accurate flow measurements. Two types of in-line sensors that can be miniaturized are calorimetric sensors and dif-

ferential pressure sensors. Jenke et al. [62] describe the difficulty of measuring the pulsed flow of a micro diaphragm pump. Within their setup the authors reach an accuracy of 5 % with the differential pressure element and 6.5 % with calorimetric measurements [62].

4. Actuation principles in microfluidics

Many possibilities to categorize the various driving principles exist, however "mechanical" and "non-mechanical" emerged as a very common classification [17,18,24,25,63,64]. Fig. 1 gives an overview of common mechanical types of microfluidic actuators that this work focuses on, since non-mechanical systems are often not bubble tolerant or do not offer the possibility of continuous, adjustable dosing. An overview of all pumps quoted in this review is given in Table 2, to allow for quick comparison. As stated above, the data of quoted pumps may not represent the optimal achievable values for each mechanism and we rather intend to introduce inventive solutions for challenges of medical applications.

A widespread approach to dose small amounts of fluids are reciprocating micro diaphragm pumps (Fig. 1, A-G). Dosing bases on a diaphragm that is moved actively up and down. This increase and decrease of the chamber volume and the resulting pressure gradient lead, in combination with mechanical or non-mechanical flow rectifiers, to directed flow. The former may be active or passive valves, e.g., flap valves, whilst the latter are commonly diffuser nozzle setups. When neglecting flow influencing effects such as liquid damping effects or bubbles, the moved volume is proportional to the numbers of strokes conducted [65,66]. This allows for adjustable flow and precise dosing. The maximal achievable resolution is the volume of the smallest possible stroke. The stroke volume can be minimized by variations of the actuation signal, though has a lower limit which is determined by many parameters, such as the opening pressure of the valves, the signal form, and the minimal achievable diaphragm displacement. The pumping mechanism applied by diaphragm pumps inevitably causes pulsatile flow, since the suction and pumping phases are consecutive. Smoothing elements such as fluidic capacitances can average the flow and reduce pressure peaks.

A major asset of diaphragm pumps is the possibility for extreme miniaturization. For example the so far smallest piezoelectric pump with only $3.5 \times 3.5 \times 0.6$ mm^3 is manufactured using MEMS processes [67]. The combination of such large volume production processes and the comparatively easy setup that often includes only a few layers, suggests economical production.

Diaphragm pumps can work with a single chamber as well as with several chambers in series making peristaltic, and therefore bidirectional actuation possible. There are various types of diaphragm actuation:

The most common actuation is the indirect *piezoelectric effect*, causing a piezoelectric ceramic to contract and expand when an altering electric field is applied [68]. A diaphragm with glued on piezoelectric actuator therefore bends up- and downwards under an altering voltage [69]. The popularity of this actuation bases on its easy use, its high attained forces as well as its energy efficiency [70]. Piezoelectric actuation allows for high actuation frequencies [70] and precise control. However, the achievable stroke is limited and requires high voltages of often several hundred Volts [71–73].

The first micropump based *thermal shape memory alloy* (SMA) actuation was developed by Benard et al. [74,75] in 1997/1998. Thermal shape memory materials recover their original shape upon heating [76] and can therefore be used to oscillate a diaphragm. Materials show either a two way or a one way shape memory behaviour and both are used for micropump actuation [77]. The two-way shape memory effect describes a transformation between two different states, while the one-way material only shows the return to its engraved state when heated but no shape change upon cooling. Hence, the one way effect requires a restoring force to push the actuator back to its zero position after deformation [74,75]. The technology is known for its high achievable displacement as well as low operating voltages; drawbacks are low operating frequencies, a limited control of the exact deformation, and a high power consumption [70].

For *electromagnetic* actuation, a magnet fixed to the diaphragm, e.g., a permanent magnet, is actuated by an alternating magnetic field. This field is induced by an oscillating electrical current through a coil (power inductor) situated in proximity to the diaphragm, which leads to alternating magnetic attraction and repulsion of the permanent magnet [78]. Electromagnetic actuation enables energy efficient fluid transport with some pumps using only 1.2 kJ/L when pumping water [79]. However, actuation requires high current as well as high magnetic fields.

The diaphragm can also be actuated via *electrostatic* forces. Two electrodes, one on a diaphragm and one on a fixed counterpart, are drawn together when a voltage is applied and the diaphragm returns to its original position by mechanical counterforces when the voltage is removed [80]. Depending on the direction of mechanical movement compared to the electric field, we distinguish lateral and normal actuation. The first pump with normal actuation was presented by Zengerle et al. [80] in 1992. The first lateral actuation was presented more than 25 years later by Uhlig et al. [81]. Manufacturing often uses standard MEMS processes without additional steps such as gluing [80]. Further miniaturization, which is limited for other actuation mechanisms by the minimal size of their actuators, appears possible.

Progress in materials research enabled another type of actuator: *electro active polymer* (EAP) actuation for micropumps was first mentioned in the early 2000s [82]. Actuation bases on the change in size or shape of certain polymers caused by an electric stimulus with a high elastic energy density [83]. The electric actuation mechanism allows to differentiate two major groups of EAPs: ionic and field-activated materials. Ionic electroactive polymers (*i*EAP) base on diffusion of ions. When applying an electric field, ions that are normally well distributed are pulled to one of the electrodes, also carrying the solvent present in the material. The latter causes deformation of the polymer membrane and therefore transforms electrical into mechanical energy [84]. Specific types of iEAPs are ionic polymer-metal composite (IPMC) and conjugated polymers (CPs). CPs consist of a semiconducting polymer doped with donor or acceptor ions [84]. The most common materials today are polypyrrole (PPy) and polyaniline (PANI) [85]. Advantages are a large bending displacement at low actuation voltages of only few volts, easy and low cost production, and the possibility of bidirectional actuator movement [86]. A disadvantage is the relatively slow response (fraction of a second) due to slow ion drift [86]. Using an electrolyte also leads to some difficulties, such as electrolysis or production of a consistent material. The electrolyte must be in wet environment, only few self-encapsulating implementations are known [86].

The second category of EAPs are field-activated ones. We distinguish ferroelectric polymers that react due to intrinsic field-induced molecular conformational changes to the elastomer, and dielectric elastomers mainly responding to extrinsic electronic charge attraction-repulsion at the surface electrodes [86]. The latter are basically capacitors that change their capacitance due to an applied electric field, essentially squeezing the polymer in thickness and hence expanding it laterally. Both mechanisms are inherent to all field-activated polymers, however usually one is clearly dominant. Advantages of field-activated EAPs are rapid response times (ms), high durability, and a high mechanical energy density [86]. Under constant electric fields, the material holds the strain without need for power. A large disadvantage is the high necessary driving voltage with electric fields of dozens of V/μm, which

Table 2
Overview of micropumps cited in this review; Pumped media are A- air, I- insulin, L-liquid, W-water and [a] saline solution, [b] methanol, [c] blood mimicking fluid, [d] sodium salicylate, [e] ethanol, [f] glycerol solution; Evaluation: 0 – not fulfilled, 1- partially fulfilled, 2- fulfilled.

	Q_{max} in µl/min	Fluid	Voltage in V	Frequency in Hz	P_{max} in kPa	Freeflow Stop	Backflow Stop	Bubble Tolerance	Dosing Precision in µl	Size in mm^3	Power in kJ/L	Life Time in cycles
Piezoelectric Actuation												
[34]	3000	W/I	36	200	22	0	2	–	0.062	Ø 15 × 8	–	–
[97]	3.5	W	24	1	3.2	1	1	1	–	30 × 10 mm^2	0.9	–
[98]	4360	W	60	35	50.5	1	1	–	–	30 × 12 × 1	–	–
[99]	50	W	110	8	30	1	1	2	0.01	45 × 30 × 25	–	–
[100]	25	W	–	500	600	2	2	2	0.088	7 × 7 × 1	–	–
[73]	240	W	230	75	36	1	1	2	–	23 × 23 × 2.2	–	–
[101]	2400	W	250	110	45	1	1	–	–	–	–	–
[102]	1.7×10^4	W	110	10	40	0	2	2	–	20 × 20 × 6	–	–
[103]	196	W/[c]	140	25	6.4	0	2	2	–	50 × 50 × 12	–	–
[67]	1400	A	145	2000	40	0	2	–	–	3.5 × 3.5 × 0.6	–	–
[104]	150	W	140	20	180	2	2	–	–	–	–	–
[105]	4698	W	200	15	–	0	0	–	–	65 × 40 × 12	–	–
[72]	4800	W	300	125	1.8	0	0	0	–	–	–	–
[106]	7.2×10^6	W/[c]	150	5	0.3	0	0	–	–	50 × 50 × 22	–	–
[107]	200	W	200	40	40	1	1	–	–	30 × 11 mm^2	–	–
[108]	70,000	W	380	30	–	0	2	–	–	Ø 20 × 1.5	–	–
[71]	1.3×10^5	W	240	400	10.8	0	2	–	–	–	–	–
[109]	1.8×10^6	W	210	120	44	0	2	1	–	–	–	–
[110]	4200	W	360	25	60	1	1	–	–	30 × 12 × 1	1.4	–
Shape Memory Alloy Actuation												
[74]	50	W	0.6	0.9	–	0	2	–	–	–	648	–
[75]	50	W	–	0.9	–	0	2	1	–	15 × 9.1 mm^2	756	–
[111]	4.8	W	–	0.2	–	0	2	–	–	10 × 20 × 1.4	5000	2170
[112]	340	W	–	60	–	0	2	–	–	6 × 6 × 1.5	–	4×10^7
[113]	235	W	–	80	–	0	0	–	–	8 × 8 × 1.8	–	2×10^6
Electromagnetic Actuation												
[78]	66	W	1.5	9	0.98	–	0	0	–	–	43.6	–
[114]	209	W	1.52	5	0.54	1	2	0	–	Ø 1.6 mm	218.2	–
[115]	400	W	–	12	1.2	0	0	0	–	36 × 22 × 3	–	–
[116]	53	–	–	240	–	0	0	0	–	–	–	–
[117]	441	W	5	45	0.35	0	0	0	–	–	96.2	–
[118]	7	–	10	110	–	0	0	0	–	–	–	>72 h
[119]	0.006	W	10	1	–	0	0	0	–	5 × 5 mm^2	23,500	–
[79]	1623	–	30	7	0.36	0	0	0	–	55 × 35 × 10	1.2	–
[120]	9.3	W	2	1.6	41	0	2	1	–	–	–	–
[121]	13.2	D	–	1.3	–	0	1	0	–	5 × 9 mm^2	–	–
[122]	0.26	W	–	4	550	0	2	–	0.001	–	1.4×10^5	–
Electrostatic Actuation												
[80]	70	W	170	25	2.5	0	2	0	0.01	7 × 7×2	–	–
[123]	850	W	200	800	31	0	2	0	–	7 × 7×2	0.4	–
[124]	136	A	90	15	–	0	–	–	–	–	–	–
[125]	1.7×10^{-3}	W/[e]	200	20	–	0	0	–	–	–	–	–

Table 2 (*Continued*)

	Q_{max} in µl/min	Fluid	Voltage in V	Frequency in Hz	P_{max} in kPa	Freeflow Stop	Backflow Stop	Bubble Tolerance	Dosing Precision in µl	Size in mm^3	Power in kJ/L	Life Time in cycles
Electroactive Polymer Actuation												
[126]	10	L	10	0.5	–	0	0	0	–	–		$>10^5$
[127]	77	W	3300	30	8.5	0	1	0	–	10 mm^2	1.3	10 h
[128]	760	–	3	3	1.5	–	1	0	–	20 × 5 × 0.6	–	few min
[129]	202	–	5	2	–	0	1	0	–	30 × 30 × 27	–	–
[130]	780	–	2	0.5	–	0	0	0	–	–	–	few min
[131]	1600	W	3	1	0.7	0	1	0	–	70 × 40 × 15	–	–
[132]	1260	–	4	0.5	1.3	0	1	0	–	25 × 25 × 10	1.4	–
[133]	83	L	2	5×10^{-4}	2.4	–	0	–	–	–	68	–
[134]	2000	L	2	1	–	–	–	–	–	–	–	–
[135]	22	[a]	1.2	–	–	0	1	–	–	30 × 20 × 6	5.5	5 days
[136]	25	[b]	5680	63	0.35	0	0	–	–	–	–	–
[82]	550	A	–	1000	–	–	–	–	–	–	–	–
[137]	0.06	[a]	1.2	0.4	–	0	1	0	0.001	–	625	$>6 \times 10^6$
[138]	–	L	8	–	–	–	–	–	–	–	–	–
[139]	2	L	2.8	–	3000	–	–	–	–	Ø 8 × 1	–	$>10^6$
Phase Change Actuation												
[140]	0.1	W	–	0.083	–	2	2	–	0.011	7 × 13 × 1	11	26×10^6
[88]	0.07	W	1	0.5	–	1	1	–	–	12 × 6 × 2	135	–
[90]	0.6	W	1.5	0.6	1.3×10^4	1	1	–	–	–	34.4	–
[89]	0.1	W/[d]	3.7	0.33	5	1	1	1	1.2×10^{-3}	8 × 8×3	–	20 min
Thermopneumatic Actuation												
[141]	1.3×10^{-5}	W	12	–	–	0	0	0	–	–	–	–
[142]	9.2	W	5	1.5	0.5	1	1	1	–	16 × 18 × 5.5	–	–
Magnetic Shape Memory Alloy Actuation												
[143]	2000	L/A	–	320	1000	2	1	2	0.105	11 × 3.1 × 2.3	7.6	–
[144]	–	L	–	–	–	–	–	–	–	20 × 16 × 59	–	–
[92]	252	L	–	–	–	–	–	–	0.26	25 × 10 × 2.5	–	–
[145]	1800	W/[f]	–	270	150	2	1	–	0.110	18 × 10 × 5	7000	$>10^6$
Rotary Pumps												
[53]	–	–	–	–	–	–	–	–	–	Ø 3.2 mm	–	–
[146]	–	–	–	–	–	–	–	–	–	–	–	–
[147]	–	–	–	–	1200	–	–	–	–	–	–	–
[148]	–	–	–	–	–	1	1	1	–	–	–	–
[149]	150	W	–	30	–	1	1	–	–	10 × 12 × 1.3	–	–
[150]	–	I	3.7	–	–	1	1	–	1	Ø 5.5 × 2	–	$>3 \times 10^3$
[30]	2050	L	1.5	14	82	2	2	1	–	30 × 15 × 14	–	–
[151]	275	W	5	180	40	2	2	2	–	Ø 24 × 40	–	–
Electrolysis Actuation												
[152]	–	W	–	–	–	0	2	–	–	20 × 15 × 10	–	30 days
[153]	520	W	–	–	–	–	–	–	–	3.9 × 2.1 × 2	57.7	–
Commercial Pumps												
Jewel Pump	360	W/I	400	3	–	2	2	2	0.2	6 × 10 mm^2	–	2.6×10^6
Omni Pod	15	I	–	30	–	2	2	–	0.5	40 × 60 × 18	–	–
Sensile Medical	2.5×10^4	L	–	20	400	2	2	2	0.25	–	–	–
iPrecio 310R	0.16	L	–	–	–	2	2	2	–	–	–	67 days
iPrecio 200	0.5	L	–	–	–	2	2	2	–	–	–	86 days
IP2000V	2.1	L	–	–	–	–	2	–	–	Ø 78 × 14	–	20 years

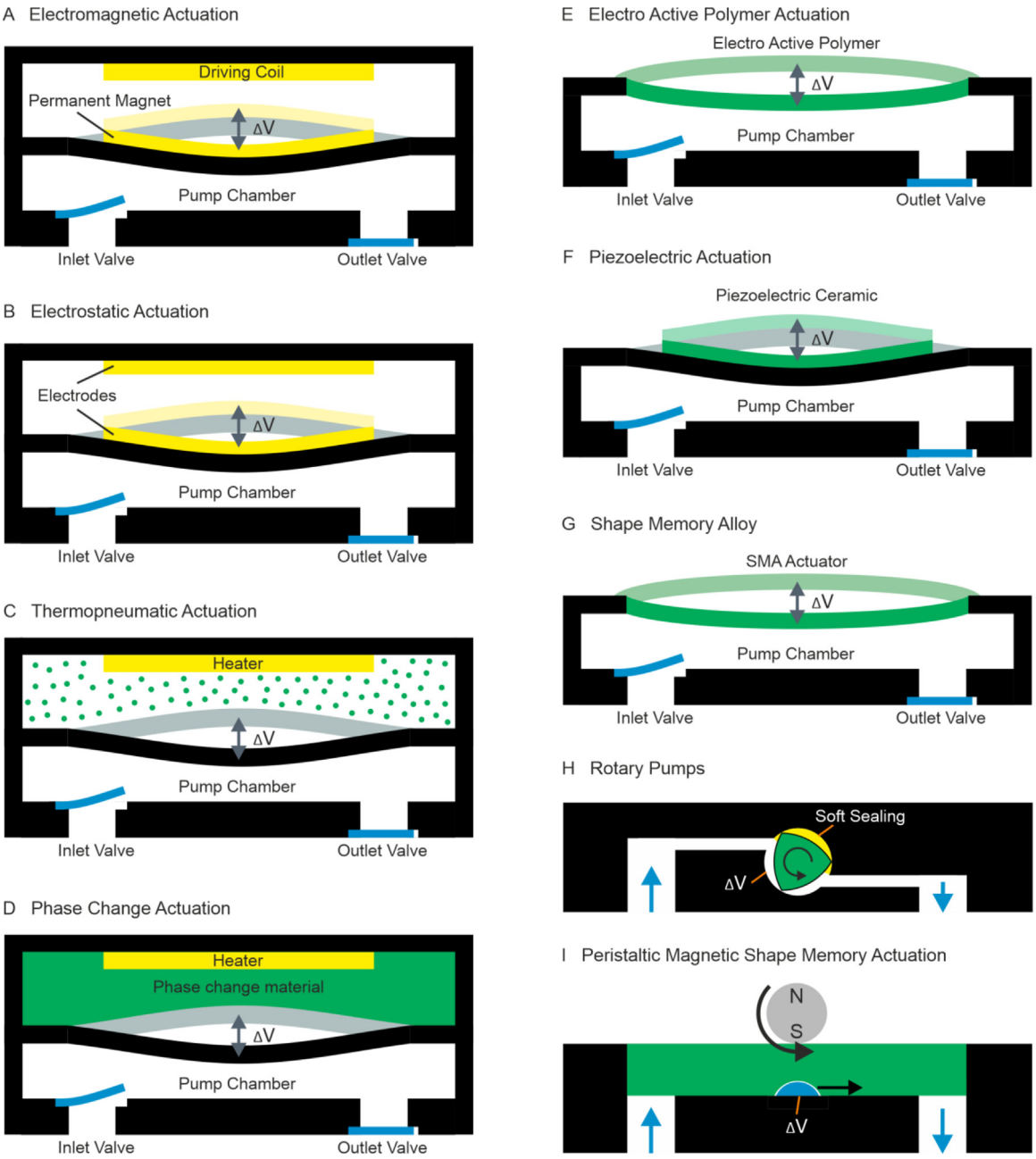

Fig. 1. Overview of mechanical pump systems. A to G: In the case of micro diaphragm pumps, a periodic movement of the diaphragm increases and decreases the volume in the pump chamber and leads in combination with flow restricting elements to directed fluid transport. Common actuation principles base on electromagnetic forces (A), electrostatic forces (B), thermal volume expansion (C) or the volume increase of a material due to phase change (D), the conformational change of electroactive polymers (E), the indirect piezoelectric effect (F) and the thermal shape memory effect (G). H: Exemplary depiction of a rotary micropump that transports fluid due to a turning motion of its actuated part (green). In this example directed flow is achieved with a flexible soft sealing preventing backwards transport (yellow). I: Peristaltic micropumps actuated with a magnetic shape memory alloy transport liquid via local deformation due to changing magnetic fields. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is close to material breakdown [86]. Furthermore, only monopolar actuation is possible due to electrostriction [86].

Another researched actuation mechanism is *thermal* actuation including thermo-pneumatic systems and phase change actuation. Thermo-pneumatic actuation bases on the expansion of volume due to heating, which pressurizes the diaphragm and deflects it [87]. Phase change micropumps use the volume expansion certain materials undergo during a phase change to move the diaphragm [88]. Thermal actuation enables large forces and hence high back-pressure capability of the actuator. The actuation voltage is low in the range of some volts to some tens volts [89,90]. However, the energy consumption to heat and cool the actuator is high leading to smaller efficiency compared to other driving mechanisms [91]. The example of Bodén et al. [88] shows a power consumption of approximately 400 mW resulting in roughly 90 kJ/L (compared to 1.2 kJ/L for electromagnetic pumps and less than 1 kJ/L for some piezoelectric pumps). The actuation frequency is often limited by the cooling cycle and restricts the achievable flow. A common actuator material is paraffin due to its large volume change, high pressure capability, adjustable melting temperature as well as low cost [88,91].

Peristaltic actuation, which is for most actuation methods realized using several bending actuators, can also be achieved with *magnetic shape memory* (MSM) actuation [92] that was so far demonstrated by two research groups. The setup and functionality

of MSM pumps differs from diaphragm pumps (Fig. 1, I). The pump chamber with a high aspect ratio comprises an in- and outlet on the far ends and is covered by a MSM layer that is locally deformed by a strong magnetic field [92]. This local cavity moves along the actuator with changing magnetic field and transports liquid in a peristaltic manner. MSM pumps work bidirectionally and operation is contact free, though the driving magnetic field is high in the range of some hundred mT [92].

Another principle of microfluidic actuation are *rotational micropumps* that transport fluid with a turning motion of their actuated parts. One example are *microgear pumps,* where the turning motion of gears moves a fluid volume from an inlet towards the outlet (Fig. 1, H). The rotating motion can also be used to squeeze liquid within a tube from an inlet to an outlet as within a miniature *peristaltic pump*. Typically, rotational micropumps enable continuous flow as well as stepless adjustment of the flow rate. The energy transfer from mechanical (revolutional speed) to fluid (flow velocity) is efficient and in comparably small space, and most pumps show a good flow direction control due to a continuous pressure gradient that enables valveless configurations. However, manufacturing requires high precision, since the gap between rotors and pump chamber must be small to reduce leakage and backflow. Rotor configurations can cause high shear forces in the fluid and the surface-to-volume-ratio is high, which might prompt interaction with the dosed medium. Compared with diaphragm pumps, this pump type is usually large. Nevertheless, based on improved manufacturing methods, such as micro injection moulding [93–95], miniaturization is pushed.

A more detailed overview of micropumps, categorized regarding their driving mechanism as well as their valves and pump chamber, can be found in the work of Mohith et al. [64]. Laser and Santiago also provide a detailed description [23]. Functionality of many driving mechanisms is well depicted by Ashraf et al. [63] and Wang and Fu [17] give a summary of recent developments. Ogden et al. [91] present a comparison of energy density as well as achievable flow rate and backpressure for selected driving mechanisms. Micropumps based on electroactive polymers are described in the review of Bar-Cohen and Anderson [86] as well as the one of Annabestani et al. [85]. Yunas et al. [96] describe electromagnetic polymer actuators for biomedical applications.

5. Micropump research for drug dosing application

Despite specific challenges, the obvious possibility of improvement has prompted research towards reliable micropumps for drug dosing. Researchers have developed improvements suited for each specific pump type to fulfil all requirements. Fig. 2 summarizes outstanding improvements that are described in more detail in the following chapter. We present selected micropumps for the common actuation technologies. The selection depends on flow characteristics and medical eligibility, as well as distinctive measures to meet the challenges described above (see chapter 2).

5.1. Diaphragm pumps

A significant amount of research addresses micro diaphragm pumps due to their various advantages, such as miniaturization and cost-efficient production. However, the tough application within drug dosing devices demands for optimized pumps.

Diaphragm pumps are especially susceptible to bubbles and bubble tolerance strongly depends on their compression ratio ε [28,164]. This ratio indicates how much volume is displaced compared to the dead volume of the pump, though its exact definition differs slightly among different publications. We calculate it as the ratio of displaced volume ΔV to dead volume V_0 (formula 1) and convert information of cited studies to this metric.

$$\varepsilon = \Delta V / V_0 \tag{1}$$

ε - compression ratio
ΔV - displaced volume
V_0 - dead volume

Worst case is a bubble filling the entire pump chamber. In this case, the compression ratio has to be large enough to compress the air further than the total backpressure Δp to transport the bubble through the chamber [28]. Capillary forces of an air-liquid interface also add to the total backpressure.

There are many approaches to increase bubble tolerance. Pečar et al. [61] show that small amounts of surfactant added to the pumped medium causes bubbles to disperse in fine foam and limits their adhesion to the wall. This approach is especially useful, where a high compression ratio or the use of tight check valves is not feasible, for instance applications with living cells [61].

A fitted surface characteristic of wetted areas also increases bubble tolerance. Wang et al. [102] show that super-hydrophilic treatment lowers the adhesion of air in the chamber. The authors compare a hydrophilic coating with silicon dioxide (contact angle of 5°) with a hydrophobic coating with silane composite (contact angle of 155°). The super hydrophilic surface increases the bubble flow capacity and reduces bubble blocking in the check valve [102].

Even though pump valves are not a focus of this review, it is important to mention that they have a large impact on the pump's performance. They determine leakage, affect bubble tolerance, and alter medium-pump interactions. While flap valves minimize leakage and increase forward flow, they are sensitive to particles [164]. Diffuser nozzle valves are less susceptible to particles. However, bubble tolerance of this valve type is limited. As the bubble enters the inlet, the actuator's movement has a tendency to push it back and forth instead of transporting it through the pump, since its dynamic viscosity is a factor of 50 times smaller than the one of water in the outlet. The situation is similar for passive flap valves with large initial and remaining gaps that cause leakage and can trap a bubble within the inlet or outlet valve. Nevertheless, there are examples of bubble tolerant pumps that employ diffuser nozzle valves [165]. The influence of flap valves on bubble tolerance is also investigated. For instance, Chen et al. [166] show that a higher valve opening increases the probability of a bubble to pass the valve. They experimented with bubbles of 0.2 mL, 0.4 mL, and 0.6 mL [166].

5.1.1. Piezoelectric actuation

Due to their high actuation forces, high possible frequencies, and low power consumption, piezoelectric actuators are frequently used in MEMS applications [70]. However, sufficient elongation is often only possible with high voltage actuation, which requires more complex driving electronics. Therefore, research advances towards lower voltage levels while maintaining sufficient flow rates.

Liu et al. [34] present a micropump for insulin therapy that consists of four serial, phase-shift actuated, piezoelectrically driven chambers with flap valves. With this specific setup, the pump achieves a flow rate of more than 3 mL/min and backpressure of 22 kPa while keeping the actuation voltage at 36 V_{pp} [34]. With a diameter of 15 mm and a height of 8 mm, the four-pump package stays small. In their study, the authors prove the possibility of insulin dosing in short term animal trials [34].

Cazorla et al. [97] use thin film piezoelectric ceramics of only 1.5 μm thickness as actuators and therewith lower the driving voltage to 24 V. However, the achieved fluidic performance is strongly decreased, with a maximal flow rate of 3.5 μL/min compared to 200 μL/min for a 200 V_{pp} piezoelectric actuator in a similar setup [97,107].

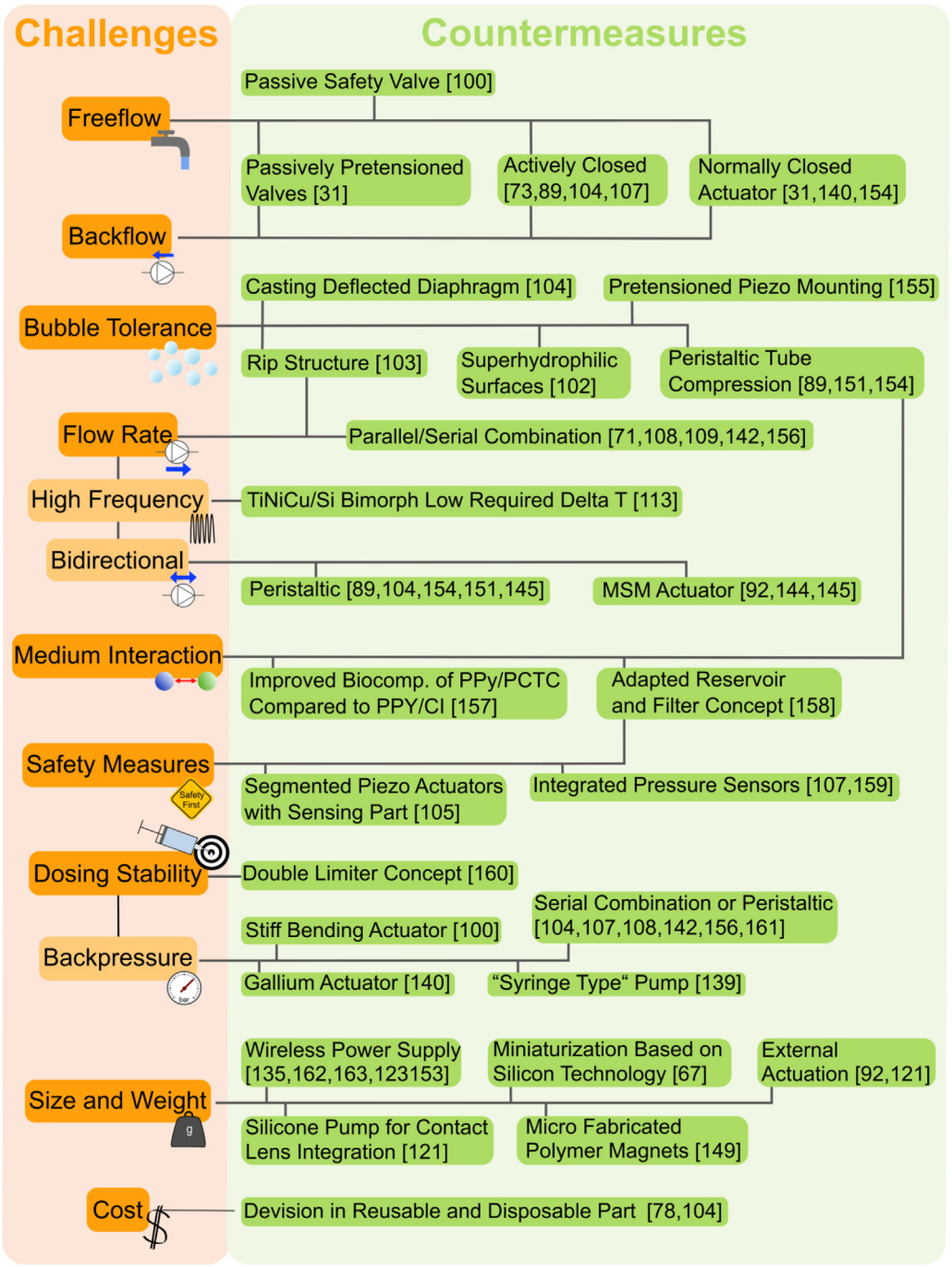

Fig. 2. Overview of technical improvements with respect to challenges in drug delivery. Depicted on the left (orange) are the specific challenges for microdosing in medical applications as summarised in Table 1. On the right (green) we present possible countermeasures to overcome these challenges and meet specific requirements that are described in this review. The selected examples are presented by or implemented in Pankhurst & Abdollahi [30]; Maillefer et al. [31]; Zhang et al. [71]; Pečar et al. [73]; Forouzandeh et al. [89]; Ullakko et al. [92]; Richter et al. [100]; Trenkle et al. [104]; Fuchs et al. [107]; Johnson & Borkholder [140]; the iPRECIO pumps [154]; Herz et al. [155]; Ma et al. [103]; Wang et al. [102]; Vinayakumar et al. [151]; Grünerbel et al. [108]; Huang et al. [156]; Peng et al. [109]; Yang and Liao [142]; Zhang et al. [113]; Smith et al. [145]; Barker et al. [144]; Yan et al. [157]; the Jewel Pump [158]; Zhang et al. [105]; Chappel et al. [159]; Chappel et al. [160]; Hiraoka et al. [139]; Geipel et al. [161]; Yan et al. [135]; Liu et al. [162]; Chee et al. [163]; Cobo et al. [152]; Khalil et al. [153]; Wang and Park [121]; and Waldschik et al. [149]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Multilayer actuators can also be used to lower the actuation voltage, though there are few examples of multilayer diaphragm pumps. A possible reason is the high effort and cost necessary to produce thin, flat multilayer actuators. Nevertheless, Lemke et al. [98] use multilayer actuation to lower the voltage needed to drive an earlier published piezoelectric pump with three actuators [167]. It delivers 4.4 mL/min with only -15/+45 V actuation [98].

Another crucial pump feature is the prevention of freeflow caused by an overpressure at the inlet. Richter et al. [100] implement a freeflow stop realized as a flexible membrane covering the pump's outlet. The other side of the so-called safety valve is connected to the fluidic inlet. If the inlet pressure is higher than the outlet pressure, the membrane blocks the outlet [168]. An outstanding asset of this valve is its flat shape and placement right under the pump chip, enabling an overall system with the same

footprint (7×7 mm^2) and negligible additional system height. This passive component prevents freeflow even in turned-off state.

Freeflow is often less problematic with peristaltic pump systems, as the fluid path can be actively blocked. For peristaltic pumping with less complex actuation and simpler electronics than for several actuators, Pečar et al. [73] introduce a peristaltic pump with one single piezoelectric actuator. The pump's outlet is connected via a small channel to the polydimethylsiloxane (PDMS) chamber. Actuation of the ceramic compresses the chamber and the outlet channel with a defined phase lag, which leads to directed flow [73]. The four manufactured prototypes (23×23 mm^2) show water flow rates up to 0.24 mL/min and a backpressure capability of 36 kPa with actuation voltages up to 230 V [73]. The authors prove bubble tolerance by introducing up to 45 μL large bubbles. The pumps' backpressure capability with air is limited to 8 kPa, which implies that bubbles are more problematic at high backpressure. A further improved version delivers up to 2.4 mL/min with a blocking pressure of 45 kPa [101].

Bubble tolerance, being challenging for diaphragm pumps in general (see chapter 5.1), is specifically tough for piezoelectric actuation. These actuators typically exhibit low stroke heights. Additionally, actuation towards negative fields is limited [169], thus the largest proportion of movement is downwards. Hence, it is difficult to reach an optimal compression. Insufficient bubble tolerance is a key reason for a slow industrialization [102].

Ma et al. [103] describe a high flow piezoelectric diaphragm pump and introduce a rib structure on the chamber bottom to improve bubble tolerance. The rib structure confines the flow in the centre of the pump, which is the shortest path, and therefore increases pumping efficiency and maximal flow [103]. Occurring bubbles are confined in the ribs and do not get caught in the chamber permanently, resulting in enhanced bubble tolerance. However, these results are not verified for backpressure.

Herz et al. [155] use a specific mounting process for their piezo ceramic actuator, the pretension technique: During the adhesion process, the ceramic is exposed to a defined electric field. Hence, bonding takes place while the ceramic is contracted. After curing, the voltage is removed and the actuator expands and bulges out the pump chamber [155]. This specific mounting enables pump designs with very high compression ratio and therefore leads to self-priming and bubble tolerant pumps. Richter et al. [100] introduce a $7 \times 7 \times 1$ mm^3 small silicon pump. It achieves an air backpressure of 90 kPa and is therefore capable of transporting bubbles even against backpressure. The latest version of their pump is a $3.5 \times 3.5 \times 0.6$ mm^3 pump that is capable of transporting air against backpressure close to 40 kPa making bubble tolerance likely even at backpressure conditions [67]. However, no water measurements of the device are available yet.

Trenkle et al. [104] form the pump chamber by casting the deflected membrane, minimizing dead volume and increasing the compression ratio. Unfortunately, no information on air backpressure capacity is available. This three-chamber peristaltic pump based on piezoelectric stack actuation possesses a disposable pump chamber and a reusable actuation unit. The device is comparatively large (several centimetres) and shows stable dosing up to 40 kPa and extrapolated zero flow at 180 kPa. Thus, it offers a solution for applications with varying high backpressures, though offering enough space.

The interaction between transported media and pump is another crucial micropump characteristic, however, little information is available. Gas-liquid interfaces, which increase protein degradation, can be caused by cavitation that can occur in piezoelectric pumps due to the actuator's fast response and high force. Jenke et al. [65] show that cavitation strongly depends on the actuation signal. To prevent denaturation, it might therefore be advantageous to adapt the actuation signal, e.g., to smaller frequencies or sine actuation. Additionally, the changed shear forces of an adapted actuation might influence interaction. However, so far no studies discuss this topic. In fact, only few studies on micropumps use solutions other than water. In a recent study, Cheng et al. [170] describe a lymphatic drainage system based on a piezoelectric pump and are able to pump 5 % albumin for 10 min (overall approx. 1800 μL) without degradation.

Safety measures to detect such degradation are required in high risk applications such as drug dosing. In their double actuator pump, Zhang et al. [105] use piezoelectric disc actuators with segmented electrodes allowing for self-sensing. The voltage signal represents the diaphragm displacement precisely and allows to deduce the flow rate. Even though further error detections should be possible, the authors do not give information on the detectability of different failure mechanisms such as air in the chamber or backpressure.

A diaphragm pump's flow often depends on the applied backpressure. Many authors describe a linear decrease in flow with increasing pressure applied at the pump's outlet [72,97,100,171]. This pressure-flow-relation is an important system parameter, since the backpressure is not constant. It is beneficial to avoid large deviations of the flow rate caused by pressure changes even without closed loop control and a high backpressure capability is necessary to overcome obstructions such as injection site occlusion.

Richter et al. [100] reduce the pressure dependence of their micropump's flow rate with an extremely stiff bending actuator. The maximal flow rate of 25.8 μL/min only decreases by 0.1 % per kPa backpressure. Linear extrapolation of the flow decrease measured up to 150 kPa indicates a maximal backpressure of 600 kPa.

Geipel et al. [161] implement piezoelectric valves and a three-phase actuation principle to achieve backpressure independent flow up to 20 kPa. An improved design with an adjustable stroke volume of 10 nL to 50 nL and a size of $45 \times 30 \times 25$ mm^3 achieves flow rates of up to 50 μL/min [99]. The pump is self-priming and bubble tolerant, however no verification under backpressure conditions was executed.

Pressure independent dosing is also achieved by Fuchs et al. [107] with a three-actuator peristaltic pump. The 30×11 mm^2 silicon pump achieves nearly stable flow rates up to 40 kPa. Due to its symmetric setup, this pump can be used bidirectionally.

A serial combination of several pumps also increases the backpressure performance. The combination of two steel micropumps is investigated by Grünerbel et al. [108] in serial and parallel setup. A serial combination does not increase the flow rate significantly compared to a single pump, however, only a small decrease in flow is detected when applying 20 kPa backpressure. Huang et al. [156] implement a serial combination of two piezoelectric metal micropumps on one pump body and therefore increase the output pressure by 80 % compared to a single pump.

Considered combination of several pumps does not only increase the backpressure capability but can achieve high maximal flow rates additionally. Within their serial-parallel hybrid combination of five actuators, Zhang et al. [71] investigate the influence of phase shifted actuation. With an optimized actuation signal the authors achieve 300 mL/min water flow, which is roughly twice the flow of a single chamber, as well as 10.8 kPa backpressure, equal to more than three times the pressure of a comparable single chamber. A device achieving extremely high flow rates up to 1845 mL/min and a backpressure capability of 44 kPa is introduced by Peng et al. [109]. The authors connect two pump bodies with two serial chambers each in parallel.

Concerning reliability and lifetime evaluations of micro diaphragm pumps, there is little information available in literature. Doll et al. [110] describe an increase of reliability of their three actuator pump described above [99,161] by adding a forth actuator. The pump chamber is not only actuated with one diaphragm as in

the original pump, but an additional actuator forms the chamber bottom. This approach enables a maximal flow of 4.2 mL/min at lower driving frequencies (35 Hz). Not only are less actuator cycles needed to transport the same volume, which prolongs the lifetime at a given mean number of cycles to failure, but also a redundancy is created: If one of the chamber actuators fails, the pump suffers a loss in fluidic performance but does not stop working completely.

5.1.2. Shape memory actuation

Shape memory actuation offers high displacement as well as low operating voltages. However, operating frequencies and the control of the exact deformation are limited and required heating power is high [70].

Pump actuation requires comparatively low voltages of 0.6–3.5 V [74]. The most common SMA for micropump actuation is nitinol. However, using this one-way effect material, pumps are complex to produce due to the necessary restoring force. If cooling is passive, operating frequencies are low and limit achievable flow rates [70]. For example, Makino et al. [111]. introduce a pump actuated with one-way SMA and a bias pressure of 100 kPa. The $10 \times 20 \times 1.4$ mm^3 pump achieves a flow rate of 4.8 μL/min. The authors report a decrease in diaphragm deflection during long term use depending on the bias force: at 200 kPa bias pressure, a strong deflection loss is observed, while at 100 kPa bias pressure and efficient cooling, the displacement reduces only by 2 μm from 95 μm to 93 μm after 2000 cycles [111].

Higher lifetime is observed for thin-film actuated pumps, as shown by Xu et al. [112]. With resistance measurements, the authors show that the SMA actuator of the $6 \times 6 \times 1.5$ mm^3 device does only undergo partial phase change. This limits the deflection, but prevents fatigue and enables more than 4×10^7 cycles. The pump is made of silicon, which results in efficient cooling due to the good heat conduction of the material. Hence, driving frequencies up to 100 Hz are possible.

A long lifetime of more than 2×10^6 cycles is also achieved by Zhang et al. [113]. The pump is actuated by a TiNiCu/Si bimorph, which demands a lower temperature difference of 9 K. Hence, higher actuation frequencies can be used leading to a flexible flow rate of up to 235 μL with actuation from 0 to 80 Hz.

5.1.3. Electromagnetic actuation

Electromagnetic actuation allows for energy efficient dosing units [78,79]. Devices in research evolved over time: Whilst early conventional electromagnetic actuators relied on a bulky magnet, the trend went to using magnet matrices and nowadays embedding magnetic particles into flexible polymers, e.g., magnetic polymer composites [96]. In addition to the lower production cost and design flexibility, polymers offer adjusted mechanical properties such as flexibility and high surface strength [96]. In general, the variety of usable materials makes biocompatibility unproblematic. Used materials are for example plastics like PDMS and poly(methyl methacrylate) (PMMA) [78,115–117].

Different implementations of the electromagnetic actuation principle generate maximal water flow rates of around 50 μL/min without backpressure [78,116], whereas others achieve up to 500 μL/min [115,117]. The maximum presented flowrate for this technology is found to be 1.6 mL/min for a polymer based electromagnet composite micropump [79]. It achieves a backpressure of 362 Pa [79]. A high dosing resolution is presented by Said et al. [119], who discuss a micropump capable of nano-dosed injections, which is shown by optical measurement of the fluid movement in a capillary. In addition to standard configuration with active, passive, or diffuser nozzle valves, there are also variants, where two diaphragms oscillate in a phase shifted manner and hence lead to forward flow [78]. Due to this two-actuator setup, Rusli et al. [78] build a bidirectional pump enabling high dosing flexibility. It achieves a bidirectional flowrate of 66 μL/min.

As described in chapter 2.2, dosing stability is important, even when bubbles enter the chamber. Yamataha et al. [115] prove that electromagnetic actuation allows bubble tolerance in a micropump. The large deflection achieved by the combination of a silicone elastomer as membrane and long-range magnetic actuation assures a sufficient compression ratio. However, the authors do not show a backpressure limit for bubble tolerance and the use of diffuser nozzle valves gives rise to the question of bubble resistance of the device.

In addition, backpressure can affect dosing stability. The investigated studies present blocking pressures of around 1 kPa [78], 1.3 kPa [115], or below 0.5 kPa [117]. A reason for comparably low backpressure capability is the use of diffuser nozzle structures. Consequently, all introduced pumps presumably show high backflow rates. Low leakage is shown by Ni et al. [122] with their planar pump incooperating flap valves. However, the pump only reaches 550 Pa of backpressure.

Electromagnetic actuation requires lower voltage than piezoelectric actuation, but higher currents. The range of power consumption spans from 48 mW for 66 μL/min [78] to around 700 mW for 500 μL/min [117] and therefore lies in the same order of magnitude than piezoelectric pumps. An outstanding energy efficient micropump is presented by Shen and Liu [79]. Their electromagnetic polymer composite pump consumes only 33 mW (30 V with 7 Hz) for a flow rate of 1.6 mL/min [79], which corresponds to 1.2 kJ/L.

Several research teams address the medical disposable market, which demands low cost, and often small device size is preferred. The smallest pump has a diameter of only 6 mm for the pump chamber plus small diffuser and fluid ports [117]. The micropump is polymer-based and therefore of low cost; similar applies for Rusli et al. [78]. In addition, Rusli et al. [78] use separable modules to enable reuse of the electronic part while preventing contamination. Further disposable applications of interest are organ-on-chips. Mi et al. [118] show improved cell growth and functionality when using an electromagnetic micropump to establish a dynamic co-culture. Experiments were conducted for up to 72 h and no pump degradation caused by the culture medium was reported [118].

Wang et al. [172] propose a micropump that combines a PDMS membrane with a magnetic nanoparticle-PDMS composite. They address the treatment of age-related macular degeneration, diabetic retinopathy, and other eye pathologies characterized by ocular neoangiogenesis. Actuation of the $5 \times 7 \times 3$ mm^3 implantable pump is external with magnetic fields that are harmless for humans (< 500 mT). A check valve prevents uncontrolled drug diffusion in turned off state. In animal trials in the macular area of a rabbit's eye, the authors show precise drug delivery *in vivo* and *in vitro* with dosed packages down to 20 nl. The amount can be adapted at any time by the external actuation. Further development of the pump fits into a contact lens (Fig. 3), due to a reduction of the thickness to less than 500 μm [121]. Since the pump is not self-priming, it needs to be filled free of bubbles. The actuation remains external, hence a battery is dispensable. A great advantage over conventional drug delivery methods such as eye drop instilling are less pre-corneal loss factors (e.g., tearing and blinking) leading to an extended drug residence time (over 30 min compared to 1–3 min) and high bioavailability (>50 % compared to 13 %). According to Wang and Park [121], the proposed micropump has a great potential not only to be embedded into contact lenses but also in periocular implants for therapy of various eye disease.

Tandon et al. [120] combine several electromagnets (outer diameter: 7.6 mm) on a polyimide fluidic structure to achieve a bidirectional pump for drug delivery inside the ear. With the number of actuators, the complexity and power consumption increases,

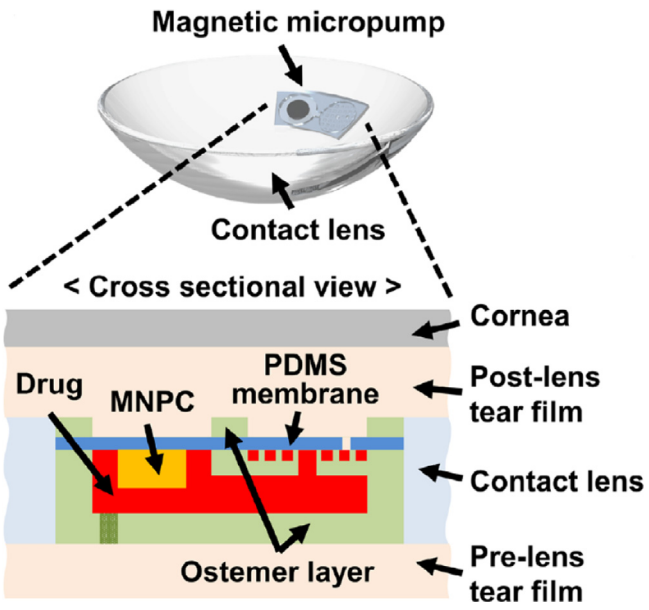

Fig. 3. Proposed micropump integrated into a contact lens for direct drug delivery; Figure modified from [121].

but also the design flexibility that even enables the precise dosage of different fluids (e.g., drug or water) [120]. Compared to a previous version [173], the authors integrated fluidic connections into one system and fabricated a robust device. Low leakage rates are achieved with normally closed valves that are held by springs. At 20.7 kPa the inlet valve shows no leakage, whereas the outlet valve shows 262 μL/day. The system achieves a blocking pressure of 40 kPa, which the authors estimate largely sufficient for in-ear applications. The single stroke volume is 1.1 ± 0.2 μL (n = 171). Hence, precise control and avoidance of unnecessary high drug doses is possible. The system was already tested as head mount devices on guinea pigs [173]. To enable battery driven devices, the authors implement several measures to reduce power consumption, e.g., the reduction of time the normally closed valves are open.

5.1.4. Electrostatic actuation

Electrostatic actuation enables cost efficient production, e.g., based on standard MEMS processes. Contrary to other actuations mechanisms that limit miniaturization, electrostatic actuators can be further reduced in size. Energy efficiency is high with power consumption of few mW [123]. A disadvantage is that the diaphragm can only be actively moved in one direction [80].

There are only few examples of experimentally characterised electrostatic pumps, since most research work focusses on analytical and numerical descriptions [174–177]. The first electrostatic micropump was realized by Zengerle et al. [80] in 1992. Further improvements lead to a bidirectional silicon pump presented in 1995 [123]. It achieves a flow rate of 800 μL/min at around 700 Hz and ± 200 V as well as a backpressure of 31 kPa. Due to a low compression ratio, the pump is neither self-priming nor bubble-tolerant.

Lee et al. [124] present a four electrode electrostatic micropump and experimentally evaluate the influence of different actuation signals. The pump chamber of the device is 5 × 32 mm^2 large and 15 μm high. Though, the device is designed for air transport and actuation bases on an active push and passive pull of the medium, meaning that the electric field is applied between the chamber bottom and the actuation diaphragm. Therefore, it is not suitable for conducting medium. For drug dosing it is necessary to use electrostatic actuation with active pull and passive push without electric connection to the pumped medium.

To be able to actuate their peristaltic pump without electric connection to the pumped fluid, Xie et al. [125] use a micro machined multilayer parylene setup. The actuation chamber is filled with air and the diaphragms can actively pull medium into the three pump chambers. The pump is capable of extremely small flow rates of up to 1.7 nL/min [125].

In 2018, a new micropump concept was presented by Uhlig et al. [81]. The flow as well as actuation of the modular device is in-plane. However, actuation is direct and only non-conductive media can be transported. No experimental results are available yet, but the authors expect higher stroke and backpressure capability (130 kPa for air and 210 kPa for isopropanol) based on their new design. The in-plane concept allows easy fabrication of several pumps parallel or in series [81].

The current state of the art electrostatic micropumps are either not bubble tolerant or the driving concept is not suitable for drug dosing applications. Additionally, little information on pressure capability is available. For pumps that do not build an electric field over the pumped medium and therefore exhibit a passive pump stroke, dosing stability against a backpressure is limited.

5.1.5. Electroactive polymer actuation

The advantages and disadvantages of electroactive polymers (EAPs) strongly depend on the physical principle of actuation. Dielectric EAPs possess high mechanical energy density and operate in air, but require high electric activation fields (>10 V/μm). Ionic EAPs typically require less than 10 V actuation voltage, but have slower response times and require a wet electrolyte.

One of the most commonly used iEAP for pumping devices are ionic polymer-metal composites. IPMCs show many merits such as high energy efficiency, large mechanical deformation, low actuation voltage, and biocompatibility providing promising features for medical and disposable applications [130]. Drawbacks include displacement hysteresis, membrane dehydration in lack of water, or hydrolysis due to ion movement [130].

Multiple implementations of ionic EAP micropumps using a disc or petal shaped actuator have been published, e.g., Wei and Guo [129] (200 μL/min, 2 Hz, 5 V), Pak et al. [126] (10 μL/min, 0.5 Hz, 10 V), Nguyen et al. [128] (760 μL/min, 3 Hz, 3 V), and Wang and Sagino [131] (1611 μL/min, 1 Hz, 3 V).

Backpressure pumping capability is seldom included in the published data, and only little pressure is achieved where it was examined (1.5 kPa [128] or 0.7 kPa [131]). This is probably due to the soft actuator material.

Long term stability is problematic for iEAP actuation, since electrolysis is a known problem that prompts a performance decrease [131]. Nguyen et al. [128] mention electrolysis of the active polymer in their EAP pump, leading to a sudden degradation after five minutes operating time. IPMC pumps also show unstable pumping performance over longer periods. McDaid et al. [178] claim to solve the problem by applying a novel online tuning method called iterative feedback tuning (IFT).

Another type of iEAP pumps are based on conjugated polymers. Fang and Tan [132] propose a petal shaped CP actuator in a PDMS based setup. During assembly, the CP is sandwiched between two annular copper tapes that work as electrodes. The system can reach 1.3 mL/min at 4 V actuation and 0.5 Hz.

In general, biocompatibility of used materials is high. According to a short review by Kaneto et al. [134], PPy does not show any negative impact in an implantation study. During a 3 months study in a rat model, no blood clotting or other obstruction were detected, hence indicating blood- and biocompatibility [134]. Also, only little difference in coagulation between heparinized and unheparinized PPy samples could be observed. Yan et al. [157] could find better biocompatibility of a PPy matrix and a macromolecular dopant of polycaprolactone-block-polytetrahydrofuran-

block-polycaprolactone (PPy/PCTC) compared to a PPy matrix with chlorine dopant (PPy/Cl^-), which is already considered biocompatible.

Dielectric polymer micropumps use electrostatic effects for actuation. Already in 1998, dielectric EAPs could achieve five to twenty times higher effective actuation pressures than conventional air gap electrostatic actuators [179]. Further advantages are very fast response times, high energy densities, and charge keeping without power loss.

An implementation of a dielectric EAP pump is described by Xu and Su [82] in 2005. The characterization addresses only diaphragm deflection and shows a maximum of 21 μm at 106 V/μm and 10 Hz driving. The achievable flowrate is estimated as 550 μL/min at 80 V/μm and 1 kHz driving [82].

As for EAPs in general, biocompatibility of dielectric polymers is unproblematic. Most pumps are made of PDMS or similar materials and biocompatibility is proven in animal trials [135]. Because of material properties and the use of mostly liquid electrolytes, hermetic sealing remains an issue [126].

The sizes of presented micropumps can get very small as shown by a bimorph actuator of only 2.2 × 2.2 mm^2 for a dielectric EAP micropump [136]. The pump by Xia et al. [136] uses a diffuser nozzle structure in combination with the electrostrictive polymer (poly(vinylidene fluoride-trifluoroethylene)) that has a large electrostrictive strain of approximately 5–7 % and a high elastic energy density of 1 J/cm^3. The device pumps methanol with 25 μL/min at 63 Hz and achieves a backpressure of 350 Pa. The main issue is a very high driving voltage of around 1.8 kV. Additionally, the small pressure capability can be inconvenient. In general, the small size and use of soft materials make it difficult to achieve high blocking pressures and most pumps remain in the hundreds of Pa to low kPa range [127,131,136].

The technologies' ability to pump high viscosity fluids such as drugs is experimentally shown with oil (400 times as viscous as water) [133]. Loverich et al. [127] also assume their pump capable of transporting high viscous media, however do not prove it experimentally.

An especially important parameter for EAP actuators is their lifetime, since corrosion may occur due to electrolyte leakage or dielectric breakdown at very high actuation fields depending on the technology. Researchers state stable operation over more than 1 × 10^5 bending cycles [126], for 2 h of operation [127], 10 h of operation [127], or even more than 6 months of continuous operation with around 6 × 10^6 strokes [137]. Another important aspect of micropump lifetime is the interaction with the pumped fluid. One group of researchers states the theoretic possibility of pumping cells harmlessly due to geometrical dimensions, but ignoring stress and strain, or accumulation caused by fluid turbulences [127]. The functionality of a drug after pumping is validated by Kwon et al. [137] using Adriamycin that is used in breast cancer therapy.

As with most materials, permanent or temporary sticking of movable structures is an important issue also for polymers, especially with regard to very small geometries, such as valves and valve seats. The effect is enhanced if small perturbations of the flap destabilize it leading to a collapse onto the valve seat and possible long-term adhesion [127]. Research to prevent sticking is ongoing.

The possible thermodynamic efficiency seems high due to high energy densities. It is proven with a value of 0.96 % [127] compared to a maximum efficiency for reciprocating displacement micropumps reported in Laser's and Santiago's review of 0.39 % [23]. Hence, some researchers focus on low power applications especially for wearable medical devices or implants. Power consumption lower than 2 mW was already proven in animal trials [135]. Kwon et al. [137] present a lab-on-chip solution for long term trials to operate over 20 months with a 1.5 V AA battery (4350 mW h), demanding for very low system power consumption. The authors do not report any degradation of the system.

One research group has reported about successful animal trials of their micropumps with diabetic mice, but still admit a long way towards a commercial product [135]. The company EAMEX [180] is the only known commercial manufacturer of EAP pumps right now.

A very recent dielectric EAP is published by Zhu et al. [181]. They apply a semi-rigid ring-shaped electrode to a dielectric EAP membrane. An analytical expression for membrane deflection of the buckling actuator as well as experimental results are given. Reducing the membrane stiffness is achieved by adjusted electrode layout (ring shaped) and implementation with softer electrode materials. The design is still in ongoing research, so that no pump characteristic is presented [181].

5.1.6. Phase change actuation

Pumps based on phase change actuation can achieve low but precise flow rates and are capable of a high-pressure build-up. The largest disadvantage of this actuation principle is its high energy consumption due to heating. There is no information available, if the induced heat impacts the dosed medication.

A four chamber peristaltic pump by Johnson and Borkholer [140] achieves flow between 18 nL/min and 104 nL/min, while remaining in a blocked state when the pump is not actuated, since gallium is used as phase change material. The pump was tested for 26 × 10^6 cycles. Thah [140] reports 1.25 years of use with an average flow of 100 nL/min. No sign of degradation was visible [140]. In contrast, Bodén et al. [88] record aging effects already after one hour of pumping caused by paraffin leakage under the membrane within their pump system.

An advantage of gallium is its comparatively high stiffness that achieves an expansion pressure of more than 10 times the expansion pressure of paraffin. The authors estimate a theoretical backpressure capability of up to 480 MPa [140], however, the pump needs to withstand this pressure. Similar accounts for paraffin actuation: Svensson et al. [90] describe a pump dosing independent of pressure up to 1300 kPa. The maximal pressure the actuator can achieve is usually not evaluated experimentally, since other parts of the pump and periphery cannot withstand such high strain.

Forouzandeh et al. [89] introduce an implantable system for drug delivery into inner ears of mice. Three paraffin actuators compress a commercial catheter, creating peristaltic fluid motion. No sharp moving parts such as flap valves are necessary and the dosed drug is only in contact with the biocompatible inner surface of the tubing. This setup limits contamination, leakage as well as dead volume and reduces clogging and bubble generation. It also eliminates the need for fluidic connectors. Actuated with a temperature difference of 10 K, the pump proves strong dosing accuracy with a resolution of 2.4 nL/min (average flow rate of 50.2 nL/min) and dosing stability with a flow rate that is not affected by ±3 °C and 10x greater than physiological backpressure (5 kPa). The simple structure of the pump allows upscaling for the use in larger animals, children or adults.

Liu et al. [162] introduce a pump based on paraffin wax/expanded graphite/nickel particle composite. The heat needed for actuation is supplied via induction. The authors therefore address a pressing problem of phase change systems: their high energy consumption. Induction makes it possible to place energy supplies outside of the pump system and therefore limit the system size. However, the authors do not give information about the dependence of flow properties on the distance between the induction coils.

5.1.7. Thermopneumatic actuation

Similar to phase change actuation, thermopneumatic pumps can deliver extremely small flow rates. In 2016, Hamid et al. [141] intro-

duced a pump that achieves flow between 0.77 nL/min and 12.5 nL/min. This range is suitable for example in animal trials on small lab animals. Driving temperatures are between 33 °C and 63 °C. The authors do not state the overall size of the pump, but the actuator diaphragm has a diameter of 2 mm.

The high energy consumption of thermopneumatic actuation can pose problems for implantable applications. Therefore, Chee et al. [163] develop a wireless energy transfer by magnetic induction to the heater. Their pump delivers single strokes of 4 μL ± 2.8 %. However, the device has not been tested for continuous delivery.

As for any type of actuation, the combination of several pump chambers and actuators in one device can increase the performance. Yang and Liao [142] describe experiments on pumps with 3, 5, or 7 serial chambers. The system is extremely small with only $16 \times 18 \times 5.5\ mm^3$ for the three-chamber pump including the driving electronics. While the maximal flow stays nearly constant, the achieved backpressure increases by 25 %.

There is no research on the impact on dosed medication of this pumps. Nevertheless, an impact of the elevated temperature is possible for some formulations.

5.2. Peristaltic magnetic shape memory actuation

Other than standard diaphragm pumps, magnetic shape memory pumps do not require valves and enable bidirectional operation due to the peristaltic motion of the actuator [92,145]. Since the actuation is not temperature based as it is the case with SMA material, high frequencies are possible. The actuators are capable of high forces, leading to high achievable pressure, however require high magnetic fields of several hundred mT [92,143,145].

A large advantage is the possibility of contact free actuation that Ullakko et al. [92] utilize to develop a disposable MSM pump for forensic DNA profiling. The pump's actuator is a Ni-MN-Ga single crystal that is driven with a cylindrical iron–boron–neodymium magnet. One single cycle transports 260 nl. The maximal flow of 4.2 μL/s is achieved with the help of a drill at 1000 rpm [92]. The authors show that the pump does not influence polymerase chain reactions (PCR) with genomic DNA. Smith et al. [145] further improved and evaluated the device in detail. With an actuation frequency of 240 Hz, the pump transports more than 1500 μL/min of water and nearly 800 μL/min of a 60 % wt. glycerol solution. This shows a large influence of the medium's viscosity, put proves the capacity of the pump to transport viscous liquids. Additionally, the pumps is able to transport air, making it self-priming and bubble tolerant. The pump still works against 150 kPa pressure and closes the fluid path up to 200 kPa when used as a valve [145]. The authors assume the limitations in pressure to be due to sealing problems, since the theoretical blocking pressure of the actuator is 2 MPa. In 2018, Saren et al. [143] investigated an optimized design of the pump and show stable dosing up to 150 kPa and a maximal backpressure capacity of 0.45 MPa (with additional clamping up to 1 MPa). The variability of individual dosing measurements is low, with the highest variation of 0.88 % at 50 Hz actuation.

Based on the results of Ullakko et al. [92] and Smith et al. [145], Barker et al. [144] use MSM actuation to develop a pump for electrophysiological experiments, since common micro syringe pumps are too large to be used in *in vivo* experiments with freely moving animals. First animal trials with Ketamine and Tetrodotoxin prove the feasibility and the pump shows to be able to overcome the physiologic pressure (up to 1.3 kPa [182]) as well as flow resistance of the brain tissue.

5.3. Rotary pumps

Pumps based on the turning motion of one or several parts enable robust dosing and continuous flow often with the possibility for step-less flow rate adjustment. A valveless configuration is usually possible due to a strong fluid guidance with little leakage or backflow. A large challenge in the field of rotary pumps is the development of highly precise, cost efficient production processes that allow for strong miniaturization. Current rotary pumps are large compared to diaphragm pumps. Nevertheless, improved manufacturing methods make further miniaturization imaginable.

5.3.1. Microgear pumps

Microgear technology allows for very high precision drug dosing due to solid and stable actuators. Just as macroscopic ones, microgears gear into each other, and thereby only allow fluid transport during operation. In theory, the systems can be designed with very low leakage and freeflow stops. The main challenge is fabrication with the required low tolerances to further miniaturize those pumps. Many studies on microgear pumps and the manufacturing of microgears have been reported [53,146–148,183]. Generally, high manufacturing costs for microgears limit the possibilities of broad design studies of new micro gear pumps and impede their market entry.

Gietzelt et al. [53] report on powder injection molding of ceramic microparts for micro annular gear pumps as small as 550 μm in diameter and 500 μm in thickness. Compared to commonly used thermoplastics or silicone, ceramics possess higher wear resistance and breaking strength. Using LIGA (German acronym for lithography, electroplating and molding applications) mold inserts and surface finishing with a lapping machine, high geometrical and surface quality precision was realised. Though two sets of zirconia annular microgear pump components were manufactured, a functioning device was not assembled and tested for fluidic performance. To knowledge of the authors of this review, no subsequent work followed this study.

Waldschik et al. [149] present a microgear pump with internal electromagnetic drive, which holds the advantage of small size and omission of a driving shaft that needs sealing. The gears consist of polymer magnets with alternating axial magnetization manufactured using micro fabrication technologies, which holds many possibilities in shaping of components. Manufacturing and actuation of the microgear pump was found to be successful with a rotational speed of up to 1800 rpm. The tolerances of gear gaps and the gap to the housing is problematic, since tight gaps for low leakage create high friction. The gaps realized here lead to high deviation of the theoretical pump flow rate from the actual pump flow rate (480 μL/min to 150 μL/min at 150 rpm, respectively).

Iacovacci et al. [150] developed a bidirectional microgear pump that aims to work with very small drug delivery systems, especially for Insulin. They propose a complete system with sensors and Insulin reservoir and micropump. A rotary gear pump operates by moving the fluid one step further during each rotational step by rotating gears. Micromachining processes and low power motors require remaining gaps between component parts. The resulting slip between those component parts is a factor reducing achievable flow rates. It describes the amount of fluid that is not moved by the gears but stays steady or is under the influence of backflow. After experimental evaluation, the authors find Nylon 6 as best suiting material for their reservoir in terms of insulin stability. The fluidic output is found to be 9.31 ± 1.74 μl per 10 cycles (dosing time not given). The authors report an achieved dosing resolution of 1 μL [150]. A stepper motor drives the test system with a 3.7 V and 220 mA h battery. The authors also experimentally prove the ability to refill the 3 mL reservoir with Insulin within 20 min [150].

5.3.2. Single rotor pumps

Pankhurst and Abdollahi [30] present another type of rotary micropump. It is a positive displacement pump with only one mov-

Table 3
Summarizing all relevant and known industrial micropumps that are commercially available.

Company	Product	Pump Type	Application Area
Insulet Cooperation	Omni Pod	Piston pump	First insulin patch pump
Debiotech S.A.	Jewel Pump	Piezoelectric diaphragm	Insulin delivery, not yet on the market; in clinical trials
Primetech Cooperation	iPrecio Pump Family	Peristaltic-type mechanism with stepper motor	Used in animal trials for several drug studies
Sensile Medical AG	Sensile Medical Pump	rotary piston pump, actuated by micro DC motor	Treatment of Parkinson disease
Tricumed Medizintechnik GmbH	IP 2000 V IP 1000 V Siromedes	Mechanically pressurized reservoir with flow restriction	Implantable infusion pump for intrathecal spasticity or pain treatment

ing part and a spring design freeflow stop. The latter also acts as an adjustable overpressure stop, hence pumping stops if a certain critical pressure (here: 83 ± 14 kPa) is reached, e.g., due to occlusion. Special focus in the design is on low cost to enable disposable use, and high dosing accuracy. The pump size is 29.8 × 14.6 × 14.0 mm with the overall system being pen sized, hence resulting in a lightweight portable device. It is designed to be patient friendly, battery powered, and with the possibility of dosage programming by the physician. Achievable flowrates range from 0.8 μL/min to more than 2000 μL/min with a standard deviation of less than 0.2 μL/min. The authors also tested fluids with different viscosities from water to glycerol with 1000 cP and show solid pumping performance [30].

5.3.3. Rotary peristaltic

Micro rotary peristaltic pumps that transport fluid by squeezing of a tube enable dosing where only the tube is in contact with the medium. The lack of sharp edges or different materials in contact with the medium can prevent undesired interaction. Additionally, no fluidic connectors are needed, limiting the risk of leakage and failure while enabling simpler connection. Vinayakumar et al. [151] present a peristaltic pump with a diameter 24 mm and a height of approx. 40 mm that creates flow rates up to 275 μL/min. Its pressure capability is high with no change in flow up to 40 kPa and a blocking pressure of over 120 kPa. The authors report the viscosity dependence of the fluid transport and show an approximately 25 μL/min smaller flow rate for DiMethylAcetamide compared to water [151].

5.4. Other pump types

In addition to diaphragm pumps and rotary micropumps, other microfluidic systems were specifically developed to address requirements of medical application and show beneficial properties. Interesting examples are summarized here below.

5.4.1. Electro active polymer actuation

Yan et al. [135] proposed a pumping system consisting of a check valve and an ionic EAP squeezer. Their system can deliver 10 μL/min at 1 V and 0.017 Hz actuation. Although the pump is still too big to be implanted, insulin dosing was tested on mice over five consecutive days. The system power (< 2 mW) is provided wirelessly.

A peristaltic like implementation is provided by Naka et al. [133] using CP. Two actuator belts around a tube create a pumping effect when actuated at 180° phase shift. The pump can handle high-viscosity fluids, such as certain drugs, without backflow. The maximum flowrate is 80 μL/min with water and 45 μL/min with high-viscosity oil at 3 kPa, with a power consumption of approximately 33 mW [133].

Hiraoka et al. [139] present a miniaturized syringe type micropump. The underlying operation principle is stacking several CP actuators (PPy-TFSI) on top of each other. The micropump generates an extremely high blocking pressure of 30 MPa with less than 2 V actuation.

5.4.2. Electrolysis actuation

Cobo et al. [152] present an implantable micropump with electrolysis actuation. The authors chose this actuation for its low power consumption, large driving forces, low heat generation, and on-demand activation including the possibility of flow rate adjustment after implantation. The pump consists of a 281 μL drug reservoir that is squeezed by a bellow when electrolysis is started due to heating. 185 μL of volume can be displaced, causing a dead volume of 96 μL. It is therefore important to fill the reservoir without bubbles. The drug reservoir is refillable after implantation and for the aimed application, the dosage of electrostatically-coupled small interfering RNA gold nanorod drug into xenograft tumours of nude mice, a refill once per week is sufficient. The work improves a previous system [184] by enabling wireless energy supply for the required power of 1 mW and therefore removing the need for the animal to be restrained during dosing. The external energy supply and possibility of refill enable the 20 × 15 × 10 mm^3 device to be light enough for the use in mice. In former studies the authors showed no significant dependence of the flow rate on the viscosity of the medium up to 6 mPas as well as only a 10 % loss in flow at physiological backpressure of 2.7 kPa with 4 tested pumps [185]. In addition, the authors evaluate the error due to misalignment of the coils for power supply: a distance of 3.5 cm leads to a 64.1 % flowrate drop and an angle of 45° to a 42.8 % drop [185]. Such large deviations in flow can therefore be caused by mice movement and require further investigation and amelioration.

A similar system is developed by Moussi et al. [153,186]. The extremely small pump of only 3.9 × 2.1 × 2 mm^3 enables the transport of 4 ± 0.5 μL in 12 s. The system is based on 3D printing technology for the reservoir as well as microneedles, and mold casting for the Parylene C micro bellow membrane. The needed power of 25 mW is supplied wirelessly.

5.4.3. Electromagnetic actuation

For a piston pump like an electromagnetic micropump, a permanent magnet that is moved by two electromagnets in a tube can act as a plunger and move the fluid [114]. A one-way valve, e.g., a ball valve, is a sufficient flow rectification for this Teflon based setup by Liu et al. [114]. The authors claim that their pump is smaller, more reliable, and easier to fabricate compared to previously described electromagnetic diaphragm pump designs. The pump generates a maximum flowrate of 200 μL/min and little leakage [114].

6. Commercial dosing units

Some micropump technologies are already close to or on the market. pc10 We introduce some of the pump systems and how they meet requirements in medical application. Table 3 gives an overview of the described drug delivery systems, and their application.

6.1. OmniPod

ulin patch pump OmniPod, the Insulet Cooperation (Massachusetts, USA) developed the first insulin patch pump commercially available [4,187]. The system comprises a disposable infusion pump (pod) of roughly 4 × 6 × 1.8 cm^3 and a Diabetes Manager remote control. It works with U-100 rapid-acting insulin and supplies the patient with up to 200 U (Units of insulin) per pod in up to 72 h [4,187–189].

The piston pump's actuation bases on a nitinol shape memory alloy wire assembly [187,189]. Applying electric current to the wire creates heat caused by electric resistance and prompts a phase change contracting the wire. With one wire on each side, the SMA wires move a handle back and forth and a gear translates this side movement into a turning motion. This motion rotates a ratchet which advances a plunger in a reservoir [187]. The plunger pushes the insulin out of the reservoir through the insertion cannula. A single actuation step delivers 0.05 U (corresponding to a volume of 0.5 μL) and accuracy is given in the user's guide with ± 5 % for basal (≥ 0.05 U/h) and bolus (≥ 1.0 U, otherwise ± 0.05 U) delivery [188]. To control functionality, the system possesses sensors for rotational and linear movement [189].

The plunger pushing insulin out of the reservoir is crucial piece of the dosing unit. It is in direct contact with the drug and therefore needs to fulfil biocompatibility requirements. In addition, single step movement is very small which requires strong dimensional stability to avoid stick-slip effects. In the OmniPod dosing unit, the plunger consists of TOPAS cyclic olefin copolymer, a biocompatible, dimensionally stable polymer known for medical applications [190,191].

As a safety measure, the pod comprises an occlusion detection. An alarm sounds when an average of three to five units are missed. Depending on the dosing rate, the time between the occlusion and the alarm can be between some minutes (for bolus) to hours (for very low basal rates) [188]. Borot et al. [58] confirm the information in the guide book. In their study, the OmniPod leaves 4.7 U uninjected before the alarm sounds, which is less than for other pumps [58].

Clinical studies show that the device leads to improvement in the insulin therapy. Zisser and Jovanovic [192] prove a significant improvement of diabetic relevant blood values already after 30 days compared to durable pump therapy. Reasons for the improvement can be that subjects never disconnected pumps (even when showering, changing, exercising, etc.) and that a patch pump sees less hydrostatic fluctuation leading to more consistent insulin delivery [187]. The finding that OmniPod increases patients well-being compared to multiple daily injections (MDI) or durable pump therapy was confirmed by other studies [189,193,194]. Further studies are conducted towards diabetes type II therapy using U-500 insulin, also showing promising results [195]. Research on future therapies, such as an artificial pancreas implant, also use the OmniPod as dosing unit [196,197].

Laboratory evaluations of the dosing accuracy are inconsistent. Studies by Bowen and Allender [7], Freckmann et al. [57], Jahn et al. [8] and Borot et al. [58] show a lower dosing accuracy of the OmniPod system compared to durable pumps. In contrast, Zisser et al. [59] and Laubner et al. [6] show a comparatively high dosing accuracy. Differences can occur from varying measuring and evaluation methods. It is important to notice that these laboratory studies differ from the real-life application, for instance in the controlled and constant pump and infusion height. Therefore, no hydrostatic pressure influences their accuracy. This is one possible reason why the OmniPod performs well in clinical trials, even if dosing accuracy within some *in vitro* setups is lower.

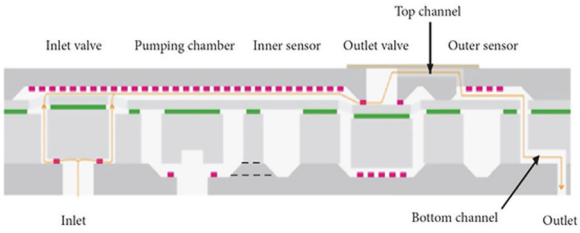

Fig. 4. Setup of the piezoelectric micropump used in the Jewel Pump. Figure reprinted from [198].

6.2. Jewel pump

The Jewel Pump (Debiotech S.A., Lausanne, Switzerland) offers several dosing speeds from 0.02 Units of insulin per minute to 3.6 Units per minute [159], which corresponds to 0.2 μL/min to 36 μL/min. It allows continuous infusion for up to 7 days. This long dosing period is possible due to a specific container concept in combination with a filter [158], which prevents insulin degradation. The system is not yet available on the market, but was already used in several clinical trials. The pump (Fig. 4) comprises two passive flap valves and a piezoelectrically actuated mesa moving the pump diaphragm and inducing fluid flow.

By implementing a double limiter concept, the stroke volume is kept constant at 200 nl [160]. This concept, restricting the diaphragm movement in upwards and downwards direction, was already implemented in earlier studies [31,199] assuring a reproducible stroke volume with a standard deviation of ± 1.1 nl. Dosing is therefore very accurate and in specified driving conditions independent of the driving frequency (up to 3 Hz), pressure (± 10 kPa at inlet or outlet), temperature, aging, and medium's viscosity (up to 10 mPas) [31,199,200]. The dosing stability is further increased by a specific actuation signal reducing errors by uncontrolled leakage through the inlet or the outlet valve [160]. The overall variation is less than 5 %.

Overpressure at the inlet does not cause immediate freeflow due to pretension of the valves of 10 kPa [31]. Leakage through these pressurized valves is not detectable and therefore smaller than 0.05 μL/h at 15 kPa applied pressure [31].

Similarly important for medical application is the pump's compression ratio. Earlier designs show a compression ratio of up to 2.3 (formula 1, see chapter 5.1) [199]. The Jewel Pump has a compression ratio of 0.8 and the fluidic channels' geometry is designed to offer minimal resistance due to surface tension. Therefore, the device shows self-priming and bubble tolerance [31,198]. To prevent particles from reaching the pump, an on-chip filter can be integrated [31].

The micropump itself is small with an area of only 6 × 10 mm^2 [199]. The whole patch pump is some centimetres large. Its size strongly depends on the drug reservoir and the battery. To our knowledge, no data concerning the battery size is published. The pump's actuation requires high voltage (± 200 V). According to the company, a single actuation cycle requires a power of 0.03 J, leading to a power consumption below 150 kJ/L for the entire system (the piezoelectric micropump's consumption itself is much lower).

Preliminary lifetime testing of the micropump shows no change in flow rate at 0.05 Hz actuation for 600 days [199]. In addition, the authors state that fatigue and stress tests proof a cycling capability above the device's required lifetime [159].

The piezoelectric pump system comprises two pressure sensors, one in the pump chamber and one after the outlet valve, that detect correct priming, reservoir overpressure, reservoir emptying, presence of air bubbles, outlet occlusion, and leakage by monitoring the pressure profile [159,201]. The Jewel Pump is therefore the only insulin pump that can fully monitor correct drug administration.

Within considerations for an industrialized functional test of their insulin pump, the authors illustrate a leak detection sensitivity of few nL/h [202]. They further describe occlusion detection within one stroke [159]. A study by Borot et al. [58] reveals indeed an exceptionally fast error detection of the Jewel Pump compared to several durable pump systems, especially for small flow rates. Additionally, the authors show a high *in vitro* dosing accuracy of the Jewel Pump compared to three durable pumps and the OmniPod patch pump. The Jewel Pump's average flow error is significantly smaller than for other systems at both 1 U/h and 0.1 U/h, while the difference is larger for smaller flow rates [58]. The *in vivo* test, where the Jewel Pump doses physiological saline in parallel to the patients' usual pump, shows no significant difference of the volume delivered by the Jewel Pump compared to the patient's durable pump after 24 h of use [58].

6.3. iPRECIO

The iPRECIO-micropump family (Primetech Corp., Tokyo, Japan) is a series of micropump systems for animal use. The pumps are implantable, refillable via a subcutaneous port, and offer a programmable dosing pattern. A first scientific paper surveying the dosing accuracy and performing an *in vivo* rat trial has been published in 2009 [203]. Since then, iPRECIO pumps have been used in numerous animal trials, including studies on various pharmaceuticals [204–206], and drug use and abuse [207,208]. Tan et al. [209] review a number of use cases.

The iPRECIO pumps use a miniaturized peristaltic-type dosing mechanism [154,210]. A micro stepper motor drives an eccentric disk cam, which sequentially actuates a number of so-called finger pins. These pins compress and release a piece of elastic tubing as the motor turns, thereby moving the liquid inside the tubing from the reservoir towards the outlet. The system blocks the fluid path when turned off, limiting backflow, freeflow, and diffusion.

Both tubing and reservoir are made from medical grade styrene-ethylene/butylene-styrene block copolymers (SEBS) [154], a material frequently used for biomedical applications [211]. The system is sold in ethylene oxide (EO) sterilized blister packages and is intended for single-use only.

There are currently two different models available: The smaller version is suitable for mice or larger (size: 24.8 × 15 × 7.2 mm^3), whereas the other one addresses rat applications (size: 7.20 cm^3). Both create flowrates beginning from 0.1 μL/h and reach up to 10 μL/h and 30 μL/h, respectively [154].

Dosing accuracy for both versions is specified as ±5 % up to 7.8 kPa backpressure [212]. Battery life for both pump types depends on the infusion rate and ranges from 8 days (10 μL/h dosing rate) to 67 days (0.1 μL/h dosing rate) [154].

6.4. Sensile medical rotary piston pump

The micropump developed by the Sensile Medical AG (Olten, Switzerland) is a rotary piston pump using a rotatable and axially slidable rotor [213], actuated by a brushless micro DC motor. Pumping stroke is generated by the axial movement of the piston, while the inlet and outlet valves are opened and closed by the angular position of the rotating piston. With different cam designs, the rotating actuation by the micromotor is translated into an axial movement to provide the stroke compression [213].

The nominal stroke volume of the patch pump is adaptable by design within a range from 250 nl to 25 mL [214,215]. A flow rate of 6 mL/min can be achieved at 5 μL stroke volume [215]. Typical liquid pumping backpressure is 150 kPa, whereas the maximal blocking pressure is above 400 kPa. Pull in pressure in dry starting condition is 40 kPa [215]. Gas bubbles and gas/liquid mixtures are unproblematic [214]. However, the influence of capillary forces might lower achievable pressures. Liquid viscosities up to 100 mPas can be handled by adaption of design [215].

In off state, the Sensile pump valves are both in a closed position, which prevents freeflow, backflow, and diffusion. The brushless DC motor is hermetically separated from the pumping part that is designed as disposable device. Therefore, it can be reused, limiting the cost of application. Using hall sensors for feedback control, the pump rotor movement can detect turning rate, speed, angle, and stroke amplitude. Additionally, those sensing capabilities allow to detect occlusion and other malfunctions of the pump while driving it. Overall dosing accuracy is given with 5 %.

6.5. Tricumed pump

The implantable infusion pump IP2000 V of Tricumed Medizintechnik GmbH (Kiel, Germany) is used for continuous intrathecal long-term medication [216]. The system is used for the treatment of intrathecal spasticity with Baclofen or the long-term pain treatment with morphine. The delivery of a constant flow between 0.25 mL/day up to 3 mL/day is achieved with a constant pressure on the drug reservoir and a flow restriction to achieve the desired flow [216]. The system is refillable via a silicone septum [217]. The system has a diameter of 78 mm and a height of 14 mm–27 mm with a reservoir size from 20 mL to 60 mL. The life time is indicated for the refill septum as 500 punctures and therefore approximately 20 years with 25 punctures per year [216,217]. This implantable pump system is MRT compatible [218]. In addition to their IP2000 V pump, Tricumed offers a paediatric implantable drug delivery pump (IP1000 V) [218,219]. With a diameter of 57 mm and a height between 20 mm and 24 mm, this system is the smallest infusion system for constant flow on the market [219].

In addition to constant flow pumps, Tricumed developed a programmable implantable infusion system, the siromedes pump, that was CE certified in 2014. Similar to the IP2000 V, the flow is generated via pressurization of the reservoir. Additionally, an active valve enables flow adaptation [220].

7. Summary of solutions for drug dosing requirements

Many of the challenges and requirements summarised in chapter 2 are discussed in micropump research, while there is little information concerning others up to date. Many dosing properties do not only depend on the fluidic actuator itself, but also on the overall system, fluidic boundary conditions and especially the valve technology. The implementation of closed loop control increases the reliability of the dosing unit and enables error detection. Furthermore, weight and size constraints have to be evaluated on system level, since driving electronics, power supply as well as a drug reservoir can be large parts to take into account. Other challenges can be solved within the micropump itself for example by design adaptations, which allow for space efficient solutions. Resourceful technical adaptations are summarized in Fig. 2.

Freeflow as well as diffusion and backflow can be prevented using active valves as presented by Pečar et al. [73], Fuchs et al. [107], and Forouzandeh et al. [89]. However, those pumps do not block the flow path when turned off. Such a normally closed state can be achieved for instance with phase change actuation based on gallium [140], since it shrinks when melted and therefore opens the fluid path when actuated. The iPRECIO pumps [204–209] prevent backflow, freeflow, and diffusion also in turned off state by their peristaltic setup. A passive freeflow and backflow stop is presented by Richter et al. [100]. The authors implement passive flap valves to prevent backflow and diffusion, in combination with a passive safety valve that blocks the fluid path when the inlet pressure exceeds the outlet pressure. Maillefer et al. [31] prevent freeflow as well as leakage with a valve pretension of the passive flap valves

of 10 kPa. Additionally, a specific actuation signal reduces errors by uncontrolled leakage through the inlet or the outlet valve during pump operation [160]. In general, rotary pumps show little leakage, freeflow, and backflow due to geometric constraints. An example is presented by Pankhurst and Abdollahi [30] with only one moving part and a spring design freeflow stop.

Bubbles, that are usually unproblematic for rotational micropumps, remain a huge challenge for diaphragm pumps. A sufficient compression ratio to move the bubble through the chamber against all counterforces is necessary. Herz et al. [155] achieve a high compression ratio with their pretension technique. By applying a positive voltage to the actuator disc during glue hardening, the authors drastically increase their pumps compression ratio. Trenkle et al. [104] increase the compression ratio of their device by casting the deflected membrane to manufacture the pump chamber. Furthermore, bubble tolerance can be increased when reducing the force needed to transport a bubble out of the pump chamber, as done by Wang et al. [102] with a super hydrophilic surface of the pump chamber and by Ma et al. [103] with a rib structure in the chamber, which guides the fluid flow.

Not many authors investigated the interaction with the transported medium and clogging. In most cases, micropump evaluations are conducted with surrogate fluids, since the use of drug formulations can complicate handling and lead to large additional costs. However, the medium can damage the pump over time and the pump might impact the drug's functionality. Especially miniaturized pumps, with a high surface to volume ratio and sharp edges in small fluidic channels, might cause damage to the drug formulation. To prevent interaction, Forouzandeh et al. [89] and Vinayakumar et al. [151] limit the contact of the medium to biocompatible tubing, through which medium is transported peristaltically. The same accounts for the iPRECIO systems. This approach enables easy fluidic connection without sharp edges and there are no sharp moving parts such as flap valves in the fluid path. DeBiotech's JewelPump utilises a specific drug reservoir in combination with a special filter to prevent insulin aggregation [158].

Often, safety measures are indispensable for medical application and space efficient integration is an advantage. The segmentation of the piezoelectric ceramic into an actuated part and a sensing part, as shown by Zhang et al. [105], allows to detect any changes in the pump chamber and can be used to monitor transport, the occurrence of bubbles or a change in backpressure, e.g., caused by clogging. For the same purpose, Fuchs et al. [107] integrate a pressure sensor onto their peristaltic pump system. To ensure stable dosing, Benard et al. [75] include an in-line filter to prevent particles and bubbles from entering the pump chamber. A similar filter concept is employed in the JewelPump [158]. Additionally, the system comprises two pressure sensors, one in the pump chamber and one after the outlet valve, for precise control and error detection. Therewith, correct priming, reservoir overpressure, reservoir emptying, presence of air bubbles, occlusion within one stroke [159], and leakage can be detected with the pressure profile [159,201].

In addition to safety relevant aspects, flow properties are highly relevant for microdosing units. To improve the maximal flow rate without increasing the pump's size is an important aim. Geometric adaptations that lower the fluidic resistance, such as the rib structure presented by Ma et al. [103], allow for higher flow rates. Furthermore, higher actuator displacement can improve maximal flow, which Zhu et al. [181] achieve with ring electrodes leading to actuator buckling instead of bending, and Yamataha et al. [115] by a soft silicone diaphragm. However, the soft diaphragm decreases the bending actuator's stiffness and therefore the maximal achievable pressure.

Not only high flow rates, but also the flexibility of bidirectional actuation can be advantageous. For instance, peristaltic actuation [89,104,151,161] or the implementation of active valves [120] enable bidirectional flow. Additionally, the peristaltic actuation using magnetic shape memory actuators can move fluid in both directions [92,144,145]. Iacovacci et al. [150] developed a bidirectional microgear pump that aims to work with very small drug delivery systems, especially for Insulin.

Dosing accuracy and precision are extremely important for drug delivery. Many authors state the single stroke volume of their pump as limit of resolution. However, little information is available on the repeatability of single strokes and many authors do not present results on dosing variation at varying environmental conditions. It is necessary that pump evaluations include repeatable and reproducible measurements to develop reliable systems and enable market entry. Detailed evaluation of dosing accuracy and precision are only available for industrial dosing units or systems close to the market as they are compared in several studies [5–8,56–58].

To ensure stable dosing at varying environmental conditions, the JewelPump comprises a double limiter concept that prevents diaphragm movement outside of fixed boundaries [160]. Therefore, the pump doses independently of the driving frequency (up to 3 Hz), pressure (± 10 kPa at inlet or outlet), temperature, aging, and medium's viscosity (up to 10 mPas) [31,199,200].

The influence of backpressure on a pump's flow rate is widely described. Ideal would be stable dosing without pressure dependence, however most pumps show a linear decrease with rising pressure. More stable dosing against varying pressure is achieved with peristaltic pump systems [104,107,142,161] or the serial combination of several pumps [108,156]. Richter et al. [100] present an extremely stiff bending actuator that shows a stroke decrease of less than 0.1 % per kPa and a corresponding flowrate decrease of only 0.025 µL/min per kPa backpressure increase. In general, phase change systems and magnetic shape memory actuation achieve extremely high backpressure [140,143].

Especially for implantable, but also for patch pump application, size and weight constrains are an important requirement. Wireless power supply [152,153,162,163] obviates the need of a battery and therefore enables systems small and light enough even for implantation into small rodents, which do not require to restrain the animal for electric contact during pump use. Specific manufacturing techniques, such as MEMS processes or 3D printing of miniaturized systems allows for extremely small pumps as shown by Richter et al. [67] (3.5×3.5 mm^2 piezoelectrically driven pump) and Moussi et al. [153,186] ($3.9 \times 2.1 \times 2$ mm^3 electrolysis actuated pump). Xia et al. [136] present an extremely miniaturized dielectric polymer actuator of only 2.2×2.2 mm^2. The pump by Wang and Park [121] is small enough to be integrated into a contact lens. Furthermore, research pushes towards miniaturization of generally larger gear pumps. Waldschik et al. [149] use polymer magnets with alternating axial magnetization manufactured using micro fabrication technologies to achieve a pump of only $10 \times 12 \times 1.3$ mm^3.

8. Conclusion

Micropumps offer great potential for the improvement of drug dosing applications. The small size enables less noticeable products and improves patients' comfort as well as disposition to follow their treatment. Another advantage is the high achievable accuracy of extremely small dosed volumes. It enables safe use of higher concentrated drugs leading to further miniaturization of dosing systems. Not only miniaturization of existing dosing units is possible, but also the development of totally new concepts enabling drug delivery in a manner and to specific tissue unimaginable up to date.

In the last decades, dedicated research on drug delivery applications has led to tremendous innovations. However, due to the high-risk aspect of this application, there are challenging requirements including safety requirements, flow requirements, and device specific challenges.

To address the specific field of drug delivery with microdosing systems, there is a variety of micropumps that differ in type and actuation principle with specific advantages and disadvantages. Most pumps in research are not fully optimized devices and in the case of most research pumps, a further increase of performance would be possible with further development steps towards better compression ratio, optimized valves, better exploitation of the maximum actuation forces, and many more detailed improvements. In general, applicability of a technology for medical dosing, resourceful solutions to overcome limitations and meet requirements, and a general idea of the state of development of each specific actuation mechanism is described above.

It is not evident to compare the fluidic performance of the presented pumps, since various experimental setups are used. Especially the measured maximal pressure ability and the maximal achievable flow depend strongly on the fluidic surroundings. Furthermore, gravimetric measurements, which are commonly used for micropump evaluation, require careful consideration to prevent errors caused by evaporation, surface tension, or buoyancy. For better comparability, the use of as similar experiments as possible, together with more detailed information on experimental setups is desirable.

Even though dosing accuracy and precision are extremely important for drug delivery, dosing variations are not commonly evaluated. The limit of resolution is often stated based on the single stroke volume of a pump, without information on the repeatability of single strokes. In future evaluations, it is necessary to focus on repeatable and reproducible measurements to develop reliable systems and enable market entry.

There is little information about lifetime in general and statistically relevant data in particular is usually not available. Especially evaluations under relevant and comparable conditions concerning for instance backpressure, temperature, and humidity are not published. It is therefore difficult to evaluate which pump type is well suited for short term or long-term application and estimations have to be based on general information about actuation principles. Furthermore, most experimental studies are conducted with surrogate fluids. Knowledge of the drug-pump interaction and its implication on the lifetime are crucial for safe use. Thus, a better understanding of interaction mechanisms as well as the influence of the surface to volume ratio or sharp edges is desirable.

Overall, micropumps prove promising for drug dosing applications. The examples on or close to the market demonstrate feasibility and numerous research works reveal innovative improvements to enable safe, small as well as energy and cost efficient systems. However, despite all recent developments, micropumps are not yet commonly used in state-of-the-art drug dosing devices. Some requirements of drug delivery still need to be addressed. Additionally, the step from today's established products to micropumps, e.g., MEMS-based actuators, is large and risky. Further investigations and improvements are necessary, especially concerning cost, production, and safety relevant aspects in order to enable market entry and improve drug dosing applications.

Author's contribution

Agnes Bußmann: Manuscript Conceptualisation and Administration; Supervision; Literature Resources; Writing-Original Draft Preparation; Visualisation; Writing-Review & Editing. **Lorenz Grünerbel:** Literature Resources; Writing-Original Draft Preparation; Writing-Review & Editing. **Claudia Durasiewicz:** Literature Resources; Writing-Original Draft Preparation; Visualisation; Writing-Review & Editing. **Thomas Thalhofer:** Literature Resources; Writing-Original Draft Preparation; Writing-Review & Editing. **Axel Wille:** Literature Resources; Writing-Original Draft Preparation; Visualisation; Writing-Review & Editing. **Martin Richter:** Writing-Original Draft Preparation.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

We are grateful to Dr. Sebastian Kibler, Christian Wald, and Henry Leistner for helpful feedback on this work. Furthermore, we thank Stephan Proennecke and Eric Chappel for their kind support concerning DeBiotech's piezoelectric pump system. We thank Aierke Yermentayeva for her support during market research.

References

[1] The Diabetes Control and Complications Trial Research Group, Hypoglycemia in the diabetes control and complications trial, Diabetes 46 (1997) 271, http://dx.doi.org/10.2337/diab.46.2.271.
[2] E.A. Doyle, S.A. Weinzimer, A.T. Steffen, J.A.H. Ahern, M. Vincent, W.V. Tamborlane, A. Randomized, Prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine, Diabetes Care 27 (2004) 1554, http://dx.doi.org/10.2337/diacare.27.7.1554.
[3] K. Jeitler, K. Horvath, A. Berghold, T.W. Gratzer, K. Neeser, T.R. Pieber, A. Siebenhofer, Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis, Diabetologia 51 (2008) 941–951, http://dx.doi.org/10.1007/s00125-008-0974-3.
[4] Henry Anhalt and Nancy J.V. Bohannon, Insulin Patch Pumps: Their Development and Future in Closed-Loop Systems.
[5] H.C. Zisser, W. Bevier, E. Dassau, L. Jovanovic, Siphon effects on continuous subcutaneous insulin infusion pump delivery performance, J. Diabetes Sci. Technol. 4 (2010) 98–103, http://dx.doi.org/10.1177/193229681000400112.
[6] K. Laubner, E. Singler, J. Straetener, T. Siegmund, G. Päth, J. Seufert, Comparative dose accuracy of durable and patch insulin pumps under laboratory conditions, Diabetes Technol. Ther. 21 (2019) 371–378, http://dx.doi.org/10.1089/dia.2019.0089.
[7] J.L. Bowen, C.J. Allender, A comparative pulse accuracy study of two commercially available patch insulin infusion pumps, Neuro Endocrinol. Lett. 12 (2016) 79–84, http://dx.doi.org/10.17925/EE.2016.12.02.79.
[8] L.G. Jahn, J.J. Capurro, B.L. Levy, Comparative dose accuracy of durable and patch insulin infusion pumps, J. Diabetes Sci. Technol. 7 (2013) 1011–1020, http://dx.doi.org/10.1177/193229681300700425.
[9] B.-B.C. Youan, Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? J. Control. Release 98 (2004) 337–353, http://dx.doi.org/10.1016/j.jconrel.2004.05.015.
[10] F. Lévi, C. Focan, A. Karaboué, V. de La Valette, D. Focan-Henrard, B. Baron, F. Kreutz, S. Giacchetti, Implications of circadian clocks for the rhythmic delivery of cancer therapeutics, Adv. Drug Deliv. Rev. 59 (2007) 1015–1035, http://dx.doi.org/10.1016/j.addr.2006.11.001.
[11] F. Levi, R. Zidani, J.-L. Misset, Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer, Lancet 350 (1997) 681–686.
[12] T.C. Chen, G.R. Napolitano, F. Adell, A.H. Schönthal, Y. Shachar, Development of the Metronomic Biofeedback Pump for leptomeningeal carcinomatosis: technical note, J. Neurosurg. 123 (2015) 362–372, http://dx.doi.org/10.3171/2014.10.JNS14343.
[13] S. Reagan-Shaw, M. Nihal, N. Ahmad, Dose translation from animal to human studies revisited, FASEB J. 22 (2008) 659–661, http://dx.doi.org/10.1096/fj.07-9574LSF.
[14] DURECT Corporation, Alzet Osmotic Pumps, 2020 https://www.alzet.com/.
[15] iPrecio, Innovative drug infusion technology for laboratory animals. https://www.iprecio.com/ (Accessed 14 August 2020).
[16] Infu e Disk, Low Cost Infusion Pumps for Veterinary and Laboratory Use. http://medecell.com/products.htm (Accessed 14 August 2020).
[17] Y.-N. Wang, L.-M. Fu, Micropumps and biomedical applications – a review, Microelectron. Eng. 195 (2018) 121–138, http://dx.doi.org/10.1016/j.mee.2018.04.008.
[18] N.-C. Tsai, C.-Y. Sue, Review of MEMS-based drug delivery and dosing systems, Sens. Actuators A Phys. 134 (2007) 555–564, http://dx.doi.org/10.1016/j.sna.2006.06.014.
[19] J.B. Steen, O. Iversen, A high precision micropump, J. Phys. E (1969) 419–420.

[20] W. Schubert, P. Baurschmidt, J. Nagel, R. Thull, M. Schaldach, An implantable artificial pancreas, Med. Biol. Eng. Comput. 18 (1980) 527–537, http://dx.doi.org/10.1007/BF02443331.
[21] J.G. Smits, Piezoelectric micropump with three valves working peristaltically, Proceedings of the 5th International Conference on Solid-State Sensors and Actuators and Eurosensors III 21 (1990) 203–206.
[22] W.J. Spencer, W.T. Corbett, L.R. Dominguez, B.D. Shafer, An electronically controlled piezoelectric insulin pump and valves, Ieee Trans. Sonics Ultrason. 25 (1978) 153–156, http://dx.doi.org/10.1109/T-SU.1978.31006.
[23] D.J. Laser, J.G. Santiago, A review of micropumps, J. Micromech. Microeng. 14 (6) (2004).
[24] Farideh Abhari, Haslina Jaafar, Nurul Amziah Md Yunus, A comprehensive study of micropumps technologies, Int. J. Electrochem. Sci. 7 (2012) 9765–9780.
[25] N.-T. Nguyen, X. Huang, T.K. Chuan, MEMS-micropumps: a review, J. Fluids Eng. 124 (2002) 384, http://dx.doi.org/10.1115/1.1459075.
[26] A. Nisar, N. Afzulpurkar, B. Mahaisavariya, A. Tuantranont, MEMS-based micropumps in drug delivery and biomedical applications, Sens. Actuators B Chem. 130 (2008) 917–942, http://dx.doi.org/10.1016/j.snb.2007.10.064.
[27] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. http://data.europa.eu/eli/reg/2017/745/oj.
[28] M. Richter, R. Linnemann, P. Woias, Robust design of gas and liquid micropumps, Sens. Actuators A Phys. 68 (1998) 480–486, http://dx.doi.org/10.1016/S0924-4247(98)00053-3.
[29] U. Kamecke, D. Waldenmaier, C. Haug, R. Ziegler, G. Freckmann, Establishing methods to determine clinically relevant bolus and basal rate delivery accuracy of insulin pumps, J. Diabetes Sci. Technol. 13 (2019) 60–67, http://dx.doi.org/10.1177/1932296818788349.
[30] P. Pankhurst, Z.M. Abdollahi, Evaluation of a novel portable micro-pump and infusion system for drug delivery, Conf. Proc. IEEE Eng. Med. Biol. Soc. 2016 (2016) 465–468, http://dx.doi.org/10.1109/EMBC.2016.7590740.
[31] D. Maillefer, H. van Lintel, G. Rey-Mermet, R. Hirschi, A high-performance silicon micropump for an implantable drug delivery system, Technical Digest, IEEE International MEMS 99 Conference. Twelfth IEEE International Conference on Micro Electro Mechanical Systems (Cat. No. 99CH36291) (2021) 541–546, http://dx.doi.org/10.1109/MEMSYS.1999.746886.
[32] N.-T. Nguyen, T.-Q. Truong, A fully polymeric micropump with piezoelectric actuator, Sens. Actuators B Chem. 97 (2004) 137–143, http://dx.doi.org/10.1016/S0925-4005(03)00521-5.
[33] Masufumi Yoshida, Louis D. Lowry, Hydrostatic pressure measurement of endolymph and perilymph in the guinea pig cochlea, Am. J. Otolaryngol. 5 (1984) 159–165, http://dx.doi.org/10.1016/S0196-0709(84)80007-1.
[34] G. Liu, C. Shen, Z. Yang, X. Cai, H. Zhang, A disposable piezoelectric micropump with high performance for closed-loop insulin therapy system, Sens. Actuators A Phys. 163 (2010) 291–296, http://dx.doi.org/10.1016/j.sna.2010.06.030.
[35] Thomas J.K. Toung, Mark I. Rossberg, Grover M. Hutchins, Volume of air in a lethal venous air embolism, Anesthesiology 94 (2001) 360–361.
[36] L. Kim, Y.-C. Toh, J. Voldman, H. Yu, A practical guide to microfluidic perfusion culture of adherent mammalian cells, Lab Chip 7 (2007) 681–694, http://dx.doi.org/10.1039/b704602b.
[37] M.A. Chappell, S.J. Payne, A physiological model of the release of gas bubbles from crevices under decompression, Respir. Physiol. Neurobiol. 153 (2006) 166–180, http://dx.doi.org/10.1016/j.resp.2005.10.006.
[38] Y. Wang, D. Lee, L. Zhang, H. Jeon, J.E. Mendoza-Elias, T.A. Harvat, S.Z. Hassan, A. Zhou, D.T. Eddington, J. Oberholzer, Systematic prevention of bubble formation and accumulation for long-term culture of pancreatic islet cells in microfluidic device, Biomed. Microdevices 14 (2012) 419–426, http://dx.doi.org/10.1007/s10544-011-9618-3.
[39] A. Chandrasekaran, M. Packirisamy, Experimental investigation of cavitation behavior in valveless micropumps, J. Micromech. Microeng. 22 (2012) 125019, http://dx.doi.org/10.1088/0960-1317/22/12/125019.
[40] J.H. Sung, M.L. Shuler, Prevention of air bubble formation in a microfluidic perfusion cell culture system using a microscale bubble trap, Biomed. Microdevices 11 (2009) 731–738, http://dx.doi.org/10.1007/s10544-009-9286-8.
[41] T. Fu, Y. Ma, Bubble formation and breakup dynamics in microfluidic devices: a review, Chem. Eng. Sci. 135 (2015) 343–372, http://dx.doi.org/10.1016/j.ces.2015.02.016.
[42] J. Jaspe, S.J. Hagen, Do protein molecules unfold in a simple shear flow? Biophys. J. 91 (2006) 3415–3424, http://dx.doi.org/10.1529/biophysj.106.089367.
[43] C.R. Thomas, D. Geer, Effects of shear on proteins in solution, Biotechnol. Lett. 33 (2011) 443–456, http://dx.doi.org/10.1007/s10529-010-0469-4.
[44] A. Nayak, A.K. Dutta, G. Belfort, Surface-enhanced nucleation of insulin amyloid fibrillation, Biochem. Biophys. Res. Commun. 369 (2008) 303–307, http://dx.doi.org/10.1016/j.bbrc.2008.01.159.
[45] W. Wang, S. Nema, D. Teagarden, Protein aggregation—pathways and influencing factors, Int. J. Pharm. 390 (2010) 89–99, http://dx.doi.org/10.1016/j.ijpharm.2010.02.025.
[46] J.G. Biddlecombe, G. Smith, S. Uddin, S. Mulot, D. Spencer, C. Gee, B.C. Fish, D.G. Bracewell, Factors influencing antibody stability at solid-liquid interfaces in a high shear environment, Biotechnol. Prog. 25 (2009) 1499–1507, http://dx.doi.org/10.1002/btpr.211.
[47] W. Wang, C.J. Roberts, Protein aggregation - mechanisms, detection, and control, Int. J. Pharm. 550 (2018) 251–268, http://dx.doi.org/10.1016/j.ijpharm.2018.08.043.
[48] T. Frachon, F. Bruckert, Q. Le Masne, E. Monnin, M. Weidenhaupt, Insulin aggregation at a dynamic solid-liquid-air triple interface, Langmuir 32 (2016) 13009–13019, http://dx.doi.org/10.1021/acs.langmuir.6b03314.
[49] A.I. Geller, N. Shehab, M.C. Lovegrove, S.R. Kegler, K.N. Weidenbach, G.J. Ryan, D.S. Budnitz, National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations, JAMA Intern. Med. 174 (2014) 678–686, http://dx.doi.org/10.1001/jamainternmed.2014.136.
[50] P.L. Yong, L. Olsen, J.M. McGinnis (Eds.), Value in Health Care: Accounting for Cost, Quality, Safety, Outcomes, and Innovation, Washington (DC), 2010.
[51] M.K. Mishra, V. Dubey, P.M. Mishra, I. Khan, MEMS technology: a review, JERR (2019) 1–24, http://dx.doi.org/10.9734/jerr/2019/v4i116891.
[52] M. Vaezi, H. Seitz, S. Yang, A review on 3D micro-additive manufacturing technologies, Int. J. Adv. Manuf. Technol. 67 (2013) 1721–1754, http://dx.doi.org/10.1007/s00170-012-4605-2.
[53] T. Gietzelt, O. Jacobi, V. Piotter, R. Ruprecht, J. Hausselt, Development of a micro annular gear pump by micro powder injection molding, J. Mater. Sci. 39 (2004) 2113–2119, http://dx.doi.org/10.1023/B:JMSC.0000017774.64153.d9.
[54] V. Baumans, Science-based assessment of animal welfare: laboratory animals, Revue Scientifique Et Technique-Office International Des Epizooties 24 (2005) 503.
[55] International Electrotechnical Commission, Medical Electrical Equipment - Part 2-24: Particular Requirements for Basic Safety and Essential Performance of Infusion Pumps and Controllers: IEC 60601-60602-24:2012, 2016.
[56] S. Pleus, U. Kamecke, D. Waldenmaier, G. Freckmann, Reporting insulin pump accuracy: trumpet curves according to IEC 60601-2-24 and beyond, J. Diabetes Sci. Technol. 13 (2019) 592–596, http://dx.doi.org/10.1177/1932296818806509.
[57] G. Freckmann, U. Kamecke, D. Waldenmaier, C. Haug, R. Ziegler, Accuracy of bolus and basal rate delivery of different insulin pump systems, Diabetes Technol. Ther. 21 (2019) 201–208, http://dx.doi.org/10.1089/dia.2018.0376.
[58] S. Borot, S. Franc, J. Cristante, A. Penfornis, P.-Y. Benhamou, B. Guerci, H. Hanaire, E. Renard, Y. Reznik, C. Simon, G. Charpentier, Accuracy of a new patch pump based on a microelectromechanical system (MEMS) compared to other commercially available insulin pumps: results of the first in vitro and in vivo studies, J. Diabetes Sci. Technol. 8 (2014) 1133–1141, http://dx.doi.org/10.1177/1932296814543946.
[59] H. Zisser, M. Breton, E. Dassau, K. Markova, W. Bevier, D. Seborg, B. Kovatchev, Novel methodology to determine the accuracy of the OmniPod insulin pump: a key component of the artificial pancreas system, J. Diabetes Sci. Technol. 5 (2011) 1509–1518, http://dx.doi.org/10.1177/193229681100500627.
[60] M. Wackerle, M. Richter, P. Woias, F. Goldschmidtböing, Sub-nl flow measurement method for microfluidic actuators, Borgmann, H.: Actuator. 7th International Conference on New Actuators and International Exhibition on Smart Actuators and Drive Systems. Conference Proceedings. Bremen: Messe Bremen Ges (2000) 507–510.
[61] B. Pečar, D. Resnik, M. Možek, U. Aljančič, T. Dolžan, S. Amon, D. Vrtačnik, Triton X-100 as an effective surfactant for micropump bubble tolerance enhancement, Electron. Comp. Mater. 43 (2013) 103–110.
[62] C. Jenke, J. Pallejà Rubio, S. Kibler, J. Häfner, M. Richter, C. Kutter, The combination of Micro diaphragm pumps and flow sensors for single stroke based liquid flow control, Sensors (Basel) 17 (2017), http://dx.doi.org/10.3390/s17040755.
[63] M.W. Ashraf, S. Tayyaba, N. Afzulpurkar, Micro electromechanical systems (MEMS) based microfluidic devices for biomedical applications: diffuser nozzle micro pump micropump, Int. J. Mol. Sci. 12 (2011) 3648–3704, http://dx.doi.org/10.3390/ijms12063648.
[64] S. Mohith, P. Navin Karanth, S.M. Kulkarni, Recent trends in mechanical micropumps and their applications: a review, Mechatronics 60 (2019) 34–55, http://dx.doi.org/10.1016/j.mechatronics.2019.04.009.
[65] C. Jenke, S. Kager, M. Richter, C. Kutter, Flow rate influencing effects of micropumps, Sens. Actuators A Phys. 276 (2018) 335–345, http://dx.doi.org/10.1016/j.sna.2018.04.025.
[66] R. Zengerle, M. Richter, Simulation of microfluid systems, J. Micromech. Microeng. 4 (1994) 192–204, http://dx.doi.org/10.1088/0960-1317/4/4/004.
[67] M. Richter, H. Leistner, Y. Congar, A. Drost, S. Kibler, S. Röhl, M. Wackerle, Piezoelektrisch angetriebene Silizium Mikropumpe der Baugröße 3,5x3,5x0,6 mm3: piezoelectric silicone micro pump sized 3.5x3.5x0.6 mm^3, Proceedings Mikro System Technik Kongress 2019 (2019).
[68] C. Kittel, P. McEuen, John Wiley & Sons, Introduction to Solid State Physics: Chapter 16: Dielectrics And Ferroelectrics, pp. 481, John Wiley & Sons, 2004.
[69] E.F. Crawley, J. de Luis, Use of piezoelectric actuators as elements of intelligent structures, AIAA J. 25 (1987) 1373–1385, http://dx.doi.org/10.2514/3.9792.
[70] B.-K. Lai, H. Kahn, S.M. Phillips, A.H. Heuer, A comparison of PZT-based and TiNi shape memory alloy-based MEMS microactuators, Ferroelectrics 306 (2004) 221–226, http://dx.doi.org/10.1080/00150190490460867.

[71] Z. Zhang, S. Chen, S. Wang, J. Kan, J. Wen, C. Yang, Performance evaluation and comparison of a serial–parallel hybrid multichamber piezoelectric pump, J. Intell. Mater. Syst. Struct. 29 (2018) 1995–2007, http://dx.doi.org/10.1177/1045389X18758181.

[72] X. He, R. Bian, N. Lin, W. Xu, Z. Deng, S. Yang, A novel valveless piezoelectric micropump with a bluff-body based on Coanda effect, Microsyst. Technol. 25 (2019) 2637–2647, http://dx.doi.org/10.1007/s00542-018-4215-5.

[73] B. Pečar, D. Križaj, D. Vrtačnik, D. Resnik, T. Dolžan, M. Možek, Piezoelectric peristaltic micropump with a single actuator, J. Micromech. Microeng. 24 (2014) 105010, http://dx.doi.org/10.1088/0960-1317/24/10/105010.

[74] W.L. Benard, H. Kahn, A.H. Heuer, M.A. Huff, A titanium-nickel shape-memory alloy actuated micropump, Proceedings of the Transducers' 97 1 (1997).

[75] W.L. Benard, H. Kahn, A.H. Heuer, M.A. Huff, Thin-film shape-memory alloy actuated micropumps, J. Microelectromech. Syst. 7 (1998) 245–251.

[76] C. Lexcellent, Shape-Memory Alloys Handbook, Wiley; iste, 2013.

[77] M.A. Zainal, S. Sahlan, M.S.M. Ali, Micromachined shape-memory-alloy microactuators and their application in biomedical devices, Micromachines 6 (2015) 879–901, http://dx.doi.org/10.3390/mi6070879.

[78] M.Q. Rusli, P.S. Chee, R. Arsat, K.X. Lau, P.L. Leow, Electromagnetic actuation dual-chamber bidirectional flow micropump, Sens. Actuators A Phys. 282 (2018) 17–27, http://dx.doi.org/10.1016/j.sna.2018.08.047.

[79] C.-Y. Shen, H.-K. Liu, Innovative composite PDMS micropump with electromagnetic drive, Sens. Mater. 22 (2010) 85–100.

[80] R. Zengerle, A. Richter, H. Sandmaier, A micro membrane pump with electrostatic actuation, Proceedings of the Micro Electro Mechanical Systems' 92 (1992).

[81] S. Uhlig, M. Gaudet, S. Langa, K. Schimmanz, H. Conrad, B. Kaiser, H. Schenk, Electrostatically driven in-plane silicon micropump for modular configuration, Micromachines 9 (4) (2018), http://dx.doi.org/10.3390/mi9040190.

[82] T.-B. Xu, J. Su, Development, characterization, and theoretical evaluation of electroactive polymer-based micropump diaphragm, Sens. Actuators A Phys. 121 (2005) 267–274, http://dx.doi.org/10.1016/j.sna.2005.01.020.

[83] T.-B. Xu, Z.-Y. Cheng, Q.M. Zhang, High-performance micromachined unimorph actuators based on electrostrictive poly(vinylidene fluoride–trifluoroethylene) copolymer, Appl. Phys. Lett. 80 (2002) 1082–1084, http://dx.doi.org/10.1063/1.1448661.

[84] T. Mirfakhrai, J.D. Madden, R.H. Baughman, Polymer artificial muscles, Mater. Today 10 (2007) 30–38, http://dx.doi.org/10.1016/S1369-7021(07)70048-2.

[85] M. Annabestani, M. Fardmanesh, Ionic electro active polymer-based soft actuators and their applications in microfluidic micropumps, microvalves, and micromixers: a review, Appl. Phys. (2019), arXiv:1904.07149 [physics.app-ph].

[86] Y. Bar-Cohen, I.A. Anderson, Electroactive polymer (EAP) actuators—background review, Mech. Soft Mater 1 (2019) 61, http://dx.doi.org/10.1007/s42558-019-0005-1.

[87] Seung-Mo Ha, Woong Cho, Yoomin Ahn, Disposable thermo-pneumatic micropump for bio lab-on-a-chip application, Microelectron. Eng. 86 (2009) 1337–1339, http://dx.doi.org/10.1016/j.mee.2008.12.046.

[88] R. Bodén, M. Lehto, U. Simu, G. Thornell, K. Hjort, J.-Å. Schweitz, A polymeric paraffin actuated high-pressure micropump, Sens. Actuators A Phys. 127 (2006) 88–93, http://dx.doi.org/10.1016/j.sna.2005.11.068.

[89] F. Forouzandeh, X. Zhu, A. Alfadhel, B. Ding, J.P. Walton, D. Cormier, R.D. Frisina, D.A. Borkholder, A nanoliter resolution implantable micropump for murine inner ear drug delivery, J. Control. Release 298 (2019) 27–37, http://dx.doi.org/10.1016/j.jconrel.2019.01.032.

[90] S. Svensson, G. Sharma, S. Ogden, K. Hjort, L. Klintberg, High-pressure peristaltic membrane micropump with temperature control, J. Microelectromech. Syst. 19 (2010) 1462–1469, http://dx.doi.org/10.1109/JMEMS.2010.2076784.

[91] S. Ogden, L. Klintberg, G. Thornell, K. Hjort, R. Bodén, Review on miniaturized paraffin phase change actuators, valves, and pumps, Microfluid Nanofluid 17 (2014) 53–71, http://dx.doi.org/10.1007/s10404-013-1289-3.

[92] K. Ullakko, L. Wendell, A. Smith, P. Müllner, G. Hampikian, A magnetic shape memory micropump: contact-free, and compatible with PCR and human DNA profiling, Smart Mater. Struct. 21 (2012) 115020, http://dx.doi.org/10.1088/0964-1726/21/11/115020.

[93] V. Piotter, Micro metal injection molding (MicroMIM), in: Handbook of Metal Injection Molding, Elsevier, 2019, pp. 333–360.

[94] V. Piotter, A. Klein, K. Plewa, K.R. Beyerlein, H.N. Chapman, S. Bajt, Development of a ceramic injection molding process for liquid jet nozzles to be applied for X-ray free-electron lasers, Microsyst. Technol. 24 (2018) 1247–1252, http://dx.doi.org/10.1007/s00542-017-3493-7.

[95] S. Zhou, A.N. Hrymak, M.R. Kamal, Microinjection molding of polypropylene/multi-walled carbon nanotube nanocomposites: the influence of process parameters, Polym. Eng. Sci. 58 (2018) E226–E234, http://dx.doi.org/10.1002/pen.24682.

[96] J. Yunas, B. Mulyanti, I. Hamidah, M. Mohd Said, R.E. Pawinanto, W.A.F. Wan Ali, A. Subandi, A.A. Hamzah, R. Latif, B. Yeop Majlis, Polymer-based MEMS electromagnetic actuator for biomedical application: a review, Polymers (Basel) 12 (2020), http://dx.doi.org/10.3390/polym12051184.

[97] P.-H. Cazorla, O. Fuchs, M. Cochet, S. Maubert, G. Le Rhun, Y. Fouillet, E. Defay, A low voltage silicon micro-pump based on piezoelectric thin films, Sens. Actuators A Phys. 250 (2016) 35–39, http://dx.doi.org/10.1016/j.sna.2016.09.012.

[98] T. Lemke, G. Biancuzzi, C. Farhat, B. Vodermayer, O. Ruthmann, T. Schmid, H.J. Schrag, P. Woias, F. Goldschmidtboeing, High performance micropumps utilizing multilayer piezo actuators, Proceedings of Eurosensors XXII (2008) 589–592.

[99] A. Geipel, F. Goldschmidtböing, A. Doll, P. Jantscheff, N. Esser, U. Massing, P. Woias, An implantable active microport based on a self-priming high-performance two-stage micropump, Sens. Actuators A Phys. 145-146 (2008) 414–422, http://dx.doi.org/10.1016/j.sna.2007.11.024.

[100] M. Richter, M. Wackerle, S. Kibler, M. Biehl, T. Koch, C. Müller, O. Zeiter, J. Nuffer, R. Halter, Miniaturized drug delivery system TUDOS with accurate metering of microliter volumes, SENSOR, International Conference on Sensors and Measurement Technology, 16, AMA Conferences (2013) 420–425.

[101] T. Dolzan, D. Vrtačnik, D. Resnik, U. Aljancic, M. Mozek, B. Pečar, S. Amon, Design of transdermal drug delivery system with PZT actuated micropump, 37th International Convention on Information and Communication Technology, Electronics and Microelectronics (MIPRO), Opatija, Croatia, IEEE, 26.05.2014 - 30.05.2014 (2014) 96–99.

[102] J. Wang, Z. Yang, Y. Liu, Y. Shen, S. Chen, J. Yu, The effect of surface wettability on the performance of a piezoelectric membrane pump, AIP Adv. 8 (2018) 45010, http://dx.doi.org/10.1063/1.5017993.

[103] H.K. Ma, R.H. Chen, Y.H. Hsu, Development of a piezoelectric-driven miniature pump for biomedical applications, Sens. Actuators A Phys. 234 (2015) 23–33, http://dx.doi.org/10.1016/j.sna.2015.08.003.

[104] F. Trenkle, S. Haeberle, R. Zengerle, Normally-closed peristaltic micropump with re-usable actuator and disposable fluidic chip, Sens. Actuators B Chem. 154 (2011) 137–141, http://dx.doi.org/10.1016/j.snb.2009.12.069.

[105] Z. Zhang, J. Kan, S. Wang, H. Wang, J. Wen, Z. Ma, Flow rate self-sensing of a pump with double piezoelectric actuators, Mech. Syst. Signal Process. 41 (2013) 639–648, http://dx.doi.org/10.1016/j.ymssp.2013.08.012.

[106] S. Mohith, Karanth P. Navin, S.M. Kulkarni, Performance analysis of valveless micropump with disposable chamber actuated through amplified Piezo Actuator (APA) for biomedical application, Mechatronics 67 (2020) 102347, http://dx.doi.org/10.1016/j.mechatronics.2020.102347.

[107] O. Fuchs, Y. Fouillet, S. Maubert, M. Cochet, C. Chabrol, N. David, X. Médal, R. Campagnolo, A novel volumetric silicon micropump with integrated sensors, Microelectron. Eng. 97 (2012) 375–378, http://dx.doi.org/10.1016/j.mee.2012.04.036.

[108] L. Grünerbel, A. Bußmann, O. Zett, Optimization of micropump flow rate by phase dependent coupling: Hochflussoptimierung von Mikromembranpumpen durch phasengesteuerte Kopplung, Proceedings Mikro System Technik Kongress 2019 (2019) 758–761.

[109] T. Peng, Q. Guo, J. Yang, J. Xiao, H. Wang, Y. Lou, X. Liang, A high-flow, self-filling piezoelectric pump driven by hybrid connected multiple chambers with umbrella-shaped valves, Sens. Actuators B Chem. 301 (2019) 126961, http://dx.doi.org/10.1016/j.snb.2019.126961.

[110] A.F. Doll, M. Wischke, A. Geipel, F. Goldschmidtboeing, O. Ruthmann, U.T. Hopt, H.-J. Schrag, P. Woias, A novel artificial sphincter prosthesis driven by a four-membrane silicon micropump, Sens. Actuators A Phys. 139 (2007) 203–209, http://dx.doi.org/10.1016/j.sna.2007.03.025.

[111] E. Makino, T. Mitsuya, T. Shibata, Fabrication of TiNi shape memory micropump, Sens. Actuators A Phys. 88 (2001) 256–262.

[112] D. Xu, L. Wang, G. Ding, Y. Zhou, A. Yu, B. Cai, Characteristics and fabrication of NiTi/Si diaphragm micropump, Proceedings of the 5th International Conference on Solid-State Sensors and Actuators and Eurosensors III 93 (2001) 87–92.

[113] H.J. Zhang, C.J. Qiu, A TiNiCu thin film micropump made by magnetron co-sputtered method, Mater. Trans. 47 (2006) 532–535, http://dx.doi.org/10.2320/matertrans.47.532.

[114] B. Liu, Z. Zhang, J. Yang, J. Yang, D. Li, An electromagnetically actuated tube type micropump with a one-way valve, JAE 56 (2017) 1–9, http://dx.doi.org/10.3233/JAE-160143.

[115] C. Yamahata, C. Lotto, E. Al-Assaf, M.A.M. Gijs, A PMMA valveless micropump using electromagnetic actuation, Microfluid Nanofluid 1 (2005) 197–207, http://dx.doi.org/10.1007/s10404-004-0007-6.

[116] Y.-H. Wang, Y.-W. Tsai, C.-H. Tsai, C.-Y. Lee, L.-M. Fu, Design and analysis of impedance pumps utilizing electromagnetic actuation, Sensors (Basel) 10 (2010) 4040–4052, http://dx.doi.org/10.3390/s100404040.

[117] R.R. Gidde, P.M. Pawar, B.P. Ronge, V.P. Dhamgaye, Design optimization of an electromagnetic actuation based valveless micropump for drug delivery application, Microsyst. Technol. 25 (2018) 509–519, http://dx.doi.org/10.1007/s00542-018-3987-y.

[118] S. Mi, H. Pu, S. Xia, W. Sun, A minimized valveless electromagnetic micropump for microfluidic actuation on organ chips, Sens. Actuators A Phys. 301 (2020) 111704, http://dx.doi.org/10.1016/j.sna.2019.111704.

[119] M. Mohd Said, J. Yunas, B. Bais, A.A. Hamzah, B. Yeop Majlis, The Design, Fabrication, and testing of an electromagnetic micropump with a matrix-patterned magnetic polymer composite actuator membrane, Micromachines 9 (2017), http://dx.doi.org/10.3390/mi9010013.

[120] V. Tandon, W.S. Kang, T.A. Robbins, A.J. Spencer, E.S. Kim, M.J. McKenna, S.G. Kujawa, J. Fiering, E.E.L. Pararas, M.J. Mescher, W.F. Sewell, J.T. Borenstein, Microfabricated reciprocating micropump for intracochlear drug delivery with integrated drug/fluid storage and electronically controlled dosing, Lab Chip 16 (2016) 829–846, http://dx.doi.org/10.1039/c5lc01396h.

[121] C. Wang, J. Park, Magnetic micropump embedded in contact lens for on-demand drug delivery, Micro Nano Syst. Lett. 8 (2020) 348, http://dx.doi.org/10.1186/s40486-019-0101-x.
[122] J. Ni, B. Wang, S. Chang, Q. Lin, An integrated planar magnetic micropump, Microelectron. Eng. 117 (2014) 35–40, http://dx.doi.org/10.1016/j.mee.2013.11.014.
[123] R. Zengerle, J. Ulrich, S. Kluge, M. Richter, A. Richter, A bidirectional silicon micropump, Sens. Actuators A Phys. 50 (1995) 81–86, http://dx.doi.org/10.1016/0924-4247(96)80088-4.
[124] I. Lee, P. Hong, C. Cho, B. Lee, K. Chun, B. Kim, Four-electrode micropump with peristaltic motion, Sens. Actuators A Phys. 245 (2016) 19–25, http://dx.doi.org/10.1016/j.sna.2016.04.010.
[125] J. Xie, J. Shih, Q. Lin, B. Yang, Y.-C. Tai, Surface micromachined electrostatically actuated micro peristaltic pump, Lab Chip 4 (2004) 495–501, http://dx.doi.org/10.1039/b403906h.
[126] J.J. Pak, J. Kim, S.W. Oh, J.H. Son, S.H. Cho, S.-K. Lee, J.-Y. Park, B. Kim, Fabrication of ionic-polymer-metal-composite (IPMC) micropump using a commercial Nafion, Proceedings of Smart Structures and Materials 2004: Electroactive Polymer Actuators and Devices (EAPAD) 272 (2004), http://dx.doi.org/10.1117/12.539671.
[127] J.J. Loverich, I. Kanno, H. Kotera, Concepts for a new class of all-polymer micropumps, Lab Chip 6 (2006) 1147–1154, http://dx.doi.org/10.1039/b605525g.
[128] T.T. Nguyen, N.S. Goo, V.K. Nguyen, Y. Yoo, S. Park, Design, fabrication, and experimental characterization of a flap valve IPMC micropump with a flexibly supported diaphragm, Sens. Actuators A Phys. 141 (2008) 640–648, http://dx.doi.org/10.1016/j.sna.2007.09.017.
[129] W. Wei, S. Guo, A novel PDMS diaphragm micropump based on ICPF actuator, Proceedings of the 2010 IEEE International Conference on Robotics and Biomimetics (2010) 1577–1583, http://dx.doi.org/10.1109/ROBIO.2010.5723565.
[130] J. Wang, A.J. McDaid, C.Z. Lu, K.C. Aw, A compact ionic polymer-metal composite (IPMC) actuated valveless pump for drug delivery, IEEE. ASME (2017) 196–205, http://dx.doi.org/10.1109/TMECH.2016.2624762.
[131] Y. Wang, T. Sugino, Ionic Polymer Actuators: Principle, Fabrication and Applications, IntechOpen, 2018, http://dx.doi.org/10.5772/intechopen.75085.
[132] Y. Fang, X. Tan, A novel diaphragm micropump actuated by conjugated polymer petals: fabrication, modeling, and experimental results, Sens. Actuators A Phys. 158 (2010) 121–131, http://dx.doi.org/10.1016/j.sna.2009.12.012.
[133] Y. Naka, M. Fuchiwaki, K. Tanaka, A micropump driven by a polypyrrole-based conducting polymer soft actuator, Polym. Int. 59 (2010) 352–356, http://dx.doi.org/10.1002/pi.2762.
[134] K. Kaneto, E.W.H. Jager, G. Alici, H. Okuzaki, Conducting Polymers as EAPs: Applications, 2016, pp. 1–27, http://dx.doi.org/10.1007/978-3-319-31767-0_16-1.
[135] B. Yan, D. An, X. Wang, B.J. DeLong, A. Kiourti, K. Dungan, J.L. Volakis, M. Ma, L. Guo, Battery-free implantable insulin micropump operating at transcutaneously radio frequency-transmittable power, Med. Devices Sens. (2019) 105941G, http://dx.doi.org/10.1002/mds3.10055.
[136] F. Xia, S. Tadigadapa, Q.M. Zhang, Electroactive polymer based microfluidic pump, Sens. Actuators A Phys. 125 (2006) 346–352, http://dx.doi.org/10.1016/j.sna.2005.06.026.
[137] G.H. Kwon, G.S. Jeong, J.Y. Park, J.H. Moon, S.-H. Lee, A low-energy-consumption electroactive valveless hydrogel micropump for long-term biomedical applications, Lab Chip 11 (2011) 2910–2915, http://dx.doi.org/10.1039/c1lc20288j.
[138] Seung-Ki Lee, Fabrication of electroactive polymer actuator composed of polypyrrole and solid-polymer electrolyte and its application to micropump, in: Polypyrrole, Solid Polymer Electrolyte, Parylene, Actuator, Micropump, 2000.
[139] M. Hiraoka, P. Fiorini, J. O'Callaghan, I. Yamashita, C. van Hoof, M. op de Beeck, Miniature conductive polymer actuators for high pressure generation in lab on chip systems, Sens. Actuators A Phys. 177 (2012) 23–29, http://dx.doi.org/10.1016/j.sna.2011.08.024.
[140] D.G. Johnson, D.A. Borkholder, Towards an implantable, low flow micropump that uses no power in the blocked-flow state, Micromachines 7 (2016), http://dx.doi.org/10.3390/mi7060099.
[141] N.A. Hamid, B.Y. Majlis, J. Yunas, A.R. Syafeeza, Y.C. Wong, M. Ibrahim, A stack bonded thermo-pneumatic micro-pump utilizing polyimide based actuator membrane for biomedical applications, Microsyst. Technol. 23 (2016) 4037–4043, http://dx.doi.org/10.1007/s00542-016-2951-y.
[142] Y.-J. Yang, H.-H. Liao, Development and characterization of thermopneumatic peristaltic micropumps, J. Micromech. Microeng. 19 (2009) 25003, http://dx.doi.org/10.1088/0960-1317/19/2/025003.
[143] A. Saren, A.R. Smith, K. Ullakko, Integratable magnetic shape memory micropump for high-pressure, precision microfluidic applications, Microfluid Nanofluid 22 (2018) 1, http://dx.doi.org/10.1007/s10404-018-2058-0.
[144] S. Barker, E. Rhoads, P. Lindquist, M. Vreugdenhil, P. Muellner, Magnetic shape memory micropump for submicroliter intracranial drug delivery in rats, J. Med. Device. 10 (4) (2016) 041009, http://dx.doi.org/10.1115/1.4034576 (6 pages) Paper No: MED-16-1203.
[145] A.R. Smith, A. Saren, J. Järvinen, K. Ullakko, Characterization of a high-resolution solid-state micropump that can be integrated into microfluidic systems, Microfluid Nanofluid 18 (2015) 1255–1263, http://dx.doi.org/10.1007/s10404-014-1524-6.
[146] L. Rodionov, P. Rekadze, Experimental vibroacoustic research of a gear pump made of different materials, Samara, Russia, in: Proceedings of the 3rd International Conference on Dynamics and Vibroacoustics of Machines (DVM2016) June 29–July 01, 2016, 176, 2017, pp. 636–644, http://dx.doi.org/10.1016/j.proeng.2017.02.307.
[147] L.V. Rodionov, P.D. Rekadze, Experimental research into noise emission of a gear micropump with plastic rotor, IOP Conf. Ser.: Mater. Sci. Eng. 302 (2018) 12011, http://dx.doi.org/10.1088/1757-899x/302/1/012011.
[148] Z. Shi, T. Zhao, Y. Wan, X. Zhang, Development of a micropump composed of three gears with Logix tooth profiles fabricated by micromilling technology, Int. J. Adv. Manuf. Technol. 92 (2017) 1507–1517, http://dx.doi.org/10.1007/s00170-017-0219-z.
[149] A. Waldschik, S. Büttgenbach, Micro gear pump with internal electromagnetic drive, Microsyst. Technol. 16 (2010) 1581–1587, http://dx.doi.org/10.1007/s00542-010-1028-6.
[150] V. Iacovacci, I. Tamadon, M. Rocchi, P. Dario, A. Menciassi, Toward dosing precision and insulin stability in an artificial pancreas system, J. Med. Device. 13 (2019).
[151] K.B. Vinayakumar, G. Nadiger, V.R. Shetty, N.S. Dinesh, M.M. Nayak, K. Rajanna, Packaged peristaltic micropump for controlled drug delivery application, Rev. Sci. Instrum. 88 (2017) 15102, http://dx.doi.org/10.1063/1.4973513.
[152] A. Cobo, R. Sheybani, H. Tu, E. Meng, A wireless implantable micropump for chronic drug infusion against cancer, Sens. Actuators A Phys. 239 (2016) 18–25, http://dx.doi.org/10.1016/j.sna.2016.01.001.
[153] Khalil Moussi, Abdullah Bukhamsin, Jurgen Kosel, Implantable 3D printed drug delivery system, Proceedings of Transducers 2019 - EUROSENSORS XXXIII (2019).
[154] DURECT Corporation, iPRECIO Programmable Infusion Pump, 2020 (Accessed 11 November 2020) https://www.alzet.com/iprecio-pump/iprecio-overview/.
[155] M. Herz, M. Richter, M. Wackerle US9410641B2, 2016.
[156] F.S. Huang, J.W. Kan, Z.H. Zhang, Z.H. Ma, S.Y. Wang, G.M. Cheng, Fabrication and performance of a double-chamber serial piezoelectric micropump, AMR 655-657 (2013) 1164–1168, http://dx.doi.org/10.4028/www.scientific.net/AMR.655-657.1164.
[157] B. Yan, B. Li, F. Kunecke, Z. Gu, L. Guo, Polypyrrole-based implantable electroactive pump for controlled drug microinjection, ACS Appl. Mater. Interfaces (2015) 14563–14568, http://dx.doi.org/10.1021/acsami.5b04551.
[158] F. Bianchi, C. Conan US 8,257,308 B2, 2010.
[159] E. Chappel, C. Conan, S. Mefti, F. Cannehan, G.-L. Lettieri, S. Proennecke, L. Zanotti, M. Ferrera, A. Merassi, L. Oggioni, Infusion Micro-Pump Development Using MEMS Technology, HAL Archives Ouvertes, 2012.
[160] E. Chappel, S. Mefti, G.-L. Lettieri, S. Proennecke, C. Conan, High precision innovative micropump for artificial pancreas, Microfluidics, BioMEMS, and Medical Microsystems XII 8976 (2014) 89761C-1–89761C-12, http://dx.doi.org/10.1117/12.2036068.
[161] A. Geipel, A. Doll, F. Goldschmidtboing, P. Jantscheff, N. Esser, U. Massing, P. Woias, Pressure-independent micropump with piezoelectric valves for low flow drug delivery systems, in: 19th IEEE International Conference on Micro Electro Mechanical Systems, Istanbul, Turkey, 2006, pp. 786–789, IEEE, 22-26 Jan.
[162] B. Liu, J. Yang, Z. Zhang, J. Yang, D. Li, A phase change microactuator based on paraffin wax/expanded graphite/nickel particle composite with induction heating, Sens. Actuators A Phys. 275 (2018) 129–136, http://dx.doi.org/10.1016/j.sna.2018.04.006.
[163] P.S. Chee, M.N. Minjal, P.L. Leow, M.S.M. Ali, Wireless powered thermo-pneumatic micropump using frequency-controlled heater, Sens. Actuators A Phys. 233 (2015) 1–8, http://dx.doi.org/10.1016/j.sna.2015.06.017.
[164] P. Woias, Micropumps—past, progress and future prospects, Sens. Actuators B Chem. 105 (2005) 28–38, http://dx.doi.org/10.1016/j.snb.2004.02.033.
[165] C.G.J. Schabmueller, M. Koch, M.E. Mokhtari, A.G.R. Evans, A. Brunnschweiler, H. Sehr, Self-aligning gas/liquid micropump, J. Micromech. Microeng. 12 (2002) 420–424, http://dx.doi.org/10.1088/0960-1317/12/4/313.
[166] S. Chen, Y. Liu, Y. Shen, J. Wang, Z. Yang, The structure of wheel check valve influence on air block phenomenon of piezoelectric micro-pump, Micromachines 6 (2015) 1745–1754, http://dx.doi.org/10.3390/mi6111452.
[167] A. Doll, M. Heinrichs, F. Goldschmidtboeing, H.-J. Schrag, U.T. Hopt, P. Woias, A high performance bidirectional micropump for a novel artificial sphincter system, Sens. Actuators A Phys. 130-131 (2005) 445–453, http://dx.doi.org/10.1016/j.sna.2005.10.018.
[168] M. Richter, J. Kruckow US20100290935A1, 2010.
[169] B.P. Bruno, A.R. Fahmy, M. Stürmer, U. Wallrabe, M.C. Wapler, Properties of Piezoceramic Materials in High Electric Field Actuator Applications, 2021.
[170] M.-H. Cheng, C.Y. Yang, R. Tee, Y.-T. Hong, C.-C. Lu, Efficacy validation of a lymphatic drainage device for lymphedema drainage in a rat model, J. Surg. Oncol. 120 (2019) 1162–1168, http://dx.doi.org/10.1002/jso.25707.
[171] S. Mohith, P.N. Karanth, S.M. Kulkarni, Experimental investigation on performance of disposable micropump with retrofit piezo stack actuator for biomedical application, Microsyst. Technol. 25 (2019) 4741–4752, http://dx.doi.org/10.1007/s00542-019-04414-2.
[172] C. Wang, S.-J. Seo, J.-S. Kim, S.-H. Lee, J.-K. Jeon, J.-W. Kim, K.-H. Kim, J.-K. Kim, J. Park, Intravitreal implantable magnetic micropump for on-demand

VEGFR-targeted drug delivery, J. Control. Release 283 (2018) 105–112, http://dx.doi.org/10.1016/j.jconrel.2018.05.030.
[173] V. Tandon, W.S. Kang, A.J. Spencer, E.S. Kim, E.E.L. Pararas, M.J. McKenna, S.G. Kujawa, M.J. Mescher, J. Fiering, W.F. Sewell, J.T. Borenstein, Microfabricated infuse-withdraw micropump component for an integrated inner-ear drug-delivery platform, Biomed. Microdevices 17 (2015) 37, http://dx.doi.org/10.1007/s10544-014-9923-8.
[174] T.C. Yih, C. Wei, B. Hammad, Modeling and characterization of a nanoliter drug-delivery MEMS micropump with circular bossed membrane, Nanomed. Nanotechnol. Biol. Med. 1 (2005) 164–175.
[175] M.M. Teymoori, E.A. Abbaspour-Sani, A novel electrostatic micromachined pump for drug delivery systems, in: ICONIP' 02. Proceedings of the 9th International Conference on Neural Information Processing. Computational Intelligence for the E-Age (IEEE Cat. No.02EX575), Penang, Malaysia, IEEE, 19-21 Dec., 2002, pp. 105–109.
[176] M.M. Teymoori, E. Abbaspour-Sani, Design and simulation of a novel electrostatic peristaltic micromachined pump for drug delivery applications, Sens. Actuators A Phys. 117 (2005) 222–229, http://dx.doi.org/10.1016/j.sna.2004.06.025.
[177] E. Bertarelli, A. Corigliano, A. Greiner, J.G. Korvink, Design of high stroke electrostatic micropumps: a charge control approach with ring electrodes, Microsyst. Technol. (2011) 165–173, http://dx.doi.org/10.1007/s00542-010-1185-7.
[178] A.J. McDaid, K.C. Aw, E. Haemmerle, S.Q. Xie, Control of IPMC actuators for microfluidics with adaptive "online" iterative feedback tuning, IEEE. ASME (2012) 789–797, http://dx.doi.org/10.1109/TMECH.2011.2135373.
[179] R. Pelrine, Roy Kornbluh, Jose Joseph, Electrostriction of polymer dielectrics with compliant electrodes as a means of actuation, Proceedings of the 5th International Conference on Solid-State Sensors and Actuators and Eurosensors III (1998) 77–85, http://dx.doi.org/10.1016/S0924-4247(97)01657-9.
[180] Eamex Corporation, 導電性高分子アクチュエータ(人工筋肉) (Accessed 26 August 2020) http://www.eamex.co.jp/features/koubunshi/koubunsi/.
[181] R. Zhu, U. Wallrabe, P. Woias, M. Wapler, U. Mescheder, Semi-rigid ring-shaped electrode dielectric electroactive polymer membrane as buckling actuator, J. Micromech. Microeng. 29 (2019) 55001, http://dx.doi.org/10.1088/1361-6439/ab078d.
[182] H. Wiig, R.K. Reed, Rat brain interstitial fluid pressure measured with micropipettes, Am. J. Physiol.-Heart Circul. Physiol. 244 (1983) H239–H246.
[183] A. Waldschik, S. Büttgenbach, Fabrication of internally driven micro centrifugal force pumps based on synchronous micro motors, Microsyst. Technol. 16 (2010) 1105–1110.
[184] H. Gensler, R. Sheybani, P.-Y. Li, R. Lo Mann, E. Meng, An implantable MEMS micropump system for drug delivery in small animals, Biomed. Microdevices 14 (2012) 483–496, http://dx.doi.org/10.1007/s10544-011-9625-4.
[185] A.M. Cobo, H.M. Tu, R. Sheybani, E. Meng, Characterization of a wireless implantable infusion micropump for small animal research under simulated in vivo conditions, Proceedings of IEEE Biomedical Circuits and Systems Conference (BioCAS) (2014) 348–351, http://dx.doi.org/10.1109/BioCAS.2014.6981734.
[186] Khalil Moussi, Mohammed AlDajani, Jurgen Kosel, Miniaturized Drug Delivery System for Biomedical Applications, 2021.
[187] H.C. Zisser, The OmniPod Insulin Management System: the latest innovation in insulin pump therapy, Diabetes Ther. 1 (2010) 10–24, http://dx.doi.org/10.1007/s13300-010-0004-6.
[188] Insulet Corporation, Omnipod Insulin Management UST400 User Guide: Podder's Handbook. 17845-5A-AW Rev B 09/17, 2017.
[189] T.T. Ly, J.E. Layne, L.M. Huyett, D. Nazzaro, J.B. O'Connor, Novel bluetooth-enabled tubeless insulin pump: innovating pump therapy for patients in the digital age, J. Diabetes Sci. Technol. 13 (2019) 20–26.
[190] TOPAS Advanced Polymers, Medical Applications with TOPAS® COC, 2019.
[191] F. Bundgaard, G. Perozziello, O. Geschke, Rapid prototyping tools and methods for all-Topas® cyclic olefin copolymer fluidic microsystems, Proceedings of the Institution of Mechanical Engineers, Part C: Journal of Mechanical Engineering Science 220 (2006) 1625–1632, http://dx.doi.org/10.1243/09544062JMES295.
[192] H. Zisser, L. Jovanovic, Diabetes Care (2006) 2175.
[193] J.E. Layne, C.G. Parkin, H. Zisser, Efficacy of the omnipod insulin management system on glycemic control in patients with type 1 diabetes previously treated with multiple daily injections or continuous subcutaneous insulin infusion, J. Diabetes Sci. Technol. 10 (2016) 1130–1135, http://dx.doi.org/10.1177/1932296816638674.
[194] T. Danne, A. Schwandt, T. Biester, B. Heidtmann, B. Rami-Merhar, H. Haberland, S. Müther, S. Khodaverdi, T. Haak, R.W. Holl, Long-term study of tubeless insulin pump therapy compared to multiple daily injections in youth with type 1 diabetes: data from the German/Austrian DPV registry, Pediatr. Diabetes 19 (2018) 979–984, http://dx.doi.org/10.1111/pedi.12658.
[195] W.S. Lane, S.L. Weinrib, J.M. Rappaport, T. Przestrzelski, A prospective trial of U500 insulin delivered by Omnipod in patients with type 2 diabetes mellitus and severe insulin resistance, Endocr. Pract. 16 (2010) 778–784, http://dx.doi.org/10.4158/EP10014.OR.
[196] D. Bruttomesso, A. Farret, S. Costa, M.C. Marescotti, M. Vettore, A. Avogaro, A. Tiengo, C. Dalla Man, J. Place, A. Facchinetti, S. Guerra, L. Magni, G. de Nicolao, C. Cobelli, E. Renard, A. Maran, Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: preliminary studies in Padova and Montpellier, J. Diabetes Sci. Technol. 3 (2009) 1014–1021, http://dx.doi.org/10.1177/193229680900300504.
[197] W.L. Clarke, S. Anderson, M. Breton, S. Patek, L. Kashmer, B. Kovatchev, Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience, J. Diabetes Sci. Technol. 3 (2009) 1031–1038, http://dx.doi.org/10.1177/193229680900300506.
[198] S. Fournier, E. Chappel, Modeling of a piezoelectric MEMS micropump dedicated to insulin delivery and experimental validation using integrated pressure sensors: application to partial occlusion management, J. Sens. 2017 (2017) 1–7, http://dx.doi.org/10.1155/2017/3719853.
[199] D. Maillefer, S. Gamper, B. Frehner, P. Balmer, H. van Lintel, P. Renaud, A high-performance silicon micropump for disposable drug delivery systems, Technical Digest, MEMS 2001. 14th IEEE International Conference on Micro Electro Mechanical Systems (Cat. No. 01CH37090) (2001) 413–417.
[200] N. Schneeberger, A. Blondel, B. Boutaud, E. Chappel, D. Maillefer, V. Schneider, Disposable insulin pump-a medical case study, DTIP of MEMS & MOEMS (2004) 25–27.
[201] D. Dumont-Fillon, H. Tahriou, C. Conan, E. Chappel, Insulin micropump with embedded pressure sensors for failure detection and delivery of accurate monitoring, Micromachines 5 (2014) 1161–1172, http://dx.doi.org/10.3390/mi5041161.
[202] E. Chappel, R. Allendes, F. Bianchi, G. Calcaterra, F. Cannehan, C. Conan, J. Lefrique, G.-L. Lettieri, S. Mefti, A. Noth, Industrialized functional test for insulin micropumps, Samara, Russia, in: Proceedings of the 3rd International Conference on Dynamics and Vibroacoustics of Machines (DVM2016) June 29, 25, 2011, pp. 795–798.
[203] C. Abe, T. Tashiro, K. Tanaka, R. Ogihara, H. Morita, A novel type of implantable and programmable infusion pump for small laboratory animals, J. Pharmacol. Toxicol. Methods 59 (2009) 7–12, http://dx.doi.org/10.1016/j.vascn.2008.09.002.
[204] Y. Shikida, M. Mizobuchi, T. Inoue, T. Hamada, H. Ogata, F. Koiwa, T. Shibata, Effect of continuous intravenous calcium loading on fibroblast growth factor 23 in normal and uremic rats, Calcif. Tissue Int. 103 (2018) 455–464, http://dx.doi.org/10.1007/s00223-018-0440-2.
[205] F. Streijger, K. So, N. Manouchehri, A. Gheorghe, E.B. Okon, R.M. Chan, B. Ng, K. Shortt, M.S. Sekhon, D.E. Griesdale, B.K. Kwon, A direct comparison between norepinephrine and phenylephrine for augmenting spinal cord perfusion in a porcine model of spinal cord injury, J. Neurotrauma 35 (2018) 1345–1357, http://dx.doi.org/10.1089/neu.2017.5285.
[206] H. Beverungen, S.C. Klaszky, M. Klaszky, M.-P. Côté, Rehabilitation decreases spasticity by restoring chloride homeostasis through the brain-derived neurotrophic factor-KCC2 pathway after spinal cord injury, J. Neurotrauma 37 (2020) 846–859, http://dx.doi.org/10.1089/neu.2019.6526.
[207] S.L. Withey, R.J. Doyle, E.N. Porter, J. Bergman, B.D. Kangas, Discrimination learning in oxycodone-treated nonhuman primates, Drug Alcohol Depend. 207 (2020) 107778, http://dx.doi.org/10.1016/j.drugalcdep.2019.107778.
[208] M.A. Robble, I.L. Holloway, E. Ridener, C.J. Webber, S.B. Caine, E. Meloni, R.I. Desai, W.A. Carlezon, Differential effects of nicotine and nicotine withdrawal on fear conditioning in male rats, Int. J. Neuropsychopharmacol. 23 (7) (2020) 469–479, http://dx.doi.org/10.1093/ijnp/pyaa024.
[209] T. Tan, S.W. Watts, R.P. Davis, Drug Delivery, Enabling technology for drug discovery and development. iPRECIO micro infusion pump: programmable, refillable, and implantable, Front. Pharmacol. 2 (2011) 44, http://dx.doi.org/10.3389/fphar.2011.00044.
[210] 杉浦 博之, 直也 浅井内藤, 建俊哉 稲垣 WO2015173926A1, 2014.
[211] R. Yoda, Elastomers for biomedical applications, J. Biomater. Sci. Polym. Ed. 9 (1998) 561–626, http://dx.doi.org/10.1163/156856298x00046.
[212] Primetech Corp, Performance of iPRECIO®, 2019 (Accessed 11 November 2020) https://www.iprecio.com/technology/tabid/147/Default.aspx.
[213] D. Genoud, P. Christen, F. Robin, H. Thiemer, US9222470B2, 2015.
[214] S. de Haan, Sensile Medical: Preferred by Patients. . . with improved Therapies, ON drugDELIVERY, 2016, pp. 8–12.
[215] H. Thiemer, Mix aus einweg- und wiederverwendbarem teil, MED Eng. (2010) 30–32.
[216] tricumed Medizintechnik GmbH, Tricumed. http://www.tricumed.de/ (Accessed 24 March 2021).
[217] tricumed Medizintechnik GmbH, New Quality of Life for Pain and Spasticity Patients: Complete Solution for Intrathecal Long-term Drug Delivery, 2017.
[218] Z. Daniela, D. Kildal, Medikamentenpumpen und Stimulationsverfahren, in: D. Kildal (Ed.), Medizinische Fremdkörper in der Bildgebung: Kopf, Extremitäten und Wirbelsäule, Springer, Berlin Heidelberg, Berlin, Heidelberg, 2017, pp. 485–519.
[219] E. Chappel, Implantable drug delivery devices, in: Drug Delivery Devices and Therapeutic Systems, Elsevier, 2021, pp. 129–156.
[220] D. Dressler, S. Berweck, A. Chatzikalfas, M. Ebke, B. Frank, S. Hesse, M. Huber, J.K. Krauss, K.-H. Mücke, A. Nolte, H.-D. Oelmann, P.W. Schönle, M. Schmutzler, H. Pickenbrock, C. van der Ven, N. Veelken, M. Vogel, T. Vogt, F.A. Saberi, Intrathecal Baclofen therapy in Germany: Proceedings of the IAB-Interdisciplinary Working Group for Movement Disorders Consensus Meeting, J. Neural Transm. (Vienna) 122 (2015) 1573–1579, http://dx.doi.org/10.1007/s00702-015-1425-1.

Biographies

Agnes Bußmann, M. Sc. received her Bachelor in materials science from Technical University of Darmstadt in 2014 and her Master in Mechanical Engineering from TU Munich in 2017. As a visiting researcher at the Geprovas in Strasbourg, France, she researched on failure mechanisms of vascular endografts. She currently works as a development engineer at the Fraunhofer EMFT and pursues her doctorate work in cooperation with the Institute of Engineering in Life Sciences of the Karlsruhe Institute of Technology. Her research focusses on piezoelectric micro diaphragm pumps and their biomedical application.

Lorenz Grünerbel, M. Sc. successfully graduated at the Technical University of Munich. His topmost degree is a Master degree in Electrical Engineering and Information Technology. Additionally, he received a Bachelor in Management and Technology. During his Master's he already focused on subjects of medical technology at Fraunhofer EMFT. Since March 2018, he works as doctoral student within the field of system development and high flow optimization of Fraunhofer EMFT's micropumps.

Claudia Durasiewicz, M. Sc. graduated at the Technical University of Berlin with a Master in Engineering Science specializing in fluid mechanics. During her studies she worked in the field of medical device development, e.g., studies of flow phenomena in an innovative VAD system. As a visiting scholar at the University of Arizona she investigated plasma-actuation of the flow around an airfoil on a nanosecond scale. She joined the department for Micro Dosing Systems at the Fraunhofer EMFT in 2017. In her doctorate work she focuses on microscale process technologies for micropump and microvalve development.

Thomas Thalhofer, M. Sc. graduated from the Technical University of Munich with a Master degree in Mechanical Engineering. During his studies he was working in the field of medical device development, e.g., building a mechatronic control unit for a snake-like surgical robot and testing and enhancing an innovative heart-assist system. He joined the department for Micro Dosing Systems at the Fraunhofer EMFT as a doctoral student in March 2018 and works as development engineer specialized in pump electronics and system integration.

Dr. Axel Wille studied physics at the University of Bremen (undergraduate) and graduated at the University of Konstanz. He pursuit his doctorate in Konstanz in the field of soft condensed matter. After a short employment as researcher in Konstanz Dr. Wille joined the Physik Instrumente GmbH in Karlsruhe working there for 6 years as application engineer and product manager. Since 2008, he works as scientist at the Fraunhofer EMFT. He researches in the field of micropumps and works in project management of publically funded projects.

Dr. Martin Richter studied Technical Physics at the University of Munich and received his diploma 1992. Together with Roland Zengerle he developed the electrostatically driven micropump in the early 90ies. He finished his doctoral work in the field of microfluidic systems in 1998. Since 2000 he manages the department Micro Dosing Systems at the Fraunhofer EMFT. Together with his team, he develops powerful micropumps made of silicon or metal for various applications with a focus on medical dosing units.