A HIGH-PERFORMANCE SILICON MICROPUMP FOR DISPOSABLE DRUG DELIVERY SYSTEMS

Didier Maillefer, Stephan Gamper, Béatrice Frehner, Patrick Balmer
Department of Microsystems, DEBIOTECH SA. (d.maillefer@debiotech.com), Lausanne, Switzerland
Harald van Lintel, Philippe Renaud
Institute of Microsystems, EPFL (Swiss Federal Institute of Technology), Lausanne, Switzerland

ABSTRACT

This paper describes the design, fabrication and experimental results of a new, low cost, high-performance silicon micropump developed for a disposable drug delivery system. The pump chip demonstrates linear and accurate (±5%) pumping characteristics for flow rates up to 2 ml/h with intrinsic insensitivity to external conditions. The stroke volume of 160 nl is maintained constant by the implementation of a double limiter acting on the pumping membrane. The actuator is dissociated from the pump chip.

The chip is a stack of three layers, two Pyrex wafers anodically bonded to the central silicon wafer. The technology is based on the use of SOI technology, silicon DRIE and the sacrificial etch of the buried oxide in order to release the structures. The result is a small size chip, suitable for cost-effective manufacturing in high volume.

The micropump chip is integrated into the industrial development of a miniature external insulin pump for diabetes care.

INTRODUCTION

Many micropumps recently described in the literature exhibit remarkable performances in terms of high flow rate (> 1 ml/min) and simple fabrication. In particular, the generation of single use, plastic based, valveless pumps demonstrates the validity of this approach. However, there are a number of applications requiring a low, precisely controlled flow rate (typically 10 µl/min). At MEMS’99, we reported on a high-performance micropump chip for an implantable drug delivery system [1]. The device presented here meets similar requirements of accuracy and reliability while achieving a drastic reduction of the manufacturing costs through a new design together with major size reduction and process simplification.

The micropump has been primarily developed for applications in drug delivery. Therefore it has to comply with specifications of accuracy better than ±5% over a wide range of external conditions such as pressure, temperature, viscosity. Being part of the drug’s fluidic path, the micropump chip is defined as a single use device and included into the disposable set with a lifetime ranging from several days to several months depending on the application. Drug pumps are traditionally based on the peristaltic principle (rollers on a elastomeric tube) or a syringe drive. As compared with these pumping mechanism, the use of a silicon micropump offers major advantages in terms of system miniaturization and control over low flow rates. In our case, the dosage resolution (stroke volume 160 nl) is approximately one order of magnitude better than what is achievable with peristaltic or syringe pumps. These high performances make this pump chip particularly suited for critical application of delivery of very potent drugs such as subcutaneous injection of insulin for diabetes care.

Figure1: micropump chip (size 6 mm x 10 mm)

Figure2: Schematic cross section of the pump (not to scale)
DESIGN

The micropump is based on the design published by Van Lintel and al. [5]. The working principle (shown in fig.2) is a volumetric pump with a pumping membrane (1) which compresses the pumping chamber (2). An inlet (3) and an outlet (4) check valves direct the liquid flow. The chip is a stack of three layers bonded together: one central silicon piece with micromachined pump structures sandwiched between two glass pieces, one having fluidic access holes. The actuator has not been integrated on the pump chip, essentially due to space constraints and the design of the pump being relatively independent of the nature and the characteristics of the actuator.

The performance of the pump is mainly determined by the implementation of a double limiter concept. The stroke amplitude of the pumping membrane (1) is mechanically defined by contact of its large mesa (5) to the upper (6) and lower (7) glass plates. By overdriving the actuator and controlling the range of the pumping membrane, the stroke volume is precisely determined and the pump becomes virtually insensitive to inlet pressure, outlet pressure, temperature and viscosity. Moreover this approach also allows for some latitude in the choice of actuator. Provided that the actuator is designed with enough displacement and force, the system can accommodate some tolerances of assembly and drift of characteristics. The actuator has been totally dissociated from the pumping mechanism. It is a single action (push) for the upward movement of the pumping membrane. The downward effect is ensured by the natural spring constant of the diaphragm. In our design, the membrane’s displacement has been set to approximately 20 µm, yielding to a stroke volume of approximately 160 nl.

The pump chip has been optimized for compression ratio. The dead volume has been reduced to a minimum. The resulting compression ratio is: \( \varepsilon = \frac{\Delta V + V_0}{V_0} = 3.3 \) where \( \Delta V \) is the stroke volume and \( V_0 \) is the dead volume. This ratio measures the ability of the pump to compress gas. The channels geometry have also been designed to offer minimum resistance to surface tension in the occurrence of an air-liquid interface. Consequently, the pump has the ability to pump gas, to self-prime and to pump air bubbles through. In addition, the fluid dynamic of the pump has been improved by patterning the thin layer (8) deposited on the glass surface in contact with the silicon pumping membrane, thus avoiding important squeeze film effect.

In order to prevent free flow, the outlet valve is designed with a pretension of approximately 100 mbar obtained by pre-displacement of the valve seat. If required by the application, the micropump can be protected from particulate contamination through the integration of an on-chip barrier filter. The pump fluidic path is then virtually sealed in cleanroom condition as the stack of wafers is bonded. Such an on-chip particulate filter is described in [1].

This micropump chip has been developed for disposable applications. Therefore, acceptable manufacturing costs have been obtained by a drastic reduction of the chip size. The dimensions are now 6 mm x 10 mm, which is a factor 3.2 improvement as compared with the previous implantable pump chip [1].

TECHNOLOGY

The technology is based on the use of SOI (Silicon On Insulator) wafer, silicon DRIE (Deep Reactive Ion Etching) and the sacrificial etch of the buried oxide layer in order to release the structures. This approach brings several major advantages over the more traditional silicon bulk micromachining techniques:

- It permits the design of an original inlet valve (patent pending) optimal in terms of dead volume and process compatibility with the other elements of the pump.
- It represents a major simplification of the process and brings additional design freedom. As a comparison, this process only requires 3 etch steps in silicon and a total of 5 masks while the process of the previous chip required 5 different levels and a total of 12 masks.
- It achieves a very good control over the thickness of the membranes and fluidic channels thanks to the well defined SOI thickness and the etch stop oxide layer, leading to well defined mechanical characteristics. The membranes of the different elements are located on the same side of the wafer and the dead volume is minimized.
- The deep etch with vertical walls of the backside allow high aspect ratio structure and channels and the placement of the different elements in close proximity. It also allows small size circular membranes. As a result, the whole pump becomes very compact.

Extensive process development has been necessary for the dry etch of silicon with an etch stop on oxide. The critical parameters are the etch uniformity and lateral under-etch, given the important etch depth (>300 µm) on the backside and the large distribution of area of the etched structures.

Besides this key technology, the process is also based on Pyrex-silicon anodic bonding for the assembly of the three wafers of the stack. Each of the glass plate has a thin layer of sputtered titanium (8) patterned to prevent bonding of the flexible membranes and to ensure pre-displacement of the pumping membrane and the outlet valve.

With the current design, almost 100 chips are fabricated on a 100 mm wafer, raising to over 200 per 150 mm wafer. Consequently, despite the high initial cost of SOI wafers, the
technology becomes very cost effective for high-volume production (> 1 M units/yr).

The back-end of this chip is very specific to the application. The packaging, fluidic and electrical connections as well as the design of the actuator are being developed with the specifications of the complete drug delivery system.

**EXPERIMENTAL RESULTS**

The present design is currently in the validation phase. The characterization is not complete yet and the following measurement results must be considered as preliminary.

The back-end operations necessary to permit adequate laboratory characterization of the chip simply consists of epoxy gluing the fluidic connectors for standard medical grade PVC tubes.

**Figure 4: Photo of the pump chip with laboratory back-end**

We have successfully implemented various types of actuators: piezoelectric bimorph discs, piezoelectric bimorph cantilevers and direct pneumatic (N₂ pressure) actuation on the back of the pumping membrane. We are also experimenting with electromagnetic and SMA (Shape Memory Alloy) actuation. We have obtained consistent results with various actuation methods, which validates the concept of the double limiter. Also visible on fig.4 is a steel ball glued on the pumping membrane’s mesa. This part serves as a force transmitter between the actuator and the pump in order to ensure a single point contact and a minimum transmission of torque to the membrane.

All measurements of stroke volume and flow rate have been acquired using the gravimetric method with a micro-balance Sartorius MC5 (resolution 1 µg). Pure water has been used for the tests. Pressure variations on the inlet and outlet have been applied by a water column in the range -100 mbar to +100 mbar and by a pressurized water bottle for higher and lower pressure values.

**Figure 5: Photo of the pump with laboratory piezo bimorph cantilever actuator**

- **Stroke volume:** 158 nl

**Figure 6: Plot of the volume of liquid pumped vs. time at a frequency of 0.05 Hz. The acquisition frequency is 1 Hz. The pulsatile nature of the flow rate is clearly visible with a very reproducible stroke volume (standard deviation 1.1 nl)**
**Flow rate**: 0 to 2 ml/hr

**Outlet pressure range**: -100 mbar to + 100 mbar (system specifications)

**Inlet pressure range**: -100 mbar to + 100 mbar (system specifications)

**Leakage**: The leak rate of the pump has not yet been properly characterized. However, tests on functional pumps with pressurized inlet (+50 mbar) and outlet (+100 mbar) have not revealed leak rates higher than 1 µl/h, which is sufficient for the required accuracy.

**Viscosity**: The application require that the chip pumps liquids of various compositions at temperatures ranging from 5°C to 40°C within the nominal accuracy and without compensation table. This can be achieved because of the double limiter concept. This capability was already demonstrated by the previous generation of pump [1] up to 10 mPa s.

**Accuracy**: We expect this pump to meet the required overall accuracy of ±5% within the specified conditions.

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Figure 7: Plot of the stroke volume as function of the actuation frequency. This characteristic shows that the stroke volume is almost constant, i.e. the flow rate is proportional to the frequency up to approximately 3 Hz, corresponding to a flow rate of 1.7 ml/h or a maximum of 2 ml/h in the non proportional range.

Figure 8: Plot of the stroke volume as a function of outlet pressure showing the relative insensitivity towards variations of pressure up to 200 mbar. Note that the upper limit of outlet pressure essentially depends on the power of the actuator. This pump chip has demonstrated consistent stroke volume with pressure up to 1 bar.

Figure 9: Plot of the stroke volume as a function of inlet pressure showing the relative insensitivity towards variations of pressure. Note that the upper limit of inlet pressure depends on the pretension of the outlet valve, after which the pump is in free flow mode.
• **Longevity**: The expected lifetime of this pump chip used in a disposable drug delivery set is limited to a few weeks. However, for alternative applications, this requirement will likely be extended up to one year. Although this longevity has naturally not yet been demonstrated on this chip, we have acquired reliability data for almost two years with the previous generation of pump MIP.

**Figure 10**: Plot of the flow rate stability of the MIP chip [1]. The actuation frequency is 0.05 Hz and the sampling period is one week.

• **Drug compatibility**: The materials in contact with the drug are exclusively silicon, silicon dioxide, pyrex glass and titanium, all known to be biocompatible. For a variety of drugs with a pH ranging from neutral to extreme acid, drug compatibility is ensured as follows:
  - No damage (corrosion) to the device
  - No damage to the PAI (Pharmaceutically Active Ingredient)
  - No release of toxic products in the drug

**APPLICATIONS AND CONCLUSION**

This micropump is the key component of the product in development aiming at the realization of a miniature pump for subcutaneous injection of insulin for diabetes care. The novelty of the system is essentially the level of miniaturization, allowing the patient to carry the pump directly taped onto the skin together with the injection soft needle. The system is conveniently operated from a remote control device through secured RF communication. Additional benefits of the use of MEMS pumping mechanism are the improved safety, resolution, programmability and autonomy. As part of the fluidic path, the micropump chip is fully disposable while the actuator remains together with the control electronics in the permanent pump housing.

Starting from this set of specifications, the pump is adaptable to a wide range of drugs with pH ranging from neutral to acidic. It is particularly suited for very potent drugs such as some peptides requiring accurate delivery at low flow rates. Besides this main application in drug delivery, it is believed that this micropump meets the requirements of a variety of micro-dosing applications such as µ-TAS or Bio-MEMS. We are currently evaluating the use of such micropumps for laboratory automation equipment. An array of pump chips would be assembled for micro-pipetting operations in 96, 384, and 1536 wells microplates.

In conclusion, this development demonstrates the feasibility of a silicon micropump with high requirements of accuracy and reliability, with manufacturing cost compatible with a single use application. This technology is now sufficiently mature to be integrated in a real industrial product development with target commercialization in three years.

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**REFERENCES**


