Concept for a gas-cell-driven drug delivery system for therapeutic applications

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Abstract: This paper presents a concept for an implantable micro-pump based on hydrogen-generating gas cells. The gas-generating cell is separated from the drug reservoir by an expandable latex membrane. The system offers linear drug delivery with flowrates ranging from 8 nl/s to 2 μl/s and a total delivery volume of up to 160 ml. Drugs can be dispensed over a wide backpressure range. The device is scalable based on the size of the gas-producing cell and requires no external energy source. Possible fields of application include *in vivo* local drug delivery for chemotherapy, diabetes, and pain management.

Keywords: implantable pump, drug delivery device, gas cell

1 INTRODUCTION

Implantable drug delivery devices are required to be small, safe, able to accurately deliver nanolitre quantities, reliable, and energy efficient [**1**–**3**]. Piezoelectric membrane pumps have high operating voltages (100–250 V) which limits their use as implants. The current generation of gas-driven pumps that are used in pain therapy are still large and need to have a gas-proof housing to be added so as to protect patients against gas leakage. Linear motors have moving parts that are difficult to miniaturize. The option to use silicon technology with dissolvable membranes has been proposed but the devices based on this technology are currently only in the prototype phase [**4**]. The same problem applies to actuated polymeric valves.

However, there is a strong demand for drug delivery systems. Local drug delivery plays an important role in individualized therapy concepts and is often more effective than established systemic methods. Implantable systems can provide constant levels of medication in the bloodstream or can locally deliver a drug bolus whenever necessary. This makes these drug-release devices important in a wide range of conditions such as individualized cancer therapy, diabetes, and pain management. When these systems are combined with an appropriate sensor unit, they could be used as closed-loop drug delivery systems for treating conditions in a minimally invasive manner over a long period of time [**5**]. Current approaches for that kind of drug dispensing rely on linear actuators [**6**], electrolysis [**7**], or piezo actuators. The use of gas cells in a drug delivery system was described in [**8**]. Gas cells acting as actuators have several advantages compared with other delivery technologies currently under investigation. They require little space, minimal external control electronics, are energy efficient, and are long lasting. With their help, continuous drug flows as well as bolus doses can be achieved. For *in vivo* application, these gas cells need to be characterized more thoroughly. There is also potential for improvement in miniaturization and in separation between the drug reservoir and the gas-generating chamber.

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2 MATERIALS AND METHODS

2.1 Gas cell

The prototype system proposed in this paper consists of a hydrogen-producing cell (Simatec,

Wangen an der Aare, Switzerland), an expandable latex membrane that separates the drug reservoir from the gas-generating chamber, and a custom-made polymethylmethacrylate (PMMA) housing (Fig. 1). These gas cells are normally used as actuators to dispense lubricating solvents into bearings. The gas-producing cell generates hydrogen once the two poles are connected. The impedance R_{out} between the two poles determines the rate of hydrogen production (V in units of milliliters per hour) which can be expressed as

$$V = \frac{448n^2U_0}{R_{out} + nR_{in}}$$

where U_0 is the voltage between the poles of the gas cell, R_{in} and R_{out} are the internal and external resistance of the gas cell, respectively, and n is the number of gas cells. Simatec produces various sizes of gas cells with total volumes ranging from 25 to 950 ml. This allows the system to be scaled to specific needs, giving a wide range of dosing regimens and different medications. In this work 160-ml cells were used in the experiments. The cells do not need any external energy source to operate, making them especially suitable for implantable systems where energy consumption is a major problem. When not in use, the gas cell can retain its functionality for up to several years.

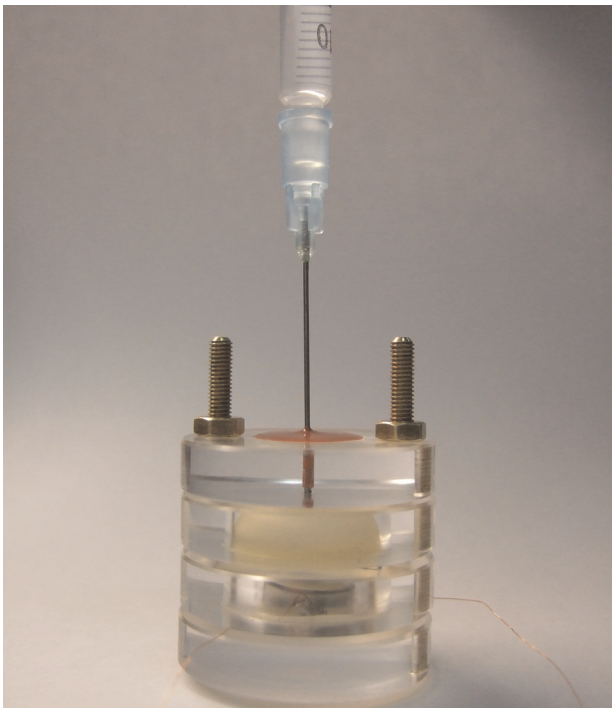

Fig. 1 Prototype system with the latex membrane at maximum displacement. The syringe was used for measuring displaced volume and flowrate

2.2 Latex membrane

In the past, gas-cell-driven systems have often relied on pistons to displace the load. Because static friction has to be overcome before the piston begins moving, controlled and reproducible actuation, especially when working with bolus dosing, can be difficult. Therefore, in this work the piston was replaced with an expandable latex membrane placed directly on top of the gas-generating chamber. The pressure in the gas-generating chamber increases with hydrogen formation, decreasing the volume of the drug reservoir. A syringe needle (with an inner diameter of 0.15 mm) was used as the opening of the drug reservoir.

2.3 Housing

A prototype was made from four PMMA rings with latex gaskets between the individual rings to prevent hydrogen and liquid leakage (Fig. 2). The top ring has a 400-μm diameter opening through which a 0.15-mm inner diameter syringe needle was inserted as the drug dispensing catheter. Two screws fastened the rings from bottom to top. This setup can easily be assembled and disassembled to exchange the gas cell and refill the drug reservoir. It also holds great potential for further miniaturization for implantable systems.

3 EXPERIMENTAL

To characterize the pump, the flowrate was measured at various backpressures and with various resistors between the poles of the gas cell. Distilled water was used as the liquid in the reservoir. It was assumed that the backpressures in the body could reach a value of 300 mbar [**9**]. A water column in a 2.5-m long plastic hose on top of the pump opening was used to simulate these conditions. Backpressures from 0 to 250 mbar could be generated by varying the height of the water column.

A calorimetric flow sensor (GeSim GmbH, Grosserkmannsdorf, Germany) was used for additional flowrate and bolus dose measurements. To assess dosing accuracy and reproducibility, the gas cell was switched on and off at known intervals and the volume dispensed determined after disconnecting the poles. To measure reproducibility and accuracy in bolus mode, a statistical analysis of $n = 12$ individual 5-min pump cycles was performed at 0 mbar backpressure. Another set of measurements was performed to examine the reproducibility and accuracy of bolus dosing at higher backpressures. In

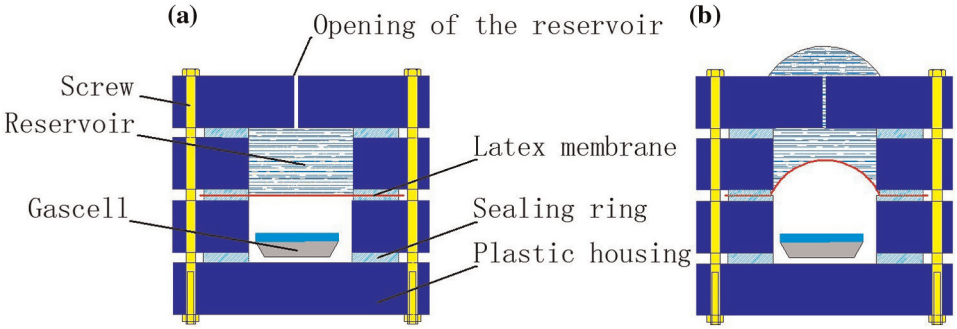

Fig. 2 Prototype of the gas-cell-driven drug delivery system (a) system in the uninflated state and (b) the inflate state (when the cell starts producing hydrogen, the membrane is displaced and squeezes the payload from the reservoir)

that case $n = 5$ individual measurements were performed at four different backpressure levels.

4 RESULTS

4.1 Continuous pumping

The backpressure increased the delay before the pump began dispensing (Figs 3(a) and (b)) and reduced the flowrate. However, linear delivery was possible over the whole backpressure range once the delay had been overcome. Figure 3(a) shows the linear increase of the dispensed volume when using a 33-Ω resistor. The first 50 μl are dispensed non-linearly as pressure builds up (Fig. 3(a)). Figure 3(b) shows the same curve for a 0-Ω resistor. The flowrates are respectively higher. Figure 4(a) shows the dispensed volume for high impedance resistors (2.2 and 3.3 kΩ). The delay before linear delivery is reached is less visible in this case. Figure 4(b) shows the dependency of the flowrate on the backpressure for the 0 and 33 Ω resistors. In both cases for a backpressure of more than 200 mbar the flowrate is one-third that observed without the backpressure.

A total of 14 trials showed linear dependency of the dispensed volume for constant backpressure over time. If there was no backpressure, the flowrate varied from 8 nl/s (3.3 kΩ, 0 mbar backpressure) to 2 μl/s (0 Ω, 0 mbar backpressure) (Figs 3(b), 4(a) and (b)). This is an acceptable range for implantable systems. With backpressures higher than 200 mbar there was a delay of up to 800 s to obtain a constant flowrate (Fig. 3(a)). This may complicate dosing accuracy for small doses and a further flow control unit may need to be integrated into the drug delivery system. For highly varying backpressures, changes in flowrate also have to be taken into account. The best results were obtained with a high resistive load between the two poles of the gas cell (Fig. 4(a)). This minimized the delay times to obtain

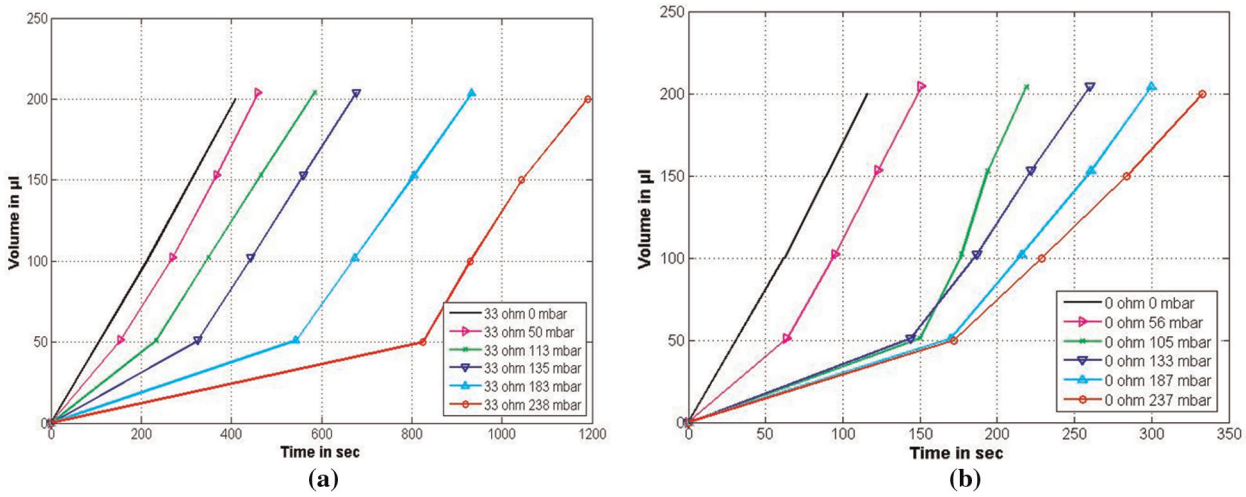

Fig. 3 Effect of different backpressures on volume dispensed when using (a) a 33-Ω resistor (a) and (b) a 0-Ω resistor

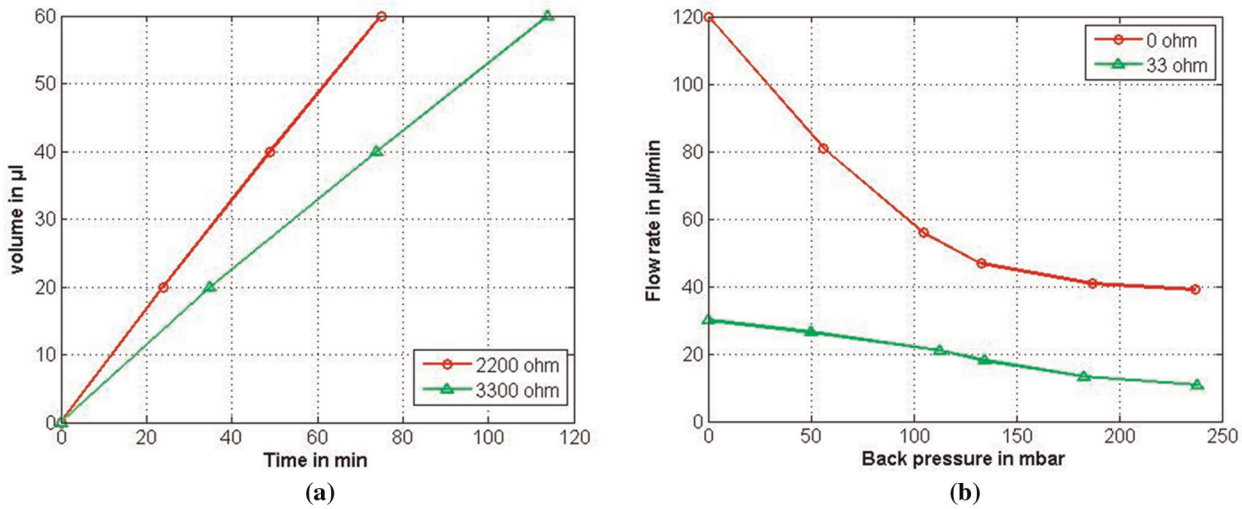

Fig. 4 Effect of high impedance (2.2 kΩ and 3.3 kΩ) between the poles of the gas cell on (a) volume dispensed and (b) change in flowrates with varying backpressures for 0-Ω and 33-Ω resistors

constant flowrates and flow ceased after switching the cell off.

4.2 Pumping accuracy in bolus mode

In the bolus mode, the displaced volume varied between 46 and 55 µ with no backpressure and a 100-Ω resistor (Fig. 5). Excess volume varied between 2.5 and 5.5 µl with a standard deviation of 3.0 µl for the dose and 1.0 µl for the excess volume.

Figure 6 shows the change in the dispensed bolus volume at different backpressure levels. Variability in the amount dispensed decreased as the backpressure increased (Fig. 6). At a 0 mbar backpressure the dispensed volume varied from 97 to 130 µl whereas at 220 mbar the absolute range was between 70 and 77 µl. The standard deviations varied between 15.5 µl (0 mbar) and 1.9 µl (220 mbar). This is a maximum deviation of 13 per cent from the mean value. The total delivered volume decreased from an average of 110 µl at 0 mbar to 74 µl at 220 mbar. These findings indicate that the technique of using the pump in bolus delivery mode is robust to backpressure changes.

5 INTENDED USE IN IMPLANTS AND SAFETY ASPECTS

The possibility of miniaturizing the drug delivery device so that it can be integrated into an implantable closed-loop system for new therapy strategies in cancer and pain management is currently being investigated by the current authors. It is intended that the PMMA rings will be substituted by a cylinder-shaped biocompatible plastic body with an integrated membrane (Fig. 7(a)). The drug-delivery component, sensor, control electronics, and a power supply will be integrated into a hermetically sealed housing made of PMMA or polyetheretherketone (PEEK), see Fig. 7(b). Both PMMA and PEEK have been extensively used as medical implant housings and are considered biocompatible and safe [**10**]. The housing will be subcutaneously attached to body tissue using the incorporated ears (Fig. 7(b)). The walls are thick enough to withstand any pressure increase if the gas cell malfunctions and allows uncontrolled release of hydrogen. However, hydrogen generation is limited because the gas cell can only produce a 160 ml at 0 mbar backpressure and

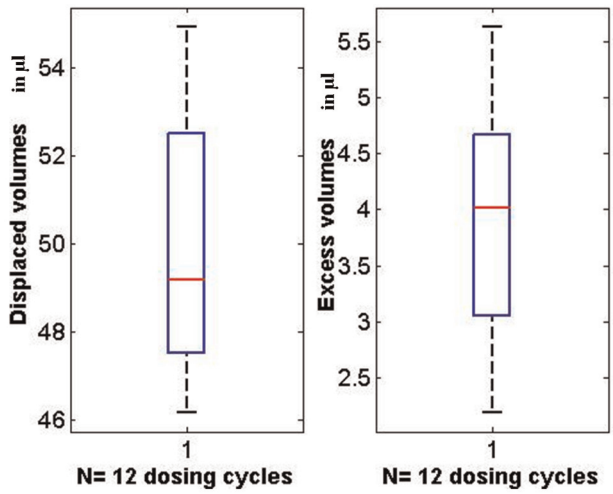

Fig. 5 Boxplot of dispensed volume and excess volume for 5-min bolus dose ($n = 12$ dosing cycles)

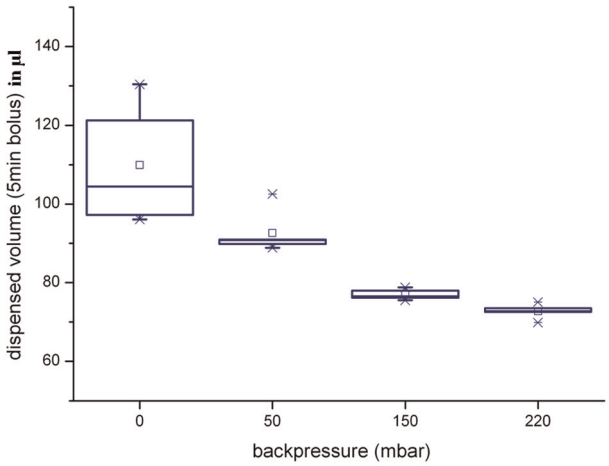

Fig. 6 Effect of backpressure on dispensed volumes for 5-min cycles in bolus mode. Resistor = 33 Ω, $n = 5$ cycles for each backpressure level

20 ◦ C. A passive check valve (LEE Technologies, Westbrook, Connecticut, USA) will prevent backflow of liquid to the pump. Additional steps to increase *in vivo* safety of the device are currently being investigated.

6 DISCUSSION

Experimental characterization of the proposed drug delivery system showed reproducibility in dispensed volumes with standard deviations of less than 13 per cent in bolus mode and only a moderate influence of backpressure changes. Some aspects for *in vivo* safety need further investigation before the technology is used for implantable drug-delivery devices. As hydrogen has a large diffusion coefficient, leakage through the latex membrane and latex gaskets may occur. Small amounts of hydrogen released to the patient's body are unlikely to cause problems but could influence release characteristics and long-term stability of the system. This could be overcome by selecting polymer systems for the housing that have low permeability for hydrogen. The generation rate of hydrogen increases with an increase in temperature. This leads to slightly higher flowrates when using the system in a 37 ◦ C environment. For accurate dosing of small amounts of medication, the effect of backpressure on flowrate also has to be considered. Therefore, integrating a flow control mechanism might be useful. The simplest implementation would be to use active or passive check-valves, which would also prevent possible leakage of medication when the pump is in off-mode or when the backpressure suddenly decreases.

7 CONCLUSIONS

A prototype of a drug delivery system based on a hydrogen-producing gas cell was developed. Backpressure characteristics and achievable flowrates were examined. Reproducibility and accuracy of the technology suggest that the system can be

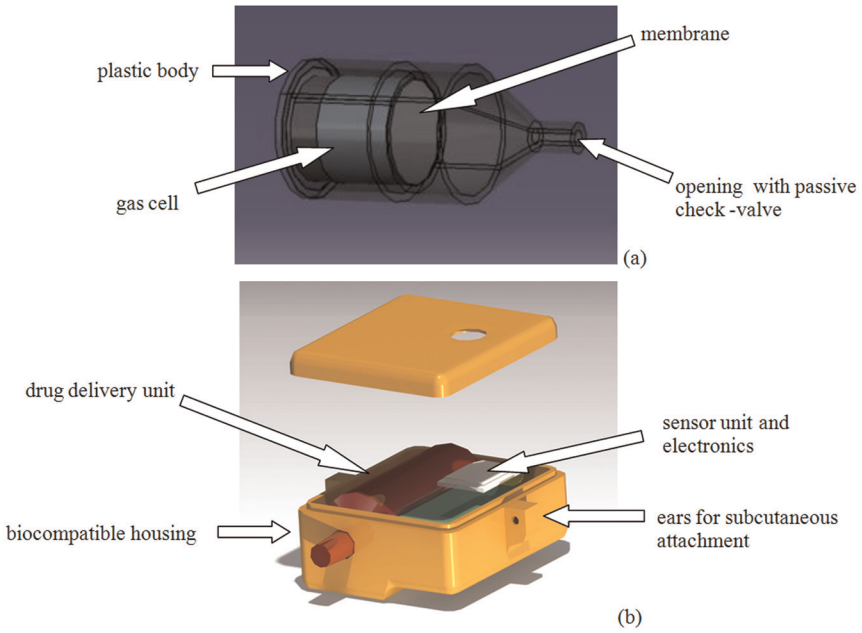

Fig. 7 (a) Miniaturized version of the drug-delivery device and (b) drug-delivery device as part of a closed-loop system incorporated in a biocompatible housing

successfully used for implantable drug-delivery systems. The trials showed that backpressure moderately decreases the achievable flowrates and leads to delays before linear delivery. A high impedance between the poles of the gas cell results in a decrease in the delay and will therefore be used for further experiments. The system seems especially suited for implantable drug-delivery devices since it has a good potential for miniaturization, is reliable, and needs no external energy source. An additional flow control unit might be useful to increase the accuracy of very small bolus doses. The next steps will be to further miniaturize the concept and further improve the dosing accuracy. This could be done with higher impedances, passive flow check-valves or by integrating a flow sensor into the opening of the drug reservoir.

FUNDING

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