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A wirelessly-controlled piezoelectric microvalve for regulated drug delivery

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ABSTRACT

This paper reports a novel wireless control of a normally-closed piezoelectric microvalve activated by a wireless inductor-capacitor (LC) resonant circuit, and enabled by an external magnetic field. The LC circuit is formed by connecting a multilayer coil to a piezoelectric actuator (PEA) that behaves as a capacitor and a resistor in parallel. The LC circuit is activated by modulating the field frequency to its resonant frequency (*fr*) of 10 kHz, which matches the optimal operating frequency of the device, while considering the resonant frequency of the PEA. The working fluid is stored in an 88.9 μL polydimethylsiloxane balloon reservoir that pumps the liquid due to the difference in pressure, which eliminates the need for a pump. The design of the device was optimized using several analytical and experimental approaches. This device was fabricated using a time and cost-effective out-of-clean-room fabrication process. The valving performance was initially characterized in air, then in phosphate buffered saline (PBS) solution to mimic the drug release kinetics into human interstitial body fluids. Maximum flow rate values of 8.91 and 7.42 μL/min are achieved in air and PBS solution respectively, at a maximum input pressure value of ~13 kPa. A programmed short-term delivery of desired liquid volumes in separate batches shows that the volumes are delivered into air and PBS solution with maximum percentage errors of 7.49% and 7.91%, respectively. Additionally, a programmed 3-day long-term reliability test shows that the device was able to achieve desired flow rate values between 160 and 320 μL/day in air and PBS solution with a maximum percentage error of 3.11% and 4.39%, respectively. The results show that the developed device has high potential to be used in drug delivery applications.

1. Introduction

The rapid development of microelectromechanical systems (MEMS)-compatible technologies has provided means to miniaturize microfluidic devices, which are widely used in various biomedical applications. This miniaturization allows microfluidic devices to manipulate small volumes of liquids precisely within a short amount of time. Not only requiring less human intervention and at lower cost, these devices can maintain higher sensitivity and stability compared to traditional fluidic platforms [1]. These characteristics have promoted the integration of the transport, mixing, separation, regulation, analyzing, and delivery of biomedical samples into a single microfluidic device [2]. The integration of the aforementioned operations has led to the development of several technologies, such as drug delivery [3], lab-on-a-chip [4], and micro total analysis systems [2]. Using microvalves is essential in these technologies to perform sealing, on/off switching, and regulating of the fluids flow [5]. Several types of microvalves have been developed to achieve these tasks in different approaches that suit the desired applications. Microvalves can be classified according to their initial mode; normally open, normally closed, or bistable [6]. Among these types, normally-closed microvalves require the simplest fabrication process, while bistable microvalves are preferred in terms of power consumption [7]. Additionally, based on their working mechanism, microvalves are generally categorized as active or passive. Active microvalves require an energy source to actuate mechanical and non-mechanical moving parts, as well as external systems [6]. Active mechanical microvalves are usually operated by coupling a movable membrane to a mechanical microactuator, such as piezoelectric [8], electrostatic [2], and thermal actuators [9], while the non-mechanical microvalves are operated with the aid of smart materials, such as phase change [10] and rheological materials [11]. In addition, active microvalves

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that use external systems are generally operated using modular [12] or pneumatic [1] methods. Contrarily, passive microvalves do not require an energy source to operate (other than that required to promote the flow in microchannels) [13]. They utilize mechanical and non-mechanical moving parts, such as flaps [14] and diffusers [15] that are opened to a forward pressure only. Thus, passive microvalves are a low cost and low power consumption option compared to active microvalves [16]. However, passive microvalves suffer from a lack of efficiency, since the fluid flows in a diode-like manner. The valving efficiency of this type of microvalve depends on the input pressure, which consequently results in poor performance and a leakage flow at low pressure [6]. Active mechanical microvalves have the ability to address these issues, due to their working mechanism and their ability to generate large force values. In addition, they offer a faster response time than the active non-mechanical ones and a smaller size than the active external types [13].

Several design factors need to be considered when developing microvalves for biomedical applications such as drug delivery devices. These factors include the resistance to large pressure and leakage flow, reduction of the power consumption and dead volume, insensitivity to contamination, rapid response time, and linear performance [17]. Numerous researchers have utilized active mechanical microvalves in these devices to address the aforementioned factors. Among the actuators used in this type of microvalve, piezoelectric actuators (PEAs) have been extensively studied due to their high-generated force, high resolution, and fast response time [18,19]. Bonhoeffer et al. [20,21] developed a piezo-actuated microvalve that deposits nanosuspensions onto substrates for personalized oral drug dosage applications. The performance of the microvalve was characterized in terms of the mass flow, dispensing behavior, robustness, and accuracy using 9 drugs that have different fluid properties. The results showed that the microvalve was able to achieve a wide dosage range of 10 μg–100 mg per single dispensing event (1–1000 ms). This corresponds to a steady state mass flow rate in the range of 30–440 mg/s at 20–350 kPa, respectively, with a linear performance for opening times > 10 ms. Thoma et al [8]. presented a piezo-actuated micropump with 2 piezo-actuated microvalves on the inlet and outlet, which was connected to a storage chamber with an elastic membrane. A metering unit was used to control the amount of the dispensed drug during the dosing cycle. Lumped parameter model and experimental results showed that a maximum flow rate and back pressure of 880 μL/min and 10 kPa were achieved using a 20 Hz, −100 to 250 V square wave.

Microvalves used in implantable drug delivery applications require on-board reservoirs to store single or multiple drugs [22]. These reservoirs are usually pressurized using osmotic pressure gradients, gas, material elasticity, or mechanical springs. For instance, Evans et al. [3] developed a device that can be potentially used as an implantable regulator for intrathecal drug delivery. Compressive Elgiloy® springs were used to pressurize a 37 mL polyethylene terephthalate polymer balloon reservoir up to 15 kPa. A PEA microvalve was utilized to regulate the drug dosing of 0.1–0.2 mL/day by throttling the flow from the compressed reservoir, which therefore eliminated the need for a micropump. An on-board battery is used to power up the PEA, piezoresistive pressure sensor, and a control circuit board, which are integrated with the rest of the system within a 113 cm^3 metal casing. The authors then used a similar concept to develop an implantable multidrug delivery system for chronic pain [23]. In this case, two piezoelectric microvalves were used to throttle the flow from two reservoirs that are pressurized with a spring-loaded plate. The 130 cm^3 device was able to deliver the liquids at a flow rate of 2.30–0.51 mL/h and a pressure up to 0.52 kPa/mL from the two reservoirs that have a combined volume of 40 mL.

However, despite the promising features of the reported devices, the ability to miniaturize and implement microvalves in portable and implantable applications is still limited. For instance, pressurizing mechanisms, such as those reported in [3,23] increase the fabrication cost, complexity, and the size of the device. One possible solution is to use the elasticity of certain materials such as polydimethylsiloxane (PDMS) to form a self-pressurized balloon reservoir [24]. Another limiting factor is that the power source used to operate portable and implantable devices is usually limited to on-board batteries or biofuel cells. These approaches are not suitable for long-term operation implants due to the limited lifespan and stability of batteries and biofuel cells [25]. In addition, utilizing such power sources requires consideration of several practical issues, such as the fabrication complexity, device size, and multiple-actuators control. Passive actuators can potentially minimize the size and cost of such systems while maintaining a higher longevity and robustness when compared to active actuators [26]. Moreover, passive implantable medical devices offer less potential risk, a longer interval between replacement surgeries, and require less complicated procedures when it comes to manufacturing and sealing with biocompatible materials [27].

The wireless actuation method has been utilized to potentially address the aforementioned issues in several microfluidic applications, such as a surface acoustic wave implantable passive microvalve [28], a portable sequentially actuated thermal microvalve system [29], multiple shape-memory-alloy actuators control of a microsyringe device [30], a shape memory polymer microactuator for drug delivery [31], a thermopneumatic micropump for biomedical applications [32], and a passive thermopneumatic micromixer for multiple drug delivery [33]. The wireless actuation method offers a good solution to operate microvalves in implantable drug delivery devices. In addition, selective activation of multiple microvalves is possible using this method, which allows multiple drug delivery at different doses and concentrations. This is particularly useful for several clinical applications, such as treatments for Parkinson's disease, diabetes, and glaucoma [30]. Furthermore, the development and testing of multiple drugs in a single implantation using one animal is also possible using this approach [34].

This paper presents a novel wirelessly controlled piezoelectric microvalve to address the above-mentioned issues. Valving is achieved using a normally-closed microvalve that efficiently controls the flow of the working fluid, which is stored in a pressurized balloon reservoir. The fluid is pumped due to the pressure inside the reservoir, which is opposed by the pressure generated by the microvalve. The resonant frequency (f_r) used in the wireless power transfer (WPT) process was carefully selected to match the operating frequency (f_o) of the device while considering the resonant frequency of the PEA. WPT, piezoelectric actuation, reservoir pressure, fluid flow, and valving performances were analytically presented and experimentally verified as a demonstration of the proposed valving technique. The valving performance is initially characterized in air then in phosphate buffered saline (PBS) solution to mimic the drug release kinetics into human interstitial body fluids. The activation switching time of the microvalve is varied to achieve different flow rates over different periods of time. The performance of the device is investigated over low flow rates that are within the typical range of implantable drug delivery devices [3]. Programmed short-term delivery and 3-day long-term reliability tests are carried out to investigate the valving performance of the device. The results suggest that the developed microvalve is a biocompatible potential candidate, and the proposed concept can possibly be used in biomedical applications such as drug delivery devices. In addition, the proposed device can be fabricated using a