31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Design and Fabrication of a Low Cost Implantable Bladder Pressure Monitor

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***Abstract*—In the frame of the Flemish Community funded project Bioflex we developed and fabricated an implant for short term (< 7 days) bladder pressure monitoring, and diagnosis of incontinence. This implant is soft and flexible to prevent damaging the bladder's inner wall. It contains a standard flexible electronic circuit connected to a battery, which are embedded in surface treated silicone to enhance the biocompatibility and prevent salt deposition. This article describes the fabrication of the pill and the results of preliminary cytotoxicity tests. The electronic design and its tests, implantation and the result of the in-vivo experimentation will be presented in other articles.**

I. Introduction

In the frame of the Flemish Community funded project called Bioflex [1], research has been focused on the development of biocompatible, flexible and stretchable, electronic systems for implantation, based on PDMS substrates. This project is based on a consortium of universities and research groups. Within this consortium, the MICAS group of the Katholieke Universiteit Leuven is responsible for the design of the electronics. The CMST group of the University of Ghent is responsible for the technology development. The PBM group of the University of Ghent is responsible for the material development, and especially for the PDMS surface modification. The Histology group of the University of Ghent is responsible for the in vitro cytotoxicity tests and in vivo experimentations. The Bioflex consortium is also working with the faculty of veterinary medicine of Ghent for in-vivo implantation.

This article will be focused on a short part of the project, which is the development of a low cost flexible implantable pill for short term (7 days) pressure monitoring inside the bladder. Development of stretchable electronics has been described in several articles [2, 3]. Moreover, this article is a short introduction presentation of the implantable pill. Specific parts of the process: detailed description and results will be published afterwards.

The development of the implantable pill is done in four phases: electronic system development and tests of functionality, fabrication and encapsulation in PDMS, surface modification, and toxicology tests.

II. Methodology

In order to monitor during a short term the pressure inside the bladder for diagnostic purposes of urinal or nephrological disorders [4], the idea is to install a pill shaped implant inside, to record the pressure during one week, and then to recuperate the pill, for data analysis by the doctor [5]. The idea is to develop a low cost implant, using standard and available technologies, biocompatible enough to be inside a bladder during 7 days. As the bladder is a very stretchable organ, the implant should have a smooth surface and be conformable enough not to harm the bladder inner wall when its volume is minimal. When the bladder is filling with urine, the device can float.

This implant is pill shaped in order to enable introduction in the bladder via catheterization. For smooth passing of the catheter through the urethra, the diameter of the catheter may not exceed 7 mm, so the inner diameter of the catheter is maximal 5 mm. This anatomic restriction causes limitations to the electronic design. Fitting as many functions as possible within a maximum diameter of 5 mm, the maximal internal diameter of urinary catheters. The length of the pill is not as critical, however the smaller the better. As a trade-off between implement ability and need-for-space, a length of 40 mm has been defined. Different shapes of the implant have been tested (pill shape, pill with flaps to extend the surface of the pill, pill with whiskers to avoid undesirable evacuation), however the basic form of the implant is a pill shape, as it is the easiest to implant using a catheter.

Two solutions for the electronic system were possible. In the first solution, the pill has no battery, and it is powered using an inductive link. This inductive link is also used for communication [6]. However, the position and the orientation of the implant in the bladder are always changing. So in order to have a correct coupling between the implant and the outside, a 3D inductive coil should be set between the inside and outside the bladder, which is not a convenient solution for the patient, and is also volume consuming for the implant. The second solution is to integrate a battery and a memory in the implant. Therefore communication is not possible during the implantation; it is not possible to control the functionality or the data during experimentation. Moreover a battery is highly volume consuming, capacity is limited, and no flexible battery with enough capacity exists yet. A mixed solution which consists

in a battery and a communication system is even more volume and power consuming, even though it would be the ideal solution.

The sensor is a key part of the device. It should be protected from the fluids while it should be able to sense the pressure. The protection should hence be as minimal as possible. Therefore a window is created in the encapsulation, in order to cover the sensor with just a 100 µm thin PDMS membrane. A surface treatment of the PDMS is needed to enhance the biocompatibility and to prevent the deposition of salt on its surface. This is especially crucial for the membrane, since salt deposition could affect its mechanical properties.

III. Result

A. Electronic Design

The electronic design of this application was done taking into account the following rules: everything must fit into a 5 mm diameter capsule with a length of 40 mm including the battery; data must be stored on a memory module and read out after extraction of the implant; and the power from the battery must be able to be switched off and on between encapsulation in PDMS and implantation of the device.

The block diagram of the bladder pill is depicted in Figure 1. The device uses a surface machined capacitive absolute pressure sensor from MicroFab (E1.3N). Its range (0.5 to 1.3 bar) and size are perfectly suited for the application. This signal is digitized by a capacitance–to–digital converter from Analog Devices (AD7153). The CDC is a dedicated IC configured and controlled through I^2C. To conserve as much power as possible, it is set to single conversion mode in a range of 0.25 pF.

The backbone is a microcontroller unit (MCU) adding intelligence to the device. The choice in MCU involves an important trade-off: the physical size must be as small as possible, yet this comes with limited functionalities and programming memory. The PIC10F206 from Microchip was selected mainly for its tiny SOT23 package. Its sole useful (for this application that is) functionalities are: an on board clock oscillator and an 8 bit timer. All other needed functionalities: time tracking, configuration of the CDC at start-up, I^2C communication and the processing and storing of the results, are implemented in its 512k program memory. The MCU will fetch a CDC result every 500 ms. Data will eventually be stored in an EEPROM memory of 16 Kbit, which was selected for it also uses I^2C, and its miniature size in a 5 pin SOT23 package. It is because of this limited memory the MCU must first process the results.

A data result of 16 bits will contain only 5 bits of pressure data and 11 bits of timing data. Focus was shifted from pressure accuracy to time because in this first stage, pressure measurements do not need to be accurate, making sure that more data can be stored. Since the expected bladder pressure remains the same for long periods, this would make sure that in an ideal case where 2^{11} consecutive pressure samples, covering 1024 s of the same pressure reading, will only take up 16 bits of data.

Power to all components comes indirectly from a 3 mm diameter pin-type lithium battery with a body of 13 mm. Its capacity is a mere 13 mAh. To conserve power between production and implantation, a magnetic switch circuit is introduced with a reed switch and a D-Flip-Flop. A 0603-size LED is also used to signal the on and off state of the device.

Both measuring and power switch circuitries were then fitted onto a double-sided flex sizing 4.2x18 mm^2. From this circuit file, the component outlines were put into AutoCAD to help the production of the moulds for the actual fabrication, which will be discussed later. This AutoCAD design is shown in Figure 2. It also gives a general idea on how the pill will look like and what the relative sizes of the different components are.

The microcontroller is programmed before soldering it on the flexible substrate. When the implant is switched on, a LED is blinking and the microcontroller takes pressure measurements during 8 seconds, and then switches to sleep mode for 5 hours. Then it starts taking a pressure measurement once every 0.5 seconds until the memory is full or the battery depleted. The data are then recovered after extraction of the pill by reading directly the EEPROM.

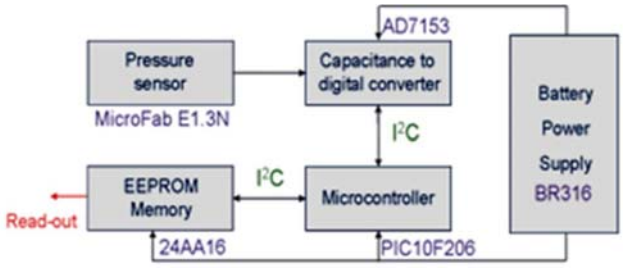

Figure 1 Block diagram of the bladder pill. Power is distributed to CDC, MCU and EEPROM. Communication between the latter three follows the I^2C protocol.

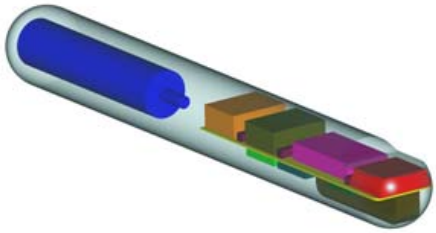

Figure 2 3D-Model of the bladder pill showing the battery (blue) and circuitry on flex containing the sensor (red) in a pill measuring ø 5 mm x 40 mm. Switching is done with a DC magnet actuating a reed switch (bottom brown).

B. Fabrication of the implant

From the electronic design layout, the photolithographic masks are edited for the fabrication flex. At first, a polyimide substrate coated on both sides with copper (UPILEX, 25 µm of polyimide, 9 µm of copper on both sides) is laser drilled to define the vias and the alignment marks). Then, a superficial layer of copper is electroless plated to make the vias conductive. Then, copper is

electroplated to obtain a total additional copper layer of 10 µm on both sides and in the vias. The following step is to process lithography on both sides, and copper is etched in $CuCl_2$ based etchant. The result of this step is shown in Figure 3 (top). After stripping in NaOH, a solder mask (ELPEMER SD 2463 Flex HD) is screen printed and cured followed by an electroless plating of a Ni/Au finish. This is shown in Figure 3 (middle).

The second step in the fabrication is the soldering of the components. A lead free solder paste (Delphine, SnAg(3%)Cu(0.5%)) is dispensed on the pads, components are placed and soldering is done in a reflow oven at 270 ºC. The result of this step is shown in Figure 3 (bottom). After soldering the two sides, the flex is cut off the substrate using a YAG laser. After functionality testing, the flexes are ready to be encapsulated.

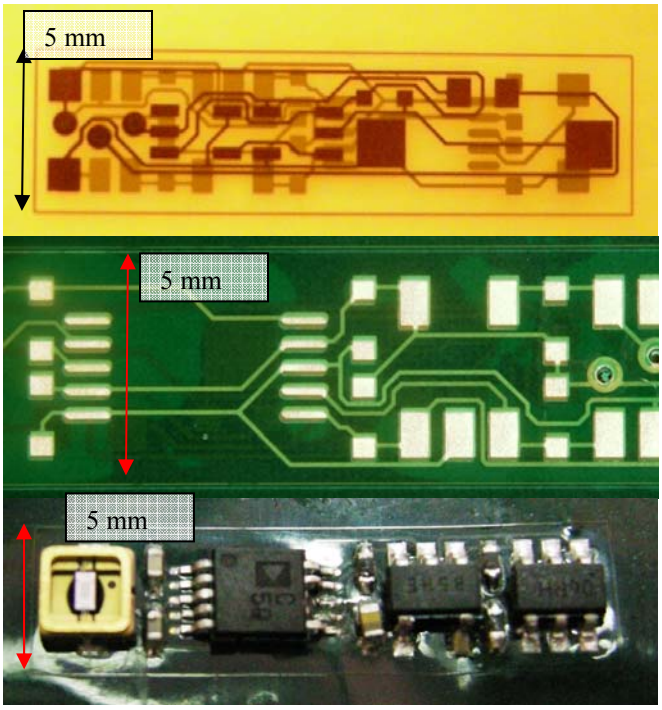

Figure 3 Fabrication steps of the flexible electronic substrate: after copper etching (top), after applying the solder mask and deposition of Ni/Au (middle) and after components soldering (bottom).

From the 3D model (Figure 2), the injection mould for the external shape of the implant and of the Teflon holder to fixate the system during moulding are designed in AutoCAD. The mould is fabricated from transparent PMMA to control the injection and to avoid any air bubble formation. The tool used to fabricate the mould is a digital milling machine. The smoothness of the mould was measured with a WYKO laser profilometer and was determined to be 13 µm. In order to fixate the flexible substrate and the battery during the moulding, a Teflon holder was processed in the same way. The precision of the Teflon holder is crucial to obtain a correct positioning of the sensor in the pill. A precision of 50 µm is obtained. Then tests to check the mould are performed, in order to control the thickness of the membrane on the top of the sensor. The thickness varies from 76 µm to 170 µm. As there is no sufficiently small battery connector, we are using a copper filament with a 40 µm diameter wrapped tidily around the battery and soldered with lead free solder. The battery is then soldered to the flex using these wires. The implant is put into switched-off state and then dipped in ethanol to be cleansed, dried at room temperature during 1 hour, and then it is dipped in biocompatible adhesion promoter (NUSIL MED6-161). After 45 minutes, the adhesion promoter is hydrolyzed enough and the system (flex and battery) is glued on the holder with MDX 4210 Biocompatible silicone rubber from Dow Corning. The glue is cured at 40 °C during 4 hours to avoid any thermal deformation of the mould and to avoid overheating the battery. The top of the system is coated again with the adhesion promoter using the same process. The top mould is then set on the holder and screwed tidily. Fully degassed MDX 4210 biocompatible PDMS is then injected using a syringe and a vacuum pomp to remove any entrapped air during the injection avoiding air bubbles.

The PDMS is then cured at room temperature during 24 hours. Afterwards, the holder is removed, and as the adhesion Silicone/PMMA is higher than the adhesion Silicone/Teflon, the moulded system stays in the top mould.

To enhance wet ability of the silicone, the moulded system is plasma treated (low pressure air plasma, 0.8 mbar air, 197 W, 30 s). To enhance the adhesion Silicone/silicone, the surface is coated with the biocompatible adhesion promoter using the same process. After sealing the bottom mould to the top mould, MDX 4210 is injected in the bottom mould. After 24 hours of curing at room temperature, the pill is un-moulded, the overflowed PDMS cut off with a sharp scalpel and the pill is cleaned in ethanol and its functionality is tested again.

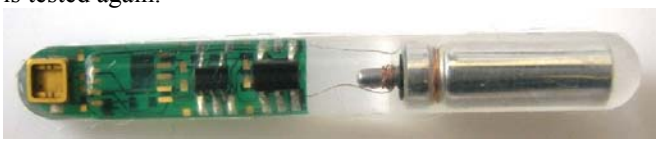

Figure 4 Implant after encapsulation in MDX 4210 PDMS. A partially soldered flex (left) is connected to the battery (right) with a copper wire.

C. PDMS surface modification

After cleaning in ethanol, the implant is prepared for surface modification, in order to increase biocompatibility and prevent salt deposition. The methodology used is the deposition of AMPS (Sodium 2-acrylamido-2-methylpropyl sulfonate) using a double plasma treatment. It consists of two subsequent treatments (Figure 5). In the first step, the PDMS film is treated with oxygen (or argon) in order to increase surface wet ability. In the next step, the pre-treated films were immersed in a monomer solution (1 M) followed by drying at ambient conditions. Afterwards, these films were treated a second time with oxygen (or argon) plasma to obtain polymerization of the adsorbed vinyl monomers. AMPS is reported to have a high thermal stability, high hydrolytical stability, a good water solubility, antimicrobial properties and heparin like properties [7]. The AMPS

grafting methodology will be reported in more detail in a forthcoming article.

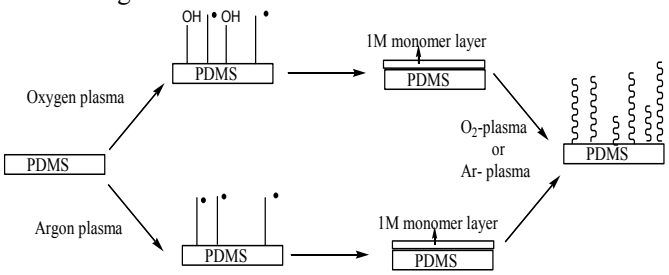

Figure 5 Schematic overview of the two steps of double plasma treatment of the PDMS surface. Either path can be taken choosing either oxygen or argon for the treatment.

D. Toxicity test

In order to control the biocompatibility (i.e. the presence of toxic leachables) of the implant (materials + process), cytotoxicity tests of 8 days are performed in triplicate, with the extraction products of the silicone materials in a culture medium, following the ISO 10 993-1 guidelines.

The samples were first sterilized by ethylene oxide gas and extracted, after being placed in 2.5 ml Hank's medium with 10 vol% fetal bovine serum at 37°C in a tube in a shaker for 8 days. This medium was subsequently added to a sub confluent cell layer of primary derived chicken embryo fibroblasts. 24 hours later, the influence of the extraction products on the cell viability was evaluated with the MTT assay. The mitochondria of viable cells reduced this MTT tetrazolium salt into a formazan product. After dissolving the formazan in isopropanol/HCl with 1% Triton X100, the absorbance could be determined spectrophotometrically (λ=580 nm). This absorbance value is proportional to the number of viable cells and can be compared to the absorbance value of control cell culture without contact with the extraction medium.

6 samples of the pill implant were tested: 2 samples containing only a battery (Battery A-B), 2 samples containing a battery and flex (Flex A-B) and 2 samples containing battery + flex + components (Components A-B). The vialibity of the samples are shown in Figure 6 and ranges from 78% to 98%.

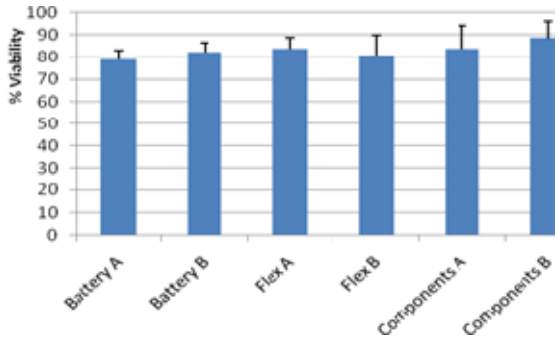

Figure 6 In Vitro biocompatibility tests of the implant. The viability rate of the cells compared to a control sample (in %) are shown for the different test samples.

Therefore it shows that the implant is not toxic for an implantation of 7 days in the bladder. Deeper analyses (sensibilisation, geno toxicity, …) will be reported in forthcoming articles.

IV. Discussion

We have been able to produce a biocompatible, soft and flexible implant to measure the pressure in the bladder, using standard PCB technologies and PDMS encapsulation. Details about functional tests of the electronic circuits, in-vivo experimentations and biological aspects of the implant will be presented later.

The production of this implant is low cost, as it uses only standard PCB technologies and commonly available components. The biocompatibility is limited to 7 days which is sufficient for a diagnostic implant. To reach this biocompatibility, the implant is embedded in a PDMS rubber (MDX 4210 from Dow Corning). Post implantation biological analysis is needed to prove the biocompatibility of this implant. Biological analysis will have to prove the biochemical and biological compatibility, as well as the mechanical compatibility: the bladder must not be harmed by the implant.

V. Conclusion

This implant is a demonstration that low cost biocompatible implants can be produced for short term implantation for diagnostic purposes. Several improvements can still be made: reducing the volume to ease the implantation i.e. through smaller catheters, improving the power management to increase the storage and working time, using bare chips instead of packaged chips to reduce the volume of the implant. However designing an implant for short term diagnostic purpose is a trade-off between volume, cost and functionality.

Acknowledgment

This research has been developed in the frame of the research program BIOFLEX, an IWT funded project in the frame of the SBO (Strategic Basic Research), contract number IWT-040101.

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