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ORIGINAL ARTICLE

Minimally invasive diagnostics and treatment using micro/nano machining

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Abstract
Several medical tools with various functions have been developed for minimally invasive diagnostics and treatment. Microfabrication techniques such as MEMS technology are useful for the realization of high-performance multifunctional minimally invasive medical tools with small sizes. An ultra-miniature pressure sensor and an intravascular ultrasonic forward-viewing imager have been developed as microsensors for use in the human body. Active bending catheters have been developed for steering catheter tips without using traction of wires from outside the body. An ultrasonic therapeutic tool for sonodynamic therapy and sonoporation, and a micro scanner for precise laser treatment have been developed as therapeutic tools for use in the human body. High-functionalized endoscopic tools and catheters will enable more precise and safe diagnostics and therapy, as well as novel diagnostics and treatment which have been impossible to date.

Key words: *Minimally invasive treatment, micromachining, MEMS, catheter, endoscope*

Introduction

Medical tools for use in the human body, such as catheters and endoscopic tools, need to be thin or small. With the progress of minimally invasive diagnostics and treatment techniques and the increasing number of their applications, these medical tools must not only be thin or small, but must also be capable of performing several functions. To meet these demands, microfabrication techniques such as MEMS (Micro Electro Mechanical Systems) technology, in addition to new material technology, are effective. MEMS is a technology which deals with the fabrication of mechanical structures on silicon wafers using integrated circuit (IC) processing techniques, such as photolithography and silicon etching. A MEMS device can incorporate several functions, such as sensor, actuator, and microelectronics. We have developed several microsensors and microactuation systems for mounting in intravascular and endoscopic medical tools for the realization of high-performance and multifunctional minimally invasive medical tools.

Active catheter and active guide wire

Active catheter

Active catheters and active guide wires which incorporate microactuators at their tips and are controlled from outside the body have been developed (1). These actuators, which incorporate Ti–Ni Shape memory alloy (SMA) microcoils, are capable of several motions such as torsional and extending motions. The actuation method and actuator mechanism design are relatively simple, since when the wire diameter of the coil is small (*e.g.* 50–100 μm), the coils can be actuated by the direct flow of electrical current through the SMA with no heater or cooler. A bias spring made of metal such as stainless steel restores the catheter shape and enables repeatable motion. By keeping the SMA microcoil

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actuator, which generates heat, separated from the catheter surface, the catheter can be actuated with a sufficiently low surface temperature to be safe in the human body. One application of the active bending mechanism is the bending of a long intestinal tube. Intestinal obstruction (ileus) is a serious passage disorder in the intestines, which is often treated nonoperatively by the insertion of a long intestinal tube made of silicone rubber into the intestine, followed by depressurization by continuous suction from outside the body. A doctor inserts the tube into the patient's nasal cavity and pushes it forward from outside the body, while monitoring its position using x-ray fluoroscopy. It is difficult to maneuver the tube through the lower opening of the stomach (pylorus) due to its narrowness. For precise manipulation of the tip of the tube, a 40 mm long unidirectional active bending mechanism using an SMA microcoil actuator is mounted in the tube for easy passage through the pylorus as shown in Figure 1. This tube can also utilize gravity to facilitate manipulation of the tip by incorporating stainless steel weights at the tip as a conventional manipulation method. The external diameter of the bending part is approximately 6 mm. Its bending angle is controlled by changing the duty ratio by pulse width modulation (PWM). Bending characteristics are shown in Figure 2. The maximum bending angle is 110° and the radius of curvature is 20 mm (2). An active bending electric endoscope using SMA microcoil actuators has also been developed not only for intestinal use but also for inspection within the abdominal cavity as shown in Figure 3. A CCD (charge-coupled device) imager (410,000 pixels) is mounted at the end of the endoscope, and the tip has an omni-directional bending mechanism using three SMA coil actuators (3).

Microfabrication technology of shape memory alloy (SMA)

A new batch fabrication process for the creation of flat meandering SMA microactuators from

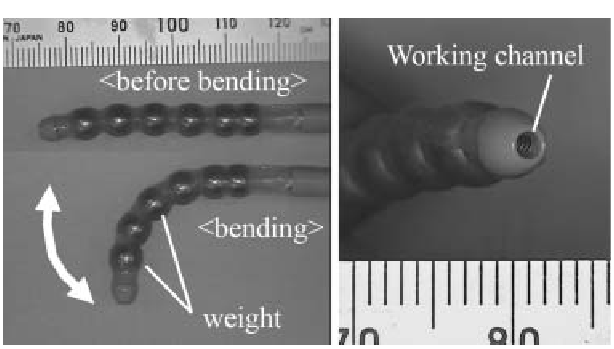

Figure 1. Active bending long intestinal tube.

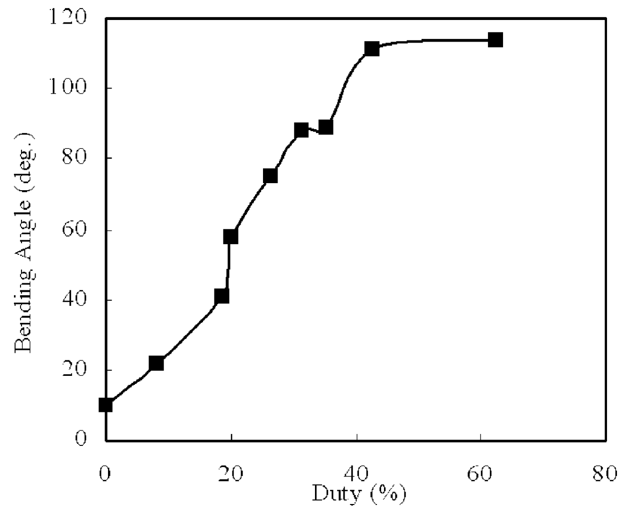

Figure 2. Bending characteristics.

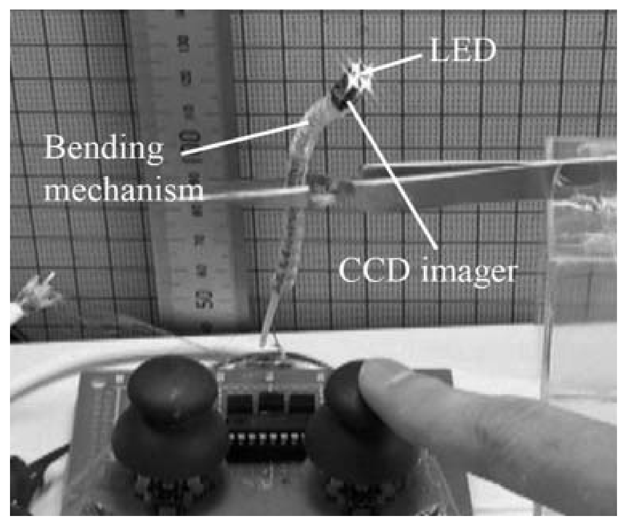

Figure 3. Active bending electric endoscope using SMA microcoil actuators.

40–50 μm thick Ti-Ni alloy sheets or small diameter Ti-Ni alloy tubes using electrochemical pulsed etching has been developed (4). An active bending guide wire 0.5 mm in outer diameter (described below) uses a microactuator fabricated by this method. To simplify the assembly process of the SMA actuators, three meandering actuators are formed from an SMA tube using photolithographic resist patterning and electrochemical etching as shown in Figure 4. Alternatively, the use of femtosecond laser ablation allows micromachining of memorized SMA with no deterioration of its shape memory effect, since the laser pulse width is very short (10^{-15} s), such that heat generation is sufficiently reduced during laser machining. Several designs of SMA microactuators can be realized with laser machining (5).

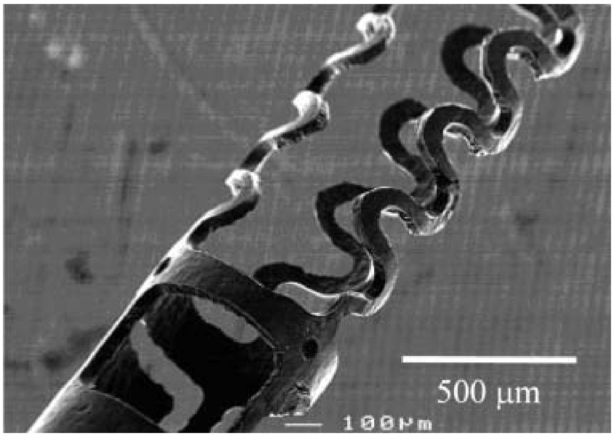

Figure 4. SMA actuator fabricated from Ni-Ti tube using photolithography and etching (external diameter: 0.5 mm).

Active bending guide wire

An active bending guide wire 0.5 mm in outer diameter has been developed. This device incorporates a Ti-Ni meandering SMA actuator, which bends unidirectionally by supplying electrical current to the SMA as shown in Figure 5 (6). Several applications for this device are expected, such as the recanalization of chronic total occlusion in blood vessels. Although the tip of the guide wire bends in unidirectionally, omnidirectional insertion can be performed by rotating the wire from outside the body. It is preferable that the external diameter of the tool be <0.35 mm (0.014 inch) for several intravascular surgical procedures.

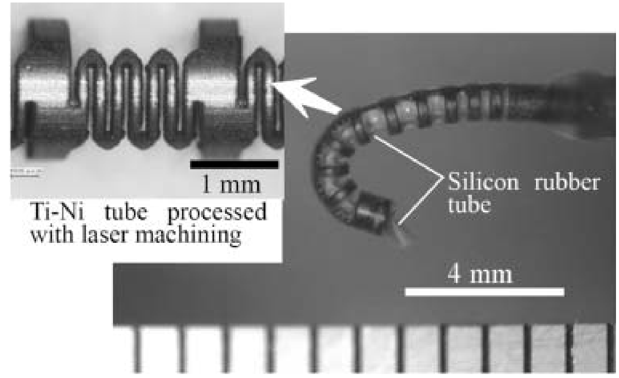

Figure 6. Hydraulic active bending catheter.

Hydraulic active bending catheter

A small diameter active bending catheter, with a bending motion controlled by suction of liquid in the catheter, has been developed (Figure 6) (7). The catheter is made of a Ti-Ni super elastic alloy (SEA) tube which is processed by laser micromachining, and a silicone rubber tube which covers the outside of the SEA tube. The active catheter is filled with water and its bending angle is controlled from outside the body by suction of the water. The tip of the silicone rubber tube functions as a valve and closes by initial suction of the water, and the catheter is bent by subsequent suction. The bending angle can be controlled by regulation of suction. In the processed SEA tube, a line of rings is connected with meandering beams to allow a large bending angle.

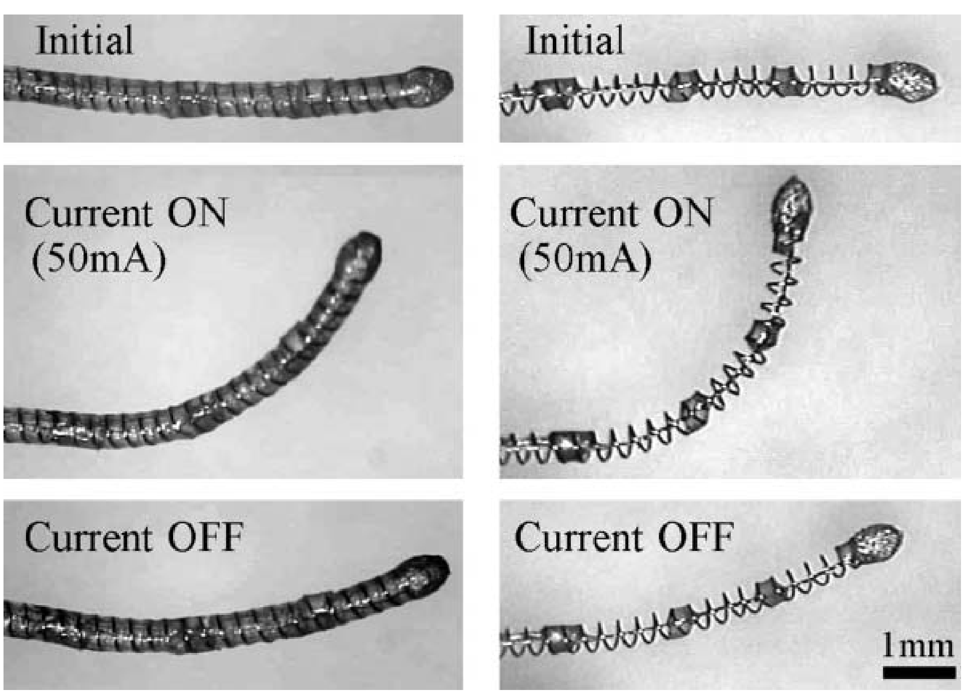

Figure 5. Active bending guide wire (external diameter: 0.5 mm) (a) tube type, (b) without external membrane.

The external diameter of the fabricated active bending catheter is 0.94 mm, with an internal diameter of 0.85 mm. The maximum bending angle of 160° and curvature radius of 1.4 mm were obtained with a 9 mm long bending part. The active catheter is effective for navigating difficult blood vessel branches with highly acute angles, and the selective embolization of arteries for treatment of tumors, such as myoma of the uterus.

Microsensors for diagnostics and treatment in the human body

Ultra-miniature fiber-optic pressure sensor

A fiber-optic pressure sensor 125 μm in diameter is shown in Fig. 7 (8). A 0.7 μm thick SiO_2 diaphragm is formed at the end of an optical fiber using MEMS technology. Deformation of the diaphragm induced by pressure, such as blood pressure, is detected by interferometric spectrum change of white light. Experiments on animals have been carried out and the monitored blood pressure in the left ventricle of a goat is shown in Figure 8. Because of the ultra-miniature sensor head, this sensor can be used in a small-diameter blood vessel or a stenosed vessel. It can also be utilized for simultaneous multi-point measurement by incorporating more than one sensor in a tool, such as a catheter or a guide wire. Furthermore, this sensor is expected to be useful in multifunctional interventional tools. The silicon column sensing element is batch fabricated on a silicon wafer by MEMS process, and is then bonded to the half-mirror coated optical fiber end. After bonding, unnecessary silicon column parts are removed by xenon difluoride (XeF_2) etching. As the diameter of the silicon column is 120 μm, approximately 100,000 sensor elements can be

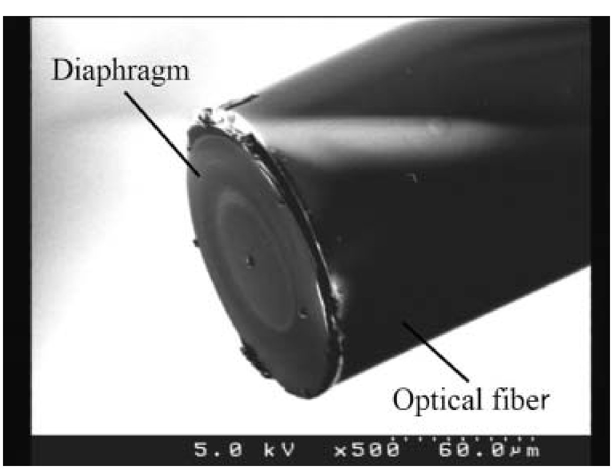

Figure 7. Ultra-miniature fiber-optic pressure sensor.

Figure 8. Continuous display of blood pressure in left ventricle of goat.

fabricated from a 4 inch silicon wafer. In animal experiments using a rat, dynamic blood pressure changes in the carotid artery have been successfully monitored.

Intravascular forward-viewing ultrasonic imager

An intravascular forward-viewing ultrasonic probe at the tip of a catheter has been developed (9). Three-dimensional visual information can be acquired without touching lesions in a blood vessel, such as stenosed lesions or occlusions. The system is expected to enable safer and more precise intravascular treatment. The ultrasonic probe has eight separated ring array 1–3 composite transceivers, which consist of PZT rod arrays in a polymer matrix. To obtain sufficiently low ultrasound beam directivity to be suitable for image construction algorithms, each 1–3 composite transducer has a convex shape, created by pressing between a polymer base and a metal mold which was fabricated using a high-speed milling machine (Figure 9) (10). Image construction is performed by computerized ultrasonic time-of-flight processing. A preliminary image construction test has been successfully performed using the fabricated forward-viewing ultrasonic probe, with a diameter of 3 mm and a working channel of 0.5 mm.

Micro treatment tools for use in the human body

Ultrasonic therapeutic tool for sonodynamic therapy and sonoporation

In recent years, sonodynamic therapy, which uses a synergistic combination of ultrasound and a

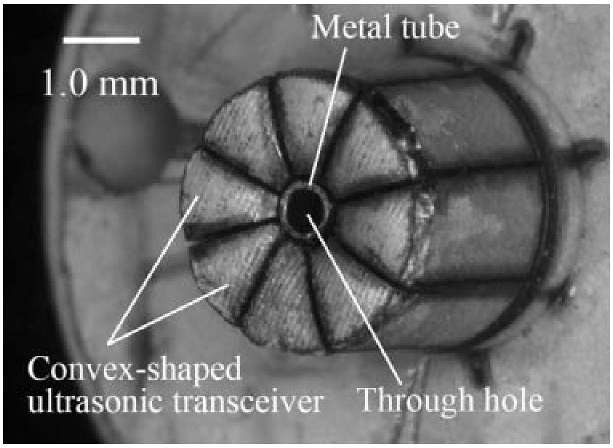

Figure 9. Intravascular forward-viewing ultrasonic imager.

chemical compound for treatment of conditions such as cancer, and sonoporation, which induces transient increases in cell membrane permeability and delivers macromolecules such as plasmid DNA, have been developed as new therapeutic methods. It is difficult to transmit ultrasound from an external transducer to points deep within the human body at adequate intensity and position, due to the attenuation of ultrasound by air, bone and tissue, and the deflection of ultrasound. A probe, which includes a focused ultrasonic transducer made of PZT at its tip, has been developed for ultrasonic treatment in the human body (Figure 10) (11). The probe will be inserted into the human body using a catheter or an endoscope. Sonoporation experiments *in vitro* have been successfully performed using a probe 5.5 mm in diameter with concave PZT elements. The concave PZT transducers were fabricated from bulk PZT using a high-speed micro-milling machine. Figure 11 shows measured ultrasonic intensity distribution of the fabricated probe, and peak intensity was 25 W/cm^2. GFP plasmid DNA as a reporter gene that expresses green fluorescence protein was transferred in Chinese hamster ovary (CHO) cells, and green fluorescence was observed. Microbubble Optison, an ultrasound contrast agent, was simultaneously administered to enhance ultrasound-induced transfer. Injection of drugs, plasmid DNA, and ultrasound transmission gel will be performed via a through hole 500 μm in diameter.

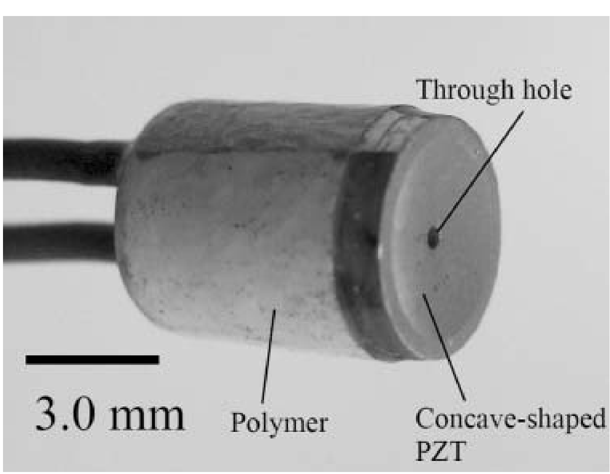

Figure 10. Ultrasonic therapeutic tool for sonodynamic therapy and sonoporation.

2D micro scanner for precise laser treatment

Laser treatments in the human body have been performed by transmitting a laser beam through an optical fiber. To realize precise laser treatment in the human body, a two-dimensional (2D) laser micro-scanner has been developed (12). The fabricated scanner is shown in Figure 12. A laser beam is transmitted through an optical fiber and a micro rod lens. The laser is reflected and scanned by a scanning Si thick mirror 1 mm in diameter and 200 μm thick, which was fabricated using a MEMS process. The laser is then focused on an objective area. The scanning mirror is actuated by three piezoelectric unimorph cantilevers. Each cantilever has a ball fixed at its tip in contact with the mirror, acting as a ball joint. The mirror is supported by a pivot under the mirror. The maximum inclination angle of the scanning mirror is 26°. Using potasium-titanyl-phosphate (KTP) laser, the laser positioning function was confirmed. By arranging the piezoelectric unimorph cantilevers parallel to each other, a large mirror inclination angle was obtained, while retaining the ability for the device to be packaged in a small diameter tube, suitable for insertion into a channel of an endoscope.

MEMS process for high performance and multi-functional medical tools

As mentioned before, it is preferable that medical tools inserted temporarily or implanted in the human body, such as endoscopic tools and catheters, be small, thin, multifunctional, and high-performance. Tubular lumens, which are required for insertion of medical tools and for injection of drugs, are necessary for endoscopes and catheters. MEMS processes on cylindrical substrates can meet these demands. However, it is difficult to apply conventional planar micro-fabrication techniques to non-planar surfaces and three-dimensional objects such as tubes. Fabrication techniques for multilayer circuits using metallization and patterning, and surface mounting of components on cylindrical

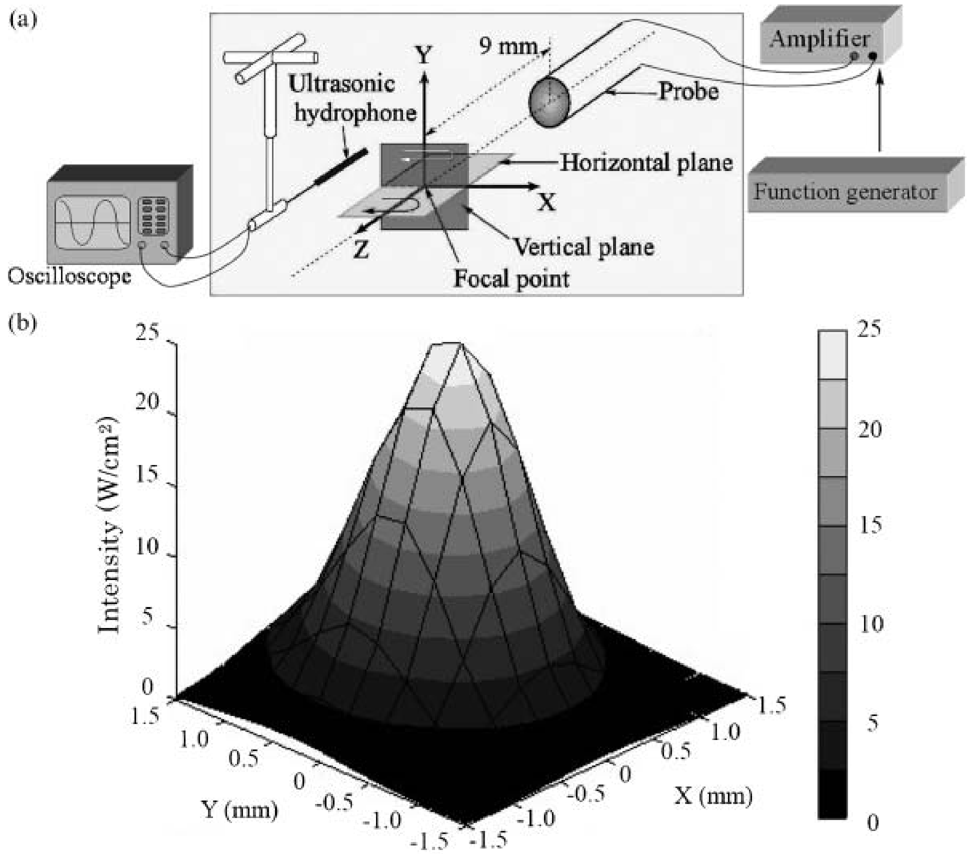

Figure 11. Ultrasonic intensity distribution: (a) Measurement setup of acoustic filed of fabricated probe using ultrasonic hydrophone, (b) ultrasonic intensity distribution on vertical plane (Z=0) at 1.83 MHz.

substrates have been developed for tubular high-performance micro medical tools with small diameters (13). A maskless exposure system for cylindrical substrates incorporating a Digital Micromirror Device (DMD) has been developed for the exposure of complex patterns. The DMD line exposure system can also realize several three-dimensional patterns using gray-scale (half-tone) lithography by precise control of the profile of exposure dose at each point, as shown in Figure 13 a. Smoothly sloped resist patterns (feature height 20 μm) were obtained on a glass tube with a

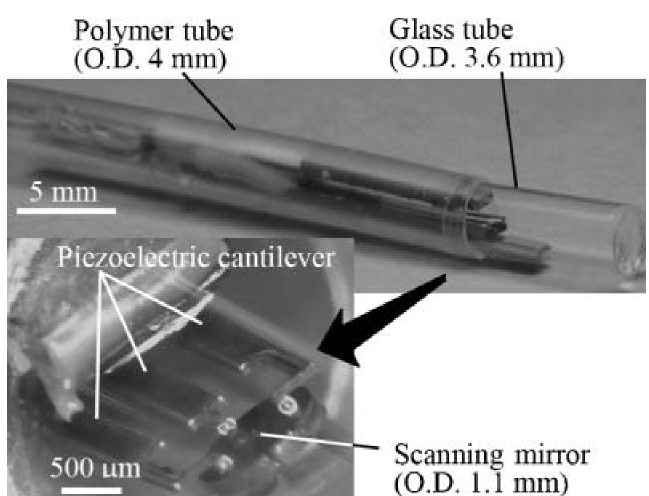

Figure 12. 2D micro scanner for precise laser treatment.

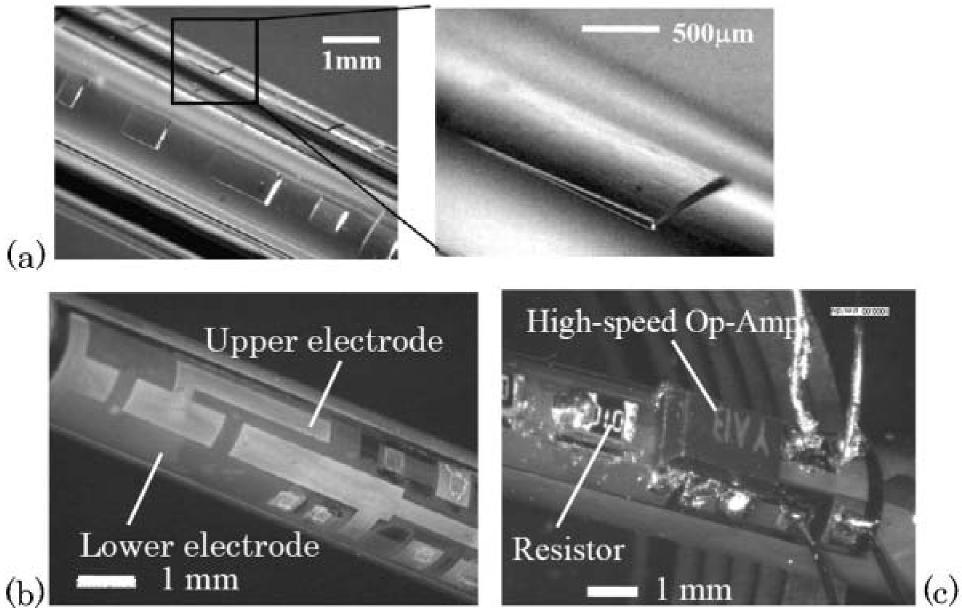

Figure 13. MEMS process on cylindrical substrates formed on glass tube (O.D./I.D. 3/2 mm): (a) Sloped resist patterns on glass tube (3 mm O.D.), (b) multilayer wiring, (c) mounting components on tube.

diameter of 2–3 mm. 7 μm thick single layer metal patterns, as well as multilayer electrode patterns (Figure 13 b), have also been formed on glass tubes (O.D./I.D. 2/1 mm and 3/2 mm respectively) using electroplating in a patterned resist structure. In order to improve the performance of small-signal micro-sensors such as ultrasonic transducers, a high-speed Op-Amp has been mounted on multilayer electrodes patterned on the tube (Figure 13 c). These techniques will realize multifunctional and high-performance tube-shaped micro medical tools with small diameters.

Conclusion

The science fiction movie "Fantastic Voyage", released in 1966, depicts treatment from inside the human body by miniaturized men in a miniaturized submarine injected into a blood vessel. Although such a fantastic scenario is unlikely, precision examination and treatment can be performed by extremely small medical devices which have several functions. Using high-performance endoscopes and catheters, more precise and safe diagnostics and treatment will be realized, and newer, more precise diagnostics and treatment, which have been impossible to date, can now be realized.

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