Proposal of Minimal Invasive Shape Memory Alloy Double-Transducer Unit for Blood Analysis or Drug Delivery*

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Abstract

The purpose of this research is to develop minimally invasive medical devices by applying heated actuations of Shape Memory Alloy (SMA) transducers using a medical Ti-Ni alloy in order to enable minimal hypodermic invasive microvolume for either blood suction or drug delivery through the use of a nontoxic and minimal edged microneedle to be created in the author's laboratory. The author has focused on lymphocytes for immunotoxin and erythrocytes for the glucose level in blood. This paper reports the double-action mechanisms of the compact unit during its development and its actions by low DC inputs. Joule's heating of an SMA coil spring transducer might be useful for indenting blood vessels whose diameter is larger than the microneedle as a result of generating an indentation stroke of 2.0 mm and recovery force of 0.25 N 0.23 s following the start of moving when applied to DC 2.0 V and 0.5 A. An octagonal-pyramidal foil transducer for blood suction recovered its plane condition as before octagonal-pyramidal forming 8.3 s following the start of moving when applied to DC 1.5 V and 2.0 A.

Key words: Minimal Invasive Medical Device, Shape Memory Alloy Double-Transducer, Blood Suction, Drug Delivery, Immunotoxin, Lymphocytes, Blood Glucose, Erythrocytes

1. Introduction

Today, Dendritic Cell Vaccine Therapy (DCVT)^(1, 2, 3) is a made-to-order cancer treatment, which applies a vaccine made of a patients' own immunocytes, and requires no major operations on patients. It has been developed by combining the technologies of Japanese original cell culture and the WT1 peptide of cancer antibodies and will be investigated worldwide. Dendrites are immunocytes with projections like branches, which understand the antigen (i.e. characteristics) of alien substances by preying on alien bodies in a patients' body, and forming T-lymphocytes, which attack the alien body by memorizing its characteristics. In short, DCVT is an epoch-making cancer treatment because the dendrites enable the lymphocytes to attack the alien body only. Concretely, by putting dendrites which have been made to memorize the characteristics of either the patient's cancerous tissue or the artificially generated antigen of the cancer back into the patients' body, dendrites allow lymphocytes to memorize the characteristics of cancer cells and enable them to attack the cancer. Therefore, DCVT is "a treatment that is severe to cancer and kind to the patient" because it never damages normal cells. Consequently, a very important problem is how to make frequent injections of vaccine minimally invasive.

*Received 7 Feb., 2011 (No. 11-0101)
[DOI: 10.1299/jbse.6.203]

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Also, the number of people with diabetes in Japan is estimated to be approximately twenty million, and they will develop various complications if left unattended. It has been found from a large-scale clinical inspection, that the outbreak and progress of three major complications of diabetes can be prevented by administering insulin many times and drastically reducing blood glucose. However, frequent injections for the delivery of drugs may place a heavy burden on a persons' life style. As for diabetes, Self-Monitoring of Blood Glucose (SMBG) is generally performed. However, there are many problems concerning the methods of blood suction and blood glucose measurement^(4, 5). The functions which are required of SMBG devises are (1) painless blood suction, (2) simplification of blood suction and blood glucose measurement, and (3) frequent real time measurements to check blood glucose conditioning through the delivery of insulin. Traditional devises to measure blood glucose during diabetes inspections at hospitals extract a few mℓ of blood using a syringe based on the pharmaceutical affairs law and carry out measurements using large-scale blood analysis systems using the centrifuge and flow-injection method. So, many people need minimal invasive blood suction and simple blood analysis.

In this research, the author has focused on either the extraction of erythrocytes for the SMBG or injection of a vaccine for DCVT. The purpose of the research is to develop a compact medical double-transducer unit applying the heated actions of Shape Memory Alloy (SMA) using a medical Ti-Ni alloy⁽⁶⁾, in order to enable either minimal hypodermic invasive microvolume blood suction or drug delivery by equipping a nontoxic and minimal edged microneedle to be created in the author's laboratory⁽⁷⁾. Regarding the blood suction system using a piezoelectric actuator, its flow volume is too small (about 0.002 mℓ a minute) and its cost per unit is very expensive because the piezoelectric actuator is disposable. So, in this paper, the author will propose a vacuum blood suction system by applying a very cheap and large deformable SMA transducer in order to overcome these problems. This system can be made available as a drug delivery system simply by conditioning the shape memory treatment of the SMA transducers. This paper reports on the indentation stroke, indentation speed and indentation force of a double-transducer unit actually generated by Joule's heating of an SMA coil spring transducer and will report the recovery deformation and response time of the double-transducer unit actually generated by Joule's heating of an octagonal-pyramidal foil transducer.

2. Method

Figure 1 shows the design of the cartridge type minimal invasive SMA double-transducer unit for either blood suction or drug injection. It can be housed in a diameter of 10 mm and depth of 16 mm. Its main components are listed in Table 1. The Joule's heated recovery action of an SMA coil spring transducer with wire diameter of 0.15 mm and coil inner diameter of 1 mm will realize minimal invasive indentation through the application a microneedle. The action of an SMA octagonal-pyramidal foil transducer with a diameter of 8 mm and thickness of 0.03 mm in the plane condition will carry out either microvolume blood suction or drug delivery through the microneedle.

Creating a vacuum between the octagonal-pyramidal foil transducer and the microneedle will enable blood suction, which otherwise requires administering a drug between them that carries out drug delivery. As for blood suction, an SMA foil with 8 slits was shape memory treated in the plane condition and formed an octagonal-pyramidal shape at room temperature. In this paper, an SMA octagonal-pyramidal foil transducer for blood suction was devised. Figure 2 shows blood suction by Joule's heating actuation of the SMA octagonal-pyramidal foil transducer. Producing small pressure between the octagonal-pyramidal foil transducer and the microneedle will enable blood suction. The octagonal-pyramidal foil transducer should be packed with thermally stable and flexible polymer film and be made to adhere to the root of the microneedle.

Figure 1. Cartridge type minimally invasive SMA double-transducer unit for either blood suction or drug injection.

Table 1. Main components of SMA double-transducer unit.

	Component	Materials and dimensions
[1]	Shaft for indentation	Heat-resistant polyimide insulator, diameter 1 mm
[2]	SMA coil spring transducer	Ti-Ni alloy, wire diameter 0.15 mm, inside diameter of coil 1 mm
[3]	SMA octagonal-pyramidal foil transducer	Ti-Ni alloy, flat state diameter 8 mm, flat state thickness 0.03 mm
[4]	Microneedle	Bio-metal, inner diameter 0.10 mm, length 3 mm

Figure 2. Blood suction by Joule's heating of SMA octagonal-pyramidal foil transducer.

In order to estimate the indentation force for the microneedle (SUS304, outer diameter 0.2 mm, cut angle 15 degrees) to penetrate the surface of the skin, indentation tests were performed by applying imitation skin, a urethane rubber whose shore hardness is A30. If it is possible to indent the imitation skin, which is harder than human skin, it will be possible for the microneedle to penetrate the surface of human skin. Figure 3 shows the experimental conditions of the actual indentation tests. Figure 3 (a) is used to evaluate the indentation force of the SMA coil spring transducer and Figure 3 (b) to evaluate its usefulness. For both Figure 3 (a) and Figure 3 (b), the steel indenter was moved by the testing machine INSTRON MODEL 3343. As for Figure 3 (b), Joule's heating was carried out on the indentation part (SMA coil spring transducer).

Figure 4 shows the forming process of the SMA octagonal-pyramidal foil at room temperature for either blood suction or drug delivery. When applying the SMA octagonal-pyramidal foil transducer to blood suction, shape memory thermal treatment in

the plane condition was carried out before the forming process. On the other hand, when applying it to drug delivery, the shape memory treatment in the octagonal-pyramidal foil will be carried out after the forming process.

Figure 3. Experimental conditions for the indentation tests.

Figure 4. Forming process of SMA octagonal-pyramidal foil at room temperature for either blood suction or drug delivery.

In this research, Joule's heating of the SMA transducers was carried out using DC power source KIKUSUI PMP16-1QU. Videos made using the digital high-speed video camera CASIO Exilim Ex-F1 at 600 frames per second were image analyzed.

3. Results and Discussion

Figure 5 shows the action of the microneedle (i.e. that of the shaft) for indentation by direct Joule's heating of the SMA coil spring transducer under DC heating conditions of 2.0 V and 0.5 A. The figure shows an actual image of the SMA double-transducer unit. Short time DC heating of the SMA coil spring transducer produced an indentation stroke of 2mm in the microneedle.

Figure 6 shows the force-indentation depth curves of the imitation skin at an indentation speed of 0.0008 mm/s. The figure shows three experimental results of the red, blue and brown plots of the static indentation. The curves had peak forces of more than 0.2 N when the indentation depths were more than 1 mm. It took more than 10 minutes for the microneedle to penetrate the imitation skin though the peak forces might cause fractures in its surface. Figure 7 shows the force-indentation depth curves of the imitation skin by the SMA coil spring transducer action applied to DC 2.0 V and 0.5 A. The figure shows three experimental results of the red, blue and brown plots of the dynamic indentation. The curves had peak forces of approximately 0.25 N when the indentation depths were approximately 0.001 mm. It took no more than 1 second for the peak forces to occur. A comparison of the two figures shows that there were large differences in the peak force level and the indentation depth due to the viscous elasticity of the imitation skin. Therefore the result of Figure 7 was more practical than that of Figure 6.

Figure 5. Action of microneedle for indentation by Joule's heating of SMA coil spring transducer.

Figure 6. Static indentation curves of imitation skin. Indentation speed was 0.05 mm a minute.

The indentation speed of the microneedle is one of the most important factors for the SMA coil spring transducer because the actual human skin has the same viscous elasticity as the imitation skin. Figure 8 shows the initial heating times of the SMA coil spring transducer for applied sets of DC voltage and current. The initial heating time expresses the time from the start of heating to the start of moving for the transducer. Figure 9 shows the stroke generating times of the SMA coil spring transducer for applied sets of DC voltage and current. The stroke generating time expresses the time for moving the transducer. As shown in Figure 8 and Figure 9, when the voltage was more than 2.0 V, both the initial heating time and the stroke generating time approached a small constant value. In this research, the stroke generating time was the smallest when the voltage was 2.0 V. Both Figure 8 and Figure 9 show that a DC heating condition of 2.0 V and 0.5 A was the best choice.

Figure 7. Dynamic indentation curves of imitation skin by SMA coil spring transducer action of applied DC 2.0 V and 0.5 A.

Figure 8. Initial heating times of SMA coil spring transducer for applied sets of DC voltage and current.

Figure 9. Stroke generating times of SMA coil spring transducer for applied sets of DC voltage and current.

The action of the SMA coil spring transducer was recorded at a rate of 600 frames per second, and the mean action time was measured. When applying DC 2.0 V and 0.5 A, the SMA coil spring transducer was activated 0.35 s from the start of heating and generated an

indentation stroke of 2.0 mm 0.23 s later. The action speed of the SMA coil spring transducer was 8.7 mm/s.

In order to decide the SMA transducer's shape for blood suction, a preliminary investigation was carried out by applying SMA plane foil without a slit. Figure 10 shows the recovery action of the SMA foil transducer without a slit which, after shape memory treatment, shown in Figure 10 (a), was compressed in a cool spherical die by using a punch with spherical head as shown in Figure 10 (b). The SMA foil transducer could not recover the memorized shape, shown in Figure 10 (c), though it was Joule's heated in a resin casing.

Therefore, the author focused on the three-dimensional wrinkled shape of Figure 10 (b) and proposed an original new design for the SMA foil transducer. The author considered shape recovery without plastic deformation by making 8 slits on the wrinkle lines in advance.

Figure 10. Recovery action of SMA foil transducer without a slit.

Figure 11 shows the actual forming process of the SMA octagonal-pyramidal foil transducer. Figure 11 (a) shows the SMA plane foil with 8 slits after shape memory thermal treatment, while Figure 11 (b) shows the SMA octagonal-pyramidal foil transducer after die forming at room temperature.

Figure 12 shows the recovery action of the SMA octagonal-pyramidal foil transducer. In heating conditions the octagonal-pyramidal foil transducer was different from the spherical transducer without a slit because of the 8 slits. The SMA plane foil with 8 slits after shape memory treatment, shown in Figure 12 (a), was compressed in a cool octagonal-pyramidal die by using a punch with an octagonal-pyramidal head as shown in Figure 12 (b). The SMA octagonal-pyramidal foil transducer completely recovered the memorized shape, as shown in Figure 12 (c).

Finally, the mean values of response time for the SMA octagonal-pyramidal foil transducer were measured by video recording under Joule's heating. The initial time, finish time and action time are listed in Table 2. The initial time is from the start of Joule's heating to the start of the transducer's action. The action time is the difference between the initial time and the finish time. The indentation speed in air can be calculated by using the action time. The action time was much longer than the one second that the author set as a goal for practical use. It was considered that heating conditions should be investigated still further.

Regarding the action of the SMA octagonal-pyramidal foil transducer for blood suction, it recovered its plane condition as before the octagonal-pyramidal forming at room temperature by applying DC 1.5 V and 2.0 A. The SMA octagonal-pyramidal foil transducer

started action 4.4 s following the start of heating and recovered the plane condition 8.3 s later. Effective lead wiring may shorten the action time of the foil transducer.

Figure 11. Actual forming of an SMA octagonal-pyramidal foil transducer.

Figure 13 shows an illustration of human skin and capillary in order to decide the indentation depth of the microneedle for either blood suction or drug delivery. From Figure 10, the indentation depth of the microneedles was decided to be 2 mm, and the outer diameter of the microneedles was not more than 0.2 mm. Figure 14 shows a microscopic view of a pure titanium microneedle with a one-face polished edge cut at an angle of 15 degrees, recently developed in the author's laboratory. The image was taken using an OMRON VC-1000 digital microscope.

Figure 12. Recovery action of SMA octagonal-pyramidal foil transducer.

Table 2. Response time of SMA octagonal-pyramidal foil transducer by Joule's heating.

	Initial time[s]	Finish time[s]	Action time[s]
Mean value	4.44	12.74	8.30

Figure 13. Consideration of indentation depth for either blood suction or drug delivery.

Figure 14. Sample photo of one-face polished edge of a microneedle cut at an angel of 15 degrees.

4. Conclusion

In this research, a minimal medical unit applying heated actuations of the medical Ti-Ni alloy SMA transducers has been developed. It will enable minimal hypodermic invasive microvolume, either by the suction of erythrocytes for blood glucose level or delivery of lymphocytes as antibodies for immunotoxin by using a nontoxic and minimal edged microneedle to be created in the author's laboratory. In this paper, the double-action mechanisms of the compact unit under development and its actions by low DC inputs were reported. The main points were as follows.

The cartridge type minimal invasive SMA double-transducer unit had a diameter of 10 mm and height of 16 mm. The main components were the SMA coil spring transducer with a wire diameter of 0.15 mm, the bio-metal microneedle with an inner diameter of 0.1 mm and the SMA octagonal-pyramidal foil transducer with a thickness of 0.03 mm.

By Joule's heating of the SMA coil spring transducer, indentation of the bio-metal microneedle with an inner diameter of 0.1 mm, the edge of which was cut at an angle of 15 degrees to the long axis, the imitation skin with a shore hardness of A30 generated a maximal force of 0.25 N at a depth of 0.001 mm, and the needle edge penetrated the imitation skin.

The action of the SMA coil spring transducer was recorded at a rate of 600 frames per second, and the mean action time was measured. When applying DC 2.0 V and 0.5 A, the SMA coil spring transducer started action 0.35 s following the start of heating and generated an indentation stroke of 2.0 mm 0.23 s later. The action speed of the SMA coil spring transducer was 8.7 mm/s.

Regarding thermal treatment of the SMA octagonal-pyramidal foil transducer, when applying it to blood suction, shape memory thermal treatment in the plane condition must be carried out before the octagonal-pyramidal forming process at room temperature.

As for the action of the SMA octagonal-pyramidal foil transducer for blood suction, it recovered its plane condition as before octagonal-pyramidal forming at room temperature through the application of DC 1.5 V and 2.0 A. It started action 4.4 s following the start of heating and recovered its plane condition 8.3 s later. Effective lead wiring may shorten the action time of the foil transducer.

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