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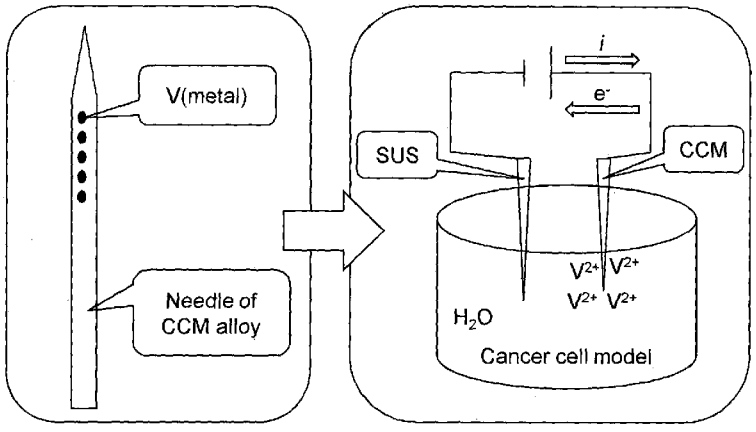
[Continued on next page]

(54) Title: A drug delivery system using an acupuncture needle

Fig. 7



(57) Abstract: An object of the present invention is to provide a drug delivery system or hyperthermia system using an acupuncture needle which is specially processed, and the present invention is a method of delivering a drug to a diseased site of a patient using an acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy on which holes are created, which comprises: loading a drug for treating a disease in the holes of the acupuncture-and-moxibustion needle; stinging the needle into the diseased site; and eluting the drug from the holes in the diseased site.

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DESCRIPTION

TITLE OF THE INVENTION

A drug delivery system using an acupuncture needle

TECHNICAL FIELD

The present invention relates to a drug delivery system and a localized hyperthermia system using an acupuncture needle.

BACKGROUND ART

Many studies have been conducted to develop drug delivery system. In some drug delivery systems, a particular device is used for drug delivery. For example, WO2007/019539 provides a micro needle device for delivering drugs.

SUMMARY OF THE INVENTION

OBJECT TO BE ATTAINED BY THE INVENTION

An object of the present invention is to provide a drug delivery system or hyperthermia system using an acupuncture needle which is specially processed.

MEANS FOR ATTAINING THE OBJECT

The present inventors tried to develop a new drug delivery system using an acupuncture-and-moxibustion needle.

The present inventors have developed a method of generating many small-diameter holes using electrical discharge machining (EDM) for an acupuncture-and-moxibustion needle made of metal.

The inventors tried to develop a drug delivery system using the needle having the holes. The inventors loaded a drug for treating a disease in the holes of the needle. Then, the needle with the drug was stung into the diseased site of a patient with another needle. Two needles were used as electrode pair and the drug was eluted from the holes into the diseased site by the principle of electrophoresis. The present inventors have completed the new drug delivery system using the acupuncture-and-moxibustion needle made of metal in this way.

Further, the present inventors tried to develop hyperthermia system

using the acupuncture-and-moxibustion needle. The present inventors processed the needle except for the apical region of the needle by insulation coating. Two needles were stung into the diseased site such as cancer site of a patient. Two needles were used as electrodes and electrified. Electricity was conducted between the apical regions of the two needles. Joule heat was generated by electrifying the needles. Cells in the diseased site were damaged or killed by the generated heat. The present inventors completed the new hyperthermia system using the acupuncture-and-moxibustion needle made of metal in this way.

Specifically, the present invention is as follows.

[1] A method of delivering a drug to a diseased site of a patient using an acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy on which holes are created, which comprises:

loading a drug for treating a disease in the holes of the acupuncture-and-moxibustion needle;

stinging the needle into the diseased site; and

eluting the drug from the holes in the diseased site.

[2] The method according to [1], wherein the drug is eluted from the holes on the needle by applying current to the needle.

[3] The method according to [1], wherein the diseased site is cancer.

[4] The method according to [1], wherein the drug is a compound which ionizes electrochemically.

[5] The method according to [4], wherein the drug is a metal vanadium which is usable as an anti-cancer drug.

[6] An acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy which has holes into which a drug is loaded, for use in the drug delivery to a diseased site.

[7] A method of hyperthermia using an acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy, which comprises:

stinging the acupuncture-and-moxibustion needle into the diseased site;

applying current to the needle; and

generating heat from the needle to damage the diseased area.

[8] The method according to [7], wherein the diseased site is cancer.

[9] An acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy for use in the hyperthermia which is coated with insulating substance on the region other than an apical region.

[10] A drug delivery system using the acupuncture-and-moxibustion needle which has holes into which a drug is loaded in the apical region, wherein the drug is eluted from the holes in the diseased site by the principle of electrophoresis.
[11] The drug delivery system according to [10], wherein the needle is made of Co-Cr-Mo alloy, cobalt or stainless-steel.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a processing image of a needle.

Figure 2 shows a schematic view of a device for electrical discharge machining.

Figure 3 shows input (Ideal removal volume) -output (Real removal volume) relations.

Figure 4 shows factor effects of SN ratio.

Figure 5 shows the results of the processing of holes.

Figure 6 is photographs of needles with holes.

Figure 7 shows the elution mechanism of the metal vanadium using the needle.

Figure 8 shows a schematic view of an electrical and chemical measurement system.

Figure9 shows the polarization curve of vanadium.

Figure10 is a graph showing an amount of deposited vanadium calculated by current value observed during the measurement based on Faraday's law.

Figure 11 shows the vanadium film before (A) and after (B) the measurement.

EMBODIMENTS FOR CARRYING OUT THE INVENTION

Drug delivery system

An acupuncture-and-moxibustion needle is used for the drug delivery system of the present invention. The needle is made of metal and has length of 40 to 100mm and diameter of the thickest part of the needle is 0.10 to 0.3mm. The commercial available acupuncture-and-moxibustion needle can be used. The metal of the needle is Co-Cr-Mo alloy, cobalt or stainless-steel.

Holes into which a drug is loaded are created on the lateral face of

the needle. The holes are created in the apical region of the needle. The apical region means to be the region from the apical end to 10 to 30mm from the apical end. The number of the holes are not limited, but preferably, 1 to 20, more preferably, 5 to 15. The diameter of the hole is about 0.1 to 0.21mm. Holes are created at a distance between holes of 2 to 10mm. The number of the holes and the diameter of the hole depend on the severity or the volume of a diseased site in a patient. The holes are created by electrical discharge machining (EDM). The details of the method for creating the holes on the needle are described in Examples. The method for the electrical discharge machining is known to a person skilled in the art.

Regions of the needle other than the apical region may be coated with insulating substance. The insulating substance includes enamel, fluorine resin such as PTFE (polytetrafluoroethylene), ceramics such as TiN ceramics, and glass. Coating can be carried out by the known method such as spin coat technology and dry process. The thickness of the coating is less than 20μm.

A drug is selected depending on a disease to be treated. For example, anti cancer drug, biologically active agent and the like can be used. The drug may be a targeted therapy medicine. A small molecule substance, monoclonal antibody can be used as the targeted therapy medicine. By the drug delivery system of the present invention, the drug can be delivered locally to the diseased site such as cancer site or a nerve cell. The needle is so fine that it can be stung into not only tissue of the diseased site but also a single cell. It is possible to treat micro cancer.

The drug is loaded in the holes of the needle. The drug can be loaded in the holes as a composition comprising the drug. If the drug is a protein, the protein is mixed with a metal such as vanadium to form a protein-metal complex. The composition (protein-metal complex) can be loaded in the holes by a method such as vacuum method and a method using ultrasonic vibration. The drug may be loaded in the holes of the needle with a carrier, a diluent, and an excipient that are generally used in the field of formulations. For example, lactose, magnesium stearate, and the like can be used as carriers or excipients.

The composition may include other ingredient such as a pharmacologically acceptable carrier, diluent or excipient, which are commonly used in the pharmaceutical field. The dosage applied depends on

symptom, age, body weight and others. Generally, it is approximately 0.001 mg to 1,000 mg per kg body weight per day for the drug, and the composition with the above dosage is administered all at once, or divided several times throughout a day.

The drug loaded in the needle is eluted into the diseased site electrochemically, for example, by the principle of electrophoresis. The needle to which the drug is loaded is stung into the diseased site. Another needle with or without holes may be stung into the diseased site or adjacent area of the diseased site concurrently with the needle to which a drug is loaded. Current is applied between two needles. Two needles act as electrode pair. Then, the drug composition is eluted from the holes into the diseased site by the principle of electrophoresis.

It is preferable that the drug to be loaded in the holes of the needle is a compound that ionizes electrochemically.

For example, vanadium can be used as anti-cancer drug to be eluted from the holes of the needle. Vanadium ionized easily. Accordingly, metal vanadium is loaded in the holes of an acupuncture-and-moxibustion needle. The needle with metal vanadium is stung into a cell or a tissue to be treated. Then, voltage is applied to the needle in order to ionize metal vanadium. The ionized metal vanadium is delivered into the cell or tissue.

Furthermore, Co (cobalt) or Cr (chrome) is eluted from Co-Cr-Mo alloy of the needle by applying voltage. These heavy metals such as Co and Cr have cytotoxic effect on cancer cells. The diseased site such as cancer site can be damaged by Co and Cr of Co-Cr-Mo alloy of the needle since Co or Cr is present at high concentration locally at the diseased site. When Co or Cr enters into blood vessel, it does not affect a living body since Co or Cr is present at low concentration in blood and functions as an essential element at low concentration.

Hyperthermia system

The present invention also provides a method of hyperthermia (heat treatment, thermal therapy) using the acupuncture-and-moxibustion needle.

The disease treated by the hyperthermia system of the present invention includes cancer.

For the hyperthermia, two needles are stung into the diseased site and current is applied between the needles by applying voltage to the

needles. The distance between the two needles is 1 to 10mm. Joule heat is generated by the conduction between the needles. Pulsed voltage may be applied to the needles. The needles are heated to the temperature more than 40℃, preferably about 43℃, and the temperature of the needles is maintained for a certain period such as for 10 to 60 minutes to damage the diseased site, for example, to kill cancer cells.

Regions of the needle other than the apical region may be coated with insulating substance. The insulating substance includes enamel, fluorine resin such as PTFE (polytetrafluoroethylene), and ceramics such as TiN ceramics. Coating can be carried out by the known method such as spin coat technology and dry process. The thickness of the coating is less than 20μm.

The acupuncture-and-moxibustion needle with holes and insulating coating can be used to carry out drug delivery and hyperthermia concurrently. The combination of drug delivery and hyperthermia may be strong tool to treat the diseased site such as cancer.

When biologically active agent such as a nerve growth factor (NGF) is used to be delivered to a cell such as a neuron cell, the delivery from the holes of the needle is completed in a short time. Short time voltage application does not generate Joule heat or induce the elution of heavy metal such as Co and Cr. Accordingly, desired treatment is chosen by changing the period of voltage application.

The acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy is biocompatible and induces no reaction of a patient such as allergic reaction.

The present invention is hereafter described in detail with reference to the following examples, although the present invention is not limited thereto.

Functions of needles used for acupuncture and moxibustion include the delivery of medicines having anti-cancer effects and treatment effects as Drug Delivery Systems (DDS). To realize DDS for needles, this study achieved two objectives. One was the development of a complete processing technique to generate numerous small-diameter holes to hold medicines, using electrical discharge machining (EDM) for Co–Cr–Mo alloy needles, for which processing conditions are unknown. (Example 1) Another objective

was development of a precise control technique to elute a quantity of medicine (Example 2).

Example 1

The objective of Example 1 was the development of a complete processing technique to generate numerous small-diameter holes using electrical discharge machining (EDM) for Co–Cr–Mo alloy needles, for which processing conditions are unknown. Results show that many advantageous effects on EDM were produced through precision processing: σ 0.9 μm (hole diameter variance (mm)) and low reduction of electrode wear ratio, 32% (tool consumption length (mm) / processing hole depth (mm)). The processing efficiency was high: 6 min 46 s per hole.

1. Introduction

Advanced processing technologies are necessary for manufacturers to satisfy design demands and develop products with high efficiency. Requirements for this product were the following: "Generate as many minute holes as possible in part of the 15 mm range the top-end forward to root direction of needle side-plane made from Co–Cr–Mo alloy and having φ0.25-mm-diameter." This study demonstrated the technology to generate numerous minute holes of Co–Cr–Mo alloy needle side-plane.

2. Experiment plan

2.1. Input–Output Relations

A processing method by which the hole diameter levels were changed was obtained by electrode swinging. The processing image is shown in Figs. 1 and 2. Fig.1 shows a diagram of a needle having holes and Fig.2 shows an electrical discharge machining (EDM) apparatus. A small hole was generated from more than φ0.1 mm to less than φ0.2 mm when using a φ0.1 mm rod electrode with added circle swinging behavior. It was set as presented in Fig. 3. The characteristic of the input value was the ideal removal volume (M; mm^3). That of y: the output value was the actual removal volume (y; mm^3) and the noise factor was the circle swinging radius (mm). Sensitivity β and SN ratio η (db) are indexes of processing efficiency. Here β indicates the processing time (mm^3/s) to generate a hole. The SN

ratio indicates the processing stability to evaluate the input–output linear relation.

2.2 Signal factor

The EDM technique of processing to produce many minute holes was determined using an arranged matrix plan for experiments with several factors to choose a high-efficiency SN ratio $\eta=\beta^2/\sigma^2$ among a combination of factors under a defined linear formula, $y=\beta M$, with the relation of input parameter M as the ideal removal volume and output parameter y as the actual removal volume (mm^3) (Table 1).

Signal factors were set so that the ideal removal volume for level 1 was 0.0079 mm^3. The signal factor was set to only one level because the priority was selected for efficient experiments. However, if many levels of signal factors were set, it was possible to obtain dynamic characteristics with added high robustness.

Table 1

Input--Output relations

Input–Output relations	Level 1
Input: Ideal removal volume (mm^3)	0.0079(M_1)
Output: Real removal volume (mm^3)	y_1

2.3. Control factors

The control factors were set to eight levels of characteristics to produce a matrix table L18 arrangement. Control factors were the following: A, micro SF circuit (2 levels, ON/OFF); B, capacitor circuit (2 levels, ON/OFF); C, voltage LOW circuit (2 levels, ON/OFF); D, ceramic guide height (mm) (3 levels, 200/100/20 μm); E, charging resistance (Ω) (3 levels, 3/6/9 notch); F, output voltage (3 levels, 280/150/80 V); G, re-approach speed (3 levels, 300/750/1200 mm/min); H, servo voltage (3 levels, 5/3/0 notch) (Table 2); the number of levels was factor A–C as two levels and factor D–H as three levels. The noise factor is shown as N_1 when not adding swinging of the electrode, and N_2 with addition of swinging of the electrode (swinging

radius, 0.0250 mm) as two levels. Factor A, Factor B, and Factor C are circuits used to adjust the microprocessing power supply. The auxiliary power (AUX) of factor E was charge resistance (Ω) in the case of a capacitor power supply. Therefore, the charge-resistance value controlled the charging time. The electric discharge phenomenon stopped time. The F circuit (GAP) of factor F was used to supply the voltage (V) for the capacitor circuit. It represents a processing power index. The processing adjustment (GAIN) of factor G was used to set the return speed (mm/s) to escape from the unsuitable electrical discharge phenomena. The adjustment value was set sufficiently high to contribute to efficient processing.

Table 2
Control factor

Control factors		Levels		
		1	2	3
A	Micro SF circuit	ON	OFF	-
B	Capacitor circuit	ON	OFF	ON
C	Voltage LOW circuit	ON	OFF	ON
D	Ceramic guide height (μm)	200	100	50
E	Charging resistance (notch)	3	6	9
F	Output voltage (V)	280	150	80
G	Re-approach speed (mm/min)	300	750	1200
H	Servo voltage (notch)	5	3	0

2.4. Noise factor and processing conditions

The noise factor was set as one characteristic. It was then divided into two levels to obtain dynamic stability in cases of a changing nominal value to represent the removal volume or hole diameter. Level 1 was set with the swinging radius as 0 mm. Level 2 was set with the swinging radius as 0.025 mm. The electrode's lower feed quantities of noise factor two levels were adjusted to set equal removal volumes because of the difference from the hole's circular area. Level 1 was set to the 0.4444 mm feed depth direction. Level 2 was set to 0.1000 mm feed. An EDM device was used as the micropower supply (EDSCAN8E; Mitsubishi Co., Ltd.).

The workpiece was a Co–Cr–Mo alloy for which minute hole processing was conducted against a flat top plane of a cubic block. The processed holes were 36 pieces that were representative of 18 experiments (matrix table L18), doubled (noise factor 2 levels).

3. Experiment results and consideration

3.1. Processing results

The relative linear wear was calculated for the electrode wear length per unit of processing hole depth and multiples 100 (%). Therefore, the removal ratio between the electrode and workpiece was presented. The inverse proportion between the processing hole depth and electrode wear length was readily apparent.

3.2. Calculation of SN ratio

Sufficient robustness was not obtained if numbers of signal factors and noise factors were not fully reflected. The optimal condition was obtained that combined to computation using two methods of SN ratio calculation methods for the type of noise factor effect used and the type of total variance effect used (Hiroshi Yano: A guide of quality engineering calculation, Japanese Standards Association, pp. 262-266 (1998)). The factor effect graph presented in Fig. 4 shows two SN ratio calculation methods. The optimal condition of noise factor type was included A1, B1, C1, *D2*, *E1*, F3, *G2*, H3, another total variance type was included A1, B1, C1, *D1*, *E2*, F3, *G1*, H3. Three factors were calculated, yielding different results using the two SN ratio calculation methods. The three factors are shown in bold and italic text above as factors D, E, and G. Final conclusions of optimal condition were determined to ascertain the level at which high precision and high efficiency were obtained. Therefore, the final combinations were A1, B1, C1, D2, E2, F3, G2, and H3. The minute hole processing of about φ0.1 mm was stabilized to high SN ratio in case of ON conditions that were factor A, factor B and factor C grouped microprocessing circuits. It was apparent that the circuits were necessary to attain high-stability processing.

3.3. Confirmation experiment

Processing to produce numerous minute holes was performed for a flat plane on a cubic block workpiece made of Co–Cr–Mo alloy, for which processing conditions were set as two types (optimal and present). The processing results are depicted in Fig. 5. The present conditions were set according to the manufacturer, showing the processing conditions database. The microprocessing circuit of factors A, B, and C is inferred to be necessary on a φ0.1 mm level minute hole processing. The two indexes of the SN ratio were not equal between estimates of the expected value 17.7 db and the experimental value of 3.3 db. Therefore, the difference was 14.4 db, which is not reliable. Regarding sensitivity, it was nearly equal between the estimated expected value of 2.4 db and the experimentally obtained value of 2.0 db. Their difference was 0.4 db. However, when the absolute value of sensitivity is small, then the reliability is low.

4. Verification experiment

The minute hole processing which was planned for continuous ten pieces holes for needle side-plane was tried to obtain optimal condition on the matrix table experiment. The experiment condition was set that workpiece was a needle of φ0.25 mm of Co–Cr–Mo alloy and the pitch between one hole's centre and the next hole's centre was 0.4 mm. Other conditions were the same as those used for the matrix table experiment. Photographs of needles after minute hole processing are presented in Fig. 6. Fig.6 A upper panel shows holes processed under optimum condition and Fig.6 A lower panel shows holes processed under present condition. Fig.6 B shows a magnified view of Fig.6 A upper panel, and Fig.6 C shows a magnified view of Fig.6 B lower panel. Results show that ten piece holes having sharp edges and precise roundness were generated in optimal conditions. Results also showed that whole through holes were only four pieces, so six holes were not generated through holes in the present condition. Comprehensive processing results of the verification experiment are presented in Table 3. The results were obtained under optimal conditions in which the average hole diameter was φ 0.1087 mm, indicating the precise reverse forming electrode diameter because the lateral gap was 8.7 μm, which is very small, and the variance of the hole diameter was 0.9 μm, which indicates high precision. Therefore the results show that precise processing was demonstrated. Moreover, the relative linear wear was indicated as

36.2%. Another, in the present processing condition, showed average hole diameter of φ0.1245 mm so that the lateral gap was 24.5 μm diameter, the hole diameter variance (σ) was 3.2 μm, and the relative linear wear was calculated as 96.8%. However, results show that the present performance was superior for processing speed because the optimal value was 0:06:46 (h:m:s), whereas the achieved time was 0:00:25 (h:m:s).

Table3
Results of verification
Average (10 holes)

Item	Optimal	Present
Diameter of hole (mm)	0.109	0.125
Lateral gap (diameter, μm)	8.7	24.5
Processing time (h:m:s)	0:06:46	0:00:25

Total (10 holes)

Item	Optimal	Present
Total relative linear wear (%)	32.6	96.8
Variance of diameter (σ, μm)	0.9	3.2
Total processing time (h:m:s)	1:07:43	0:04:11

5. Conclusions

Confirmation experiment was conducted. The two indexes of SN ratio were not equal between those of estimates of the expected value 17.7 db and the experimented value of 3.3 db. Therefore the difference of 14.4 db was not very reliable. Results showed that ten piece holes having sharp edges and precise roundness were generated in the optimal condition. Moreover, stability processing of low relative linear wear was 36.2%. In addition, a method of elution control for administration of a chosen quantity of medicine is being tested at present using potentiostat electrical and chemical measurement systems, in addition to inductively coupled plasma spectroscopy.

The method of medicine elution was examined through experimentation to elute added voltage with joule heat. Using equipment in

the medicinal elution experiment stage, an analog voltage output device was used (NI9263; National Instruments Corp.) with a temperature measurement device (NI9211) and an applied thermocouple sensor, which was T type (range: -200 K – 300 K). The analog voltage waveform added to the needle from an analog voltage output device was monitored using an analog voltage input device (±10 V, NI9215 resolution).

The programming sequence was controlled using a graphical programming language (Labview Ver. 2011). The amount of voltage given to the needle was a maximum ±10 V restricted NI9263 performance ability. The output waveforms included various waveforms such as sine waves, rectangle waves, and triangle waves. Results show that many advantageous effects on EDM were produced through precision processing: σ 0.3 μm (variance of hole diameter (mm)) and low reduction of electrode wear ratio, 32% (length of tool consumption (mm) / processing hole depth (mm)). The processing efficiency was high: 6 min 46 s per hole. Moreover, a method of elution control for administration of a proper quantity of medicine was attained to output the optimal voltage waveform.

Example 2

1. Introduction

The objective of Example 2 was development of a precise control technique to elute a quantity of medicine.

Vanadium can be used as anti-cancer drug to be eluted from the holes of the needle. Vanadium ionized easily. Accordingly, metal vanadium is stuffed into holes of an acupuncture-and-moxibustion needle. The needle with metal vanadium is pierced into a cell or a tissue to be treated. Then, voltage is applied to the needle in order to ionize metal vanadium. The ionized metal vanadium is delivered into the cell or tissue. Fig.7 shows the elution mechanism of the metal vanadium using the needle. In Fig.7, V(metal) means metal vanadium, CCM ally means Co–Cr–Mo alloy, and SUS means stainless steel.

Example 2 was carried out to study electrochemical properties of vanadium.

2. Establishment of drug delivery system using an acupuncture-and-moxibustion needle

(i) Measurement of a polarization curve of vanadium

In Example 2, vanadium was selected as an anti-cancer medicine. Vanadium ionizes easily, and the phenomenon was measured to quantify in the chemical experiment. The first, a polarization curve, was measured from the vanadium that was vapor-deposited on the glass plate made for a test sample, using potentiostat electrical and chemical measurement systems. Fig. 8 shows a schematic view of an electrical and chemical measurement system used for the present Example. The potentiostat of Fig. 8B is controlled by a computer, analysis software and so on.

A glass plate on which vanadium powder was vapor-deposited was used as a vanadium electrode. The glass plate on which vanadium powder was vapor-deposited is called a vanadium film. Table 4 shows the vanadium film manufacturing process by the conditions for the vapor-deposition.

Table 4
Vanadium film manufacturing process

Equipment	Vacuum heating type evaporation system
Machine Form	EBX (ULVAC Corp.)
Film material	Vanadium (powder)
Base	Glass plate heating to 18.5℃
Velocity	0.07nm/sec
Film thickness 1	10nm

A reference electrode was AgCl and a counter electrode was Pt (platinum) electrode. As solvent, physiological saline was used. The electrical reaction occurred in the system mimicked that occurred in a living body.

Fig.9 shows the polarization curve of vanadium. According to Fig.9, it is speculated that oxide film formed on the vanadium film was removed at about -1.1V and anode polarization initiated at about -1.03V. That is, corrosion potential was about -1.03V.

Fig.10 is a graph showing an amount of deposited vanadium calculated by current value observed during the measurement based on Faraday's law. In Fig.10, Faraday's formula is indicated. In the formula, M is deposited amount (g), z is electrochemical equivalent (g/C), i is current value (A) and t is time (s). Fig.11 shows the vanadium film before (A) and after (B) the measurement. As shown in Fig.11, a part of the vanadium film to be measured was lost by the deposition. The lost area was φ10.33mm. Based on the density of vanadium which is 5.8mg/mm3, the amount of the deposited vanadium was calculated using the following formula.

$M = \pi/4 \times (10.33)2 \times 0.1 \times 10\text{-}3 \times 5.8 = 0.049$ (mg)

The curve of Fig. 10 indicates that vanadium was lost 2200 seconds (37 minutes) after the initiation of the measurement.

(ii) IPC (Inductively coupled plasma) quantitation assay

The amount of vanadium ion in an aqueous solution used for the measurement of the polarization curve was measured by IPC (Inductively coupled plasma) quantitation assay. Three hundreds ml of the aqueous solution was used. IPC quantitation assay was carried out using IPC chemiluminescence analyzer (SPS3520 UV, SII Nano Technology Inc.).

The amount of vanadium ion in the aqueous solution was 0.0396±2% mg. The amount of the deposited vanadium was 0.049 mg as shown above. The results shows that 80% of metal vanadium in the vanadium film ionized by anode dissolution and ion elution.

3. Conclusions

The vanadium ion was generated from metal vanadium elution to operate anode polarization using electrochemical method. The quantity of vanadium to elute in the solution was measured using inductively coupled plasma (ICP spectroscopy), yielding a result of 0.0396±0.2% mg. The elution speed was calculated using Faraday's formula as 1.8×10^{-5} mg/s.

Example 2 shows that drugs in the holes of the acupuncture-and-moxibustion needle by ionization of the drugs electrochemically.

All publications, patents, and patent applications cited herein are incorporated herein by reference in their entirety.

Claims

1. A method of delivering a drug to a diseased site of a patient using an acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy on which holes are created, which comprises:
loading a drug for treating a disease in the holes of the acupuncture-and-moxibustion needle;
stinging the needle into the diseased site; and
eluting the drug from the holes in the diseased site.

2. The method according to claim 1, wherein the drug is eluted from the holes on the needle by applying current to the needle.

3. The method according to claim 1, wherein the diseased site is cancer.

4. The method according to claim 1, wherein the drug is a compound which ionizes electrochemically.

5. The method according to claim 4, wherein the drug is a metal vanadium which is usable as an anti-cancer drug.

6. An acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy which has holes into which a drug is loaded, for use in the drug delivery to a diseased site.

7. A method of hyperthermia using an acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy, which comprises:
stinging the acupuncture-and-moxibustion needle into the diseased site;
applying current to the needle; and
generating heat from the needle to damage the diseased area.

8. The method according to claim 7, wherein the diseased site is cancer.

9. An acupuncture-and-moxibustion needle made of Co-Cr-Mo alloy for use in the hyperthermia which is coated with insulating substance on the region other than an apical region.

10. A drug delivery system using the acupuncture-and-moxibustion needle which has holes into which a drug is loaded in the apical region, wherein the drug is eluted from the holes in the diseased site by the principle of electrophoresis.

11. The drug delivery system according to claim 10, wherein the needle is made of Co-Cr-Mo alloy, cobalt or stainless-steel.

Fig. 1

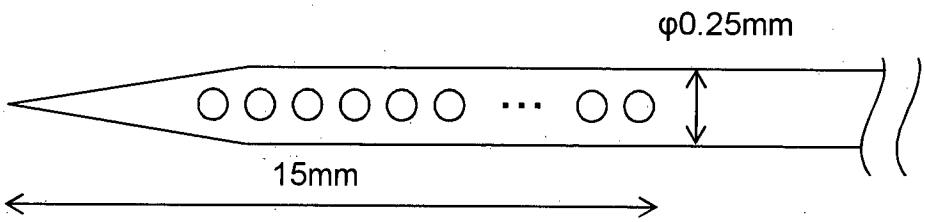


Fig. 2

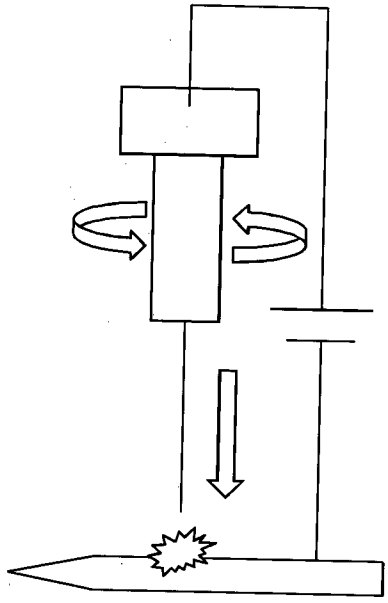


Fig. 3

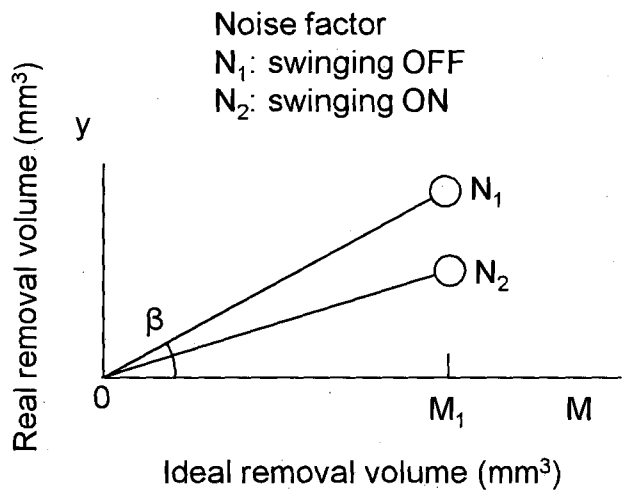

Noise factor
N1: swinging OFF
N2: swinging ON
y
N1
N2
β
0
M1
M
Real removal volume (mm3)
Ideal removal volume (mm3)

Fig. 4

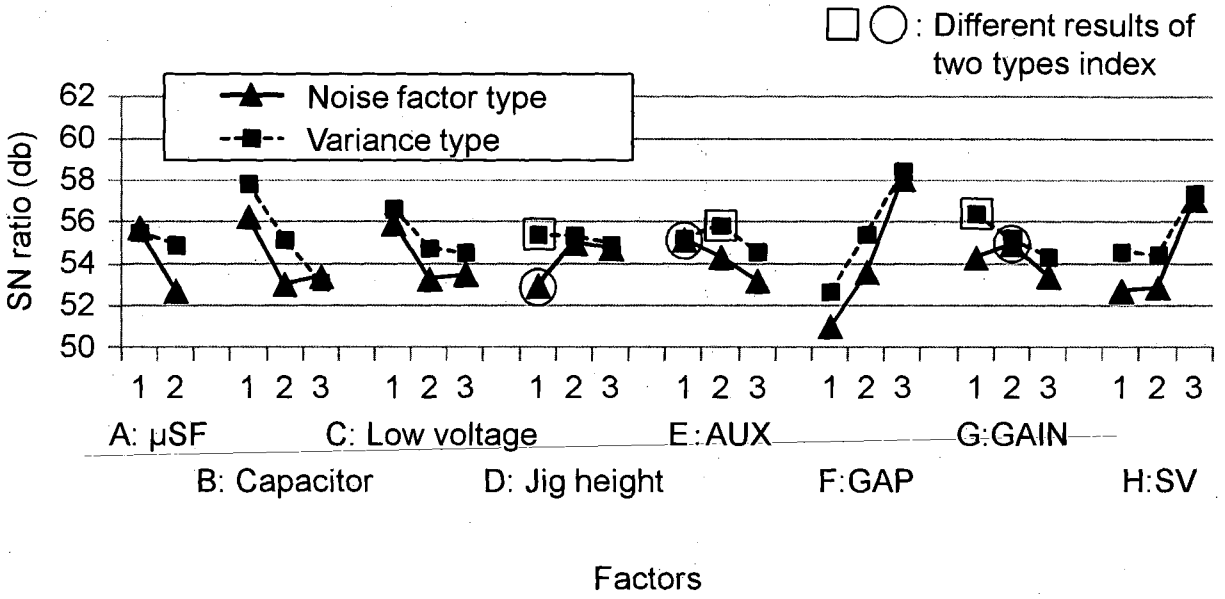

□○: Different results of two types index
Noise factor type
Variance type
SN ratio (db)
62
60
58
56
54
52
50
1 2 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3
A: μSF
C: Low voltage
E:AUX
G:GAIN
B: Capacitor
D: Jig height
F:GAP
H:SV
Factors

Fig. 5

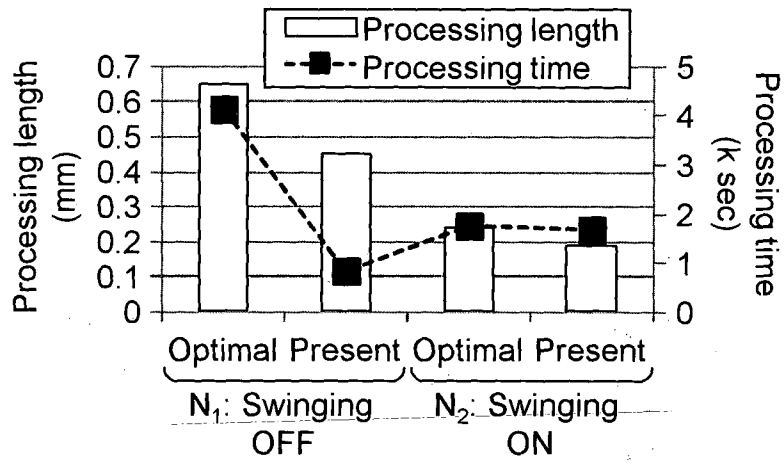

Processing length
Processing time
Processing length (mm)
Processing time (k sec)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
5
4
3
2
1
0
Optimal Present
Optimal Present
N1: Swinging OFF
N2: Swinging ON

Fig. 6

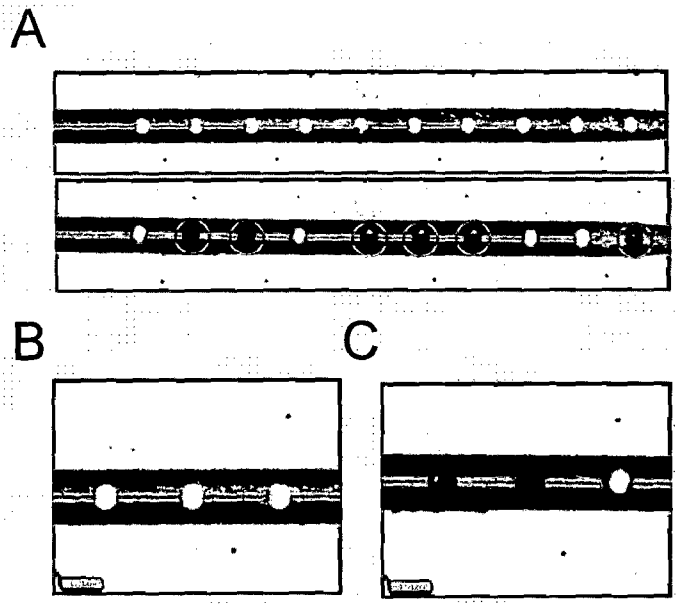


Fig. 7

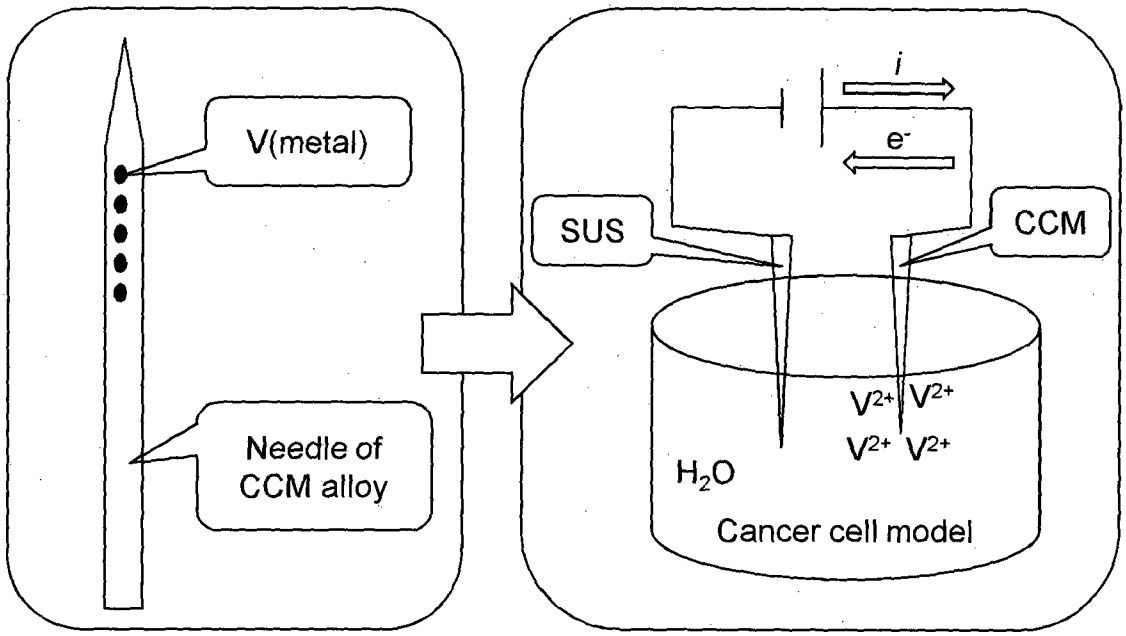

V(metal)
Needle of CCM alloy
i
e-
SUS
CCM
V2+ V2+
V2+ V2+
H2O
Cancer cell model

Fig. 8

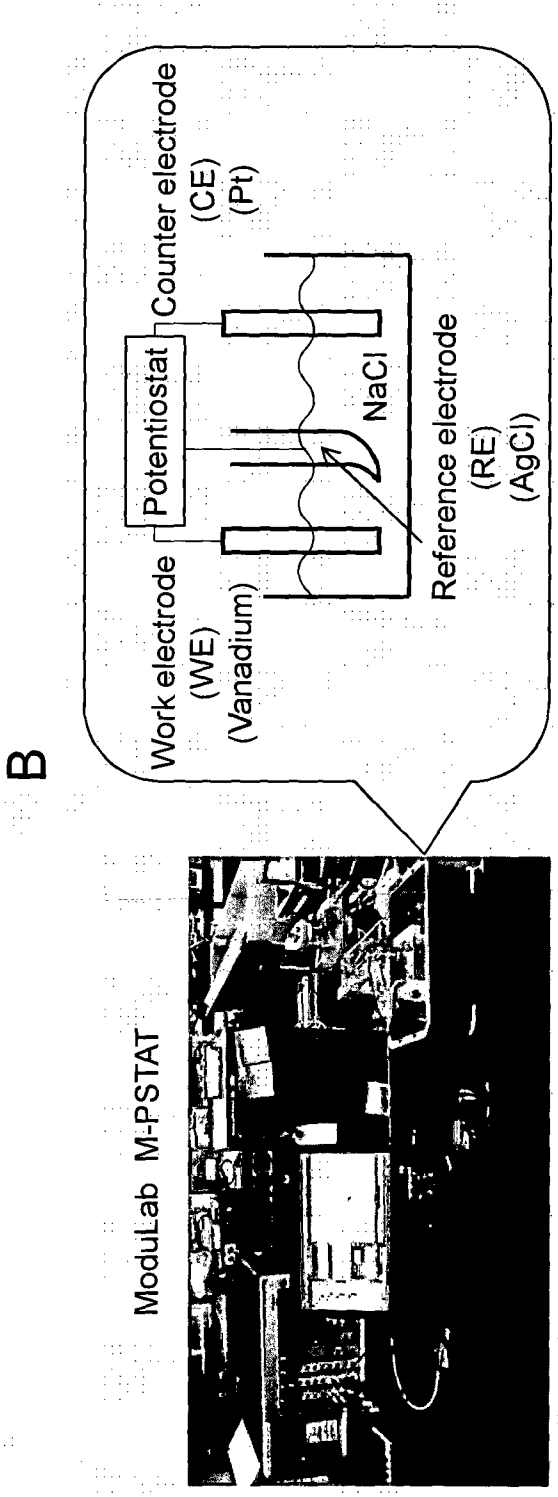

A
ModuLab M-PSTAT
B
Work electrode
(WE)
(Vanadium)
Potentiostat
Counter electrode
(CE)
(Pt)
NaCl
Reference electrode
(RE)
(AgCl)

Fig. 9

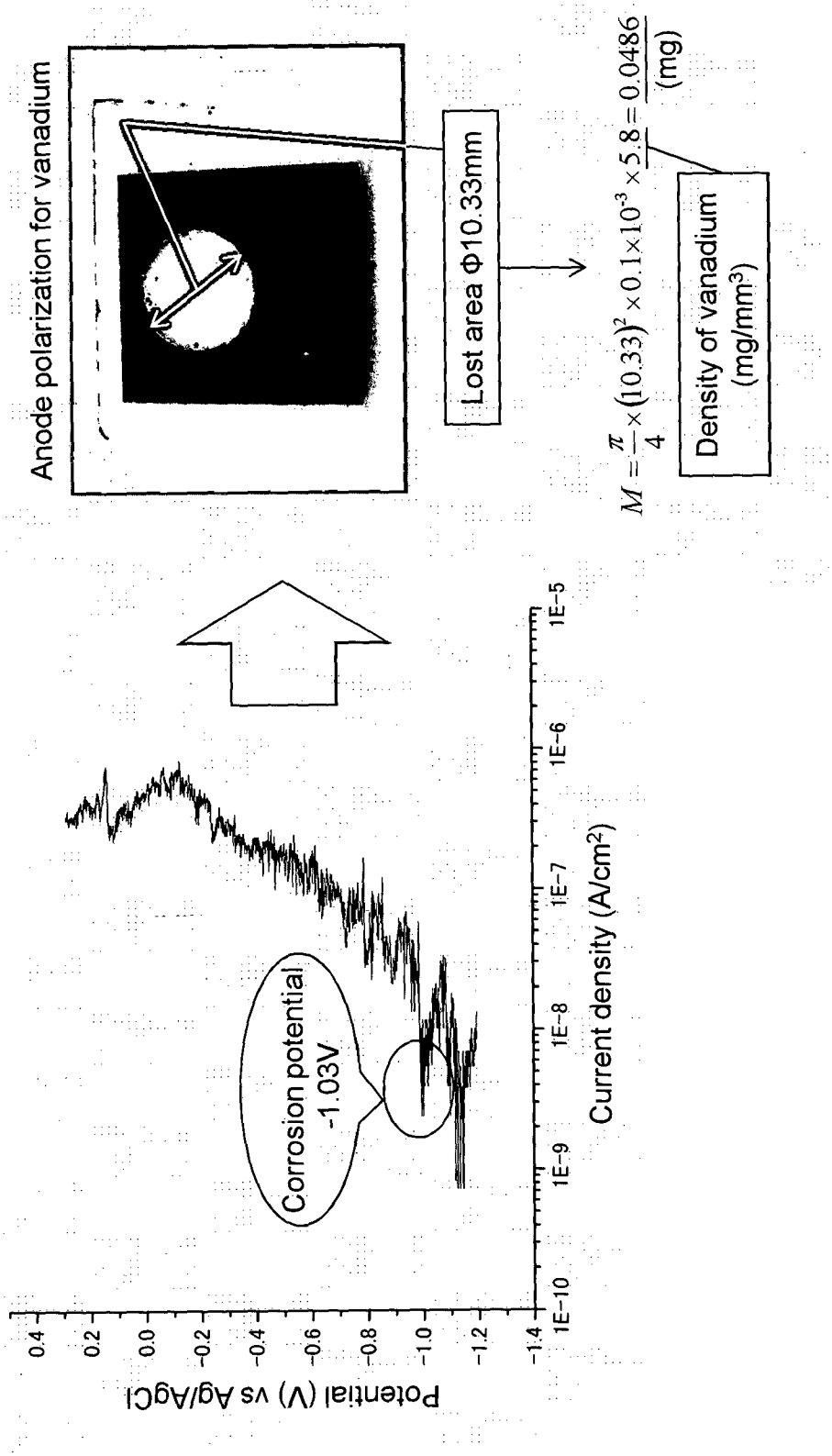

A
Potential (V) vs Ag/AgCl
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
Corrosion potential
-1.03V
1E-10
1E-9
1E-8
1E-7
1E-6
1E-5
Current density (A/cm2)
B
Anode polarization for vanadium
Lost area Φ10.33mm
$M = \frac{\pi}{4} \times (10.33)^2 \times 0.1 \times 10^{-3} \times 5.8 = \frac{0.0486}{(mg)}$
Density of vanadium
(mg/mm3)

Fig. 10

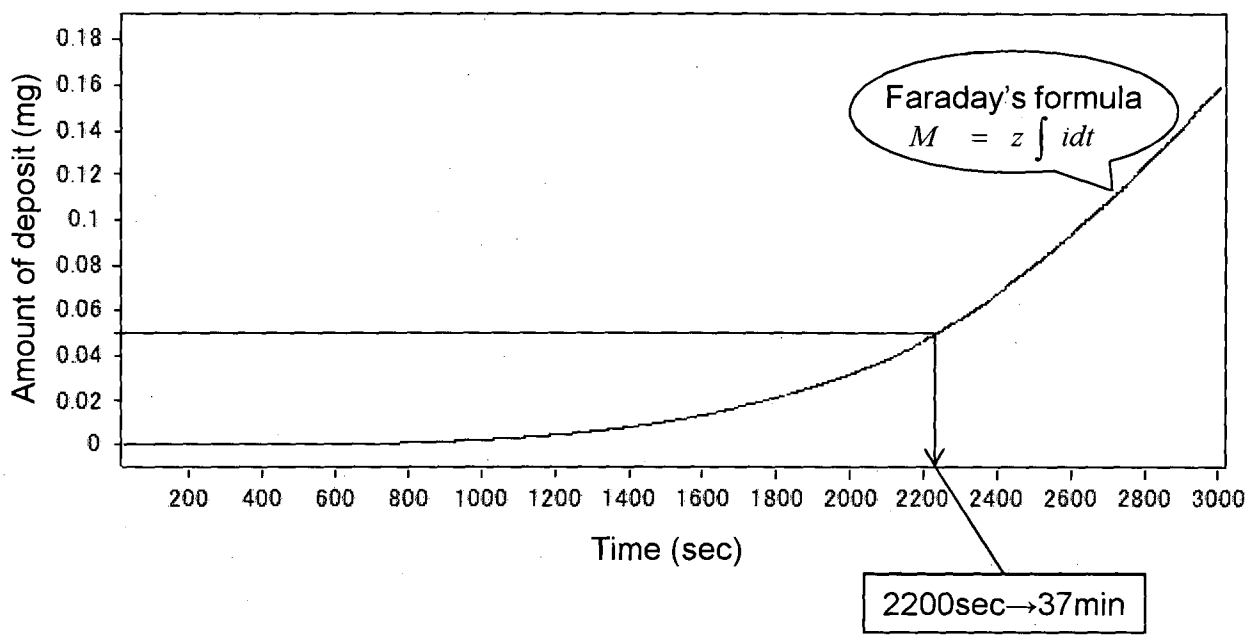
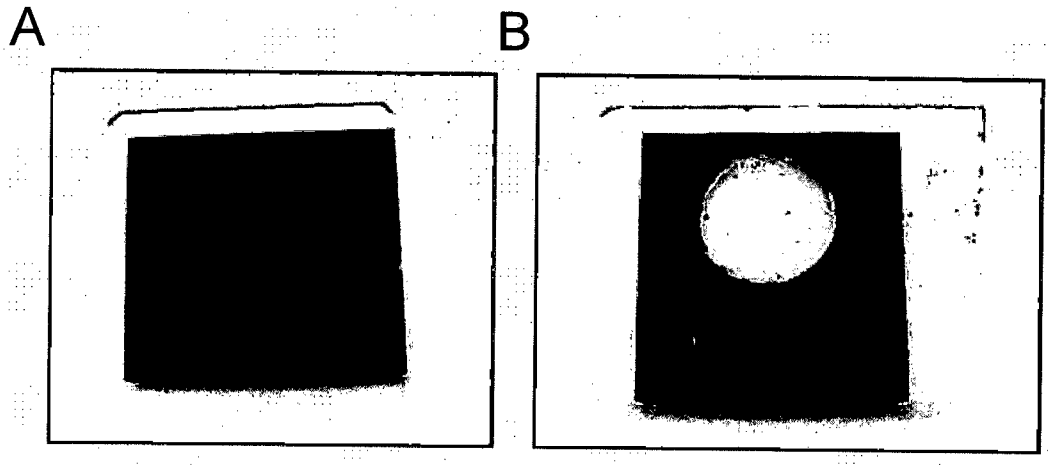

Amount of deposit (mg)
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2400
2600
2800
3000
Time (sec)
Faraday's formula
$M = z \int idt$
2200sec→37min

Fig. 11



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2013/066287

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. A61M37/00(2006.01)i, A61H39/08(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. A61M37/00, A61H39/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2013
Registered utility model specifications of Japan 1996-2013
Published registered utility model applications of Japan 1994-2013

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2006-296924 A (SEIRIN CORPORATION) 2006.11.02, paragraphs [0001], [0011], [0022], [0023], Figure 6 (No Family)	6,10-11
Y	WO 2010/111502 A2 (ETHICON, INC.) 2010.09.30, page 9, lines 12 to 17 & JP 2012-521804 A & US 2010/0249927 A1 & CA 2756732 A1 & CN 102448504 A	6,9

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03.09.2013	10.09.2013

Name and mailing address of the ISA/JP	Authorized officer
Japan Patent Office 3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan	NAGATOMI, Hiroyuki 3E 4658 Telephone No. +81-3-3581-1101 Ext. 3344

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2013/066287

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 6-78967 A (HAYASHI, Naritada) 1994.03.22, paragraphs [0005] to [0024], Figure 3 (No Family)	9
Y	WO 2003/013647 A2 (CYTO PULSE SCIENCES, INC.) 2003.02.20, page 21, line 22 - page 22, line 29, page 34, line 28 - page 36, line 14 & JP 2005-502399 A & CN 1539012 A	10-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2013/066287

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 1-5, 7-8
because they relate to subject matter not required to be searched by this Authority, namely:
See extra sheet.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

The subject matter of claims 1-5, relates to a method for treatment of the human body by delivering a drug, which does not require an international search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(iv)].

The subject matter of claims 7-8, relates to a method for treatment of the human body by hyperthermia therapy, which does not require an international search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(iv)].