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Declarations under Rule 4.17:

— as to the identity of the inventor (Rule 4.17(i))

[Continued on next page]

(54) Title: INTRAUTERINE DEVICE WITH CONTROLLED COPPER ION ELUTION

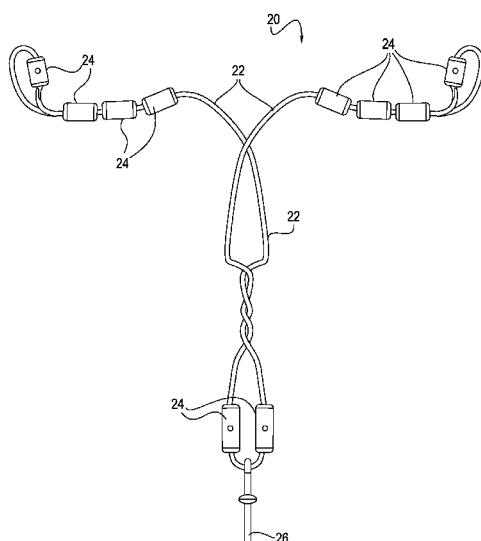


FIG. 3

(57) Abstract: An intrauterine contraceptive device may include a frame made completely or partially of a first metal having a first galvanic potential and at least one metallic member coupled with the frame that is made of a second metal having a second galvanic potential different from the first galvanic potential. In some embodiments, the first galvanic potential may be more anodic than the second galvanic potential. In alternative embodiments, the first galvanic potential may be more cathodic than the second galvanic potential. In one embodiment, the first metal is Nitinol, and the second metal is copper. In some embodiments, the first and second galvanic potentials may be configured to achieve, at least approximately, a desired copper ion elution rate for the intrauterine device.



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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- Published:**
- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

INTRAUTERINE DEVICE WITH CONTROLLED COPPER ION ELUTION

FIELD OF THE INVENTION

[0001] The present invention relates to medical devices. More specifically, the invention relates to intrauterine devices for contraception.

BACKGROUND

[0002] An intrauterine device (IUD) is a small, often T-shaped device, containing copper or hormone (e.g., levonorgestrel), which is inserted into the uterus to provide long-acting, reversible contraception. As of 2007, IUDs are the most widely used form of reversible contraception, with more than 180 million users worldwide. IUDs typically are one of two types—copper or hormonal.

[0003] Copper IUDs primarily work by disrupting sperm motility and damaging sperm so that the sperm are prevented from joining with an egg. Copper acts as a spermicide within the uterus, increasing levels of copper ions, prostaglandins, and white blood cells within the uterine and tubal fluids. The increased copper ions in the cervical mucus inhibit the sperm's motility and viability, preventing sperm from traveling through a thickened cervical mucus and/or destroying it as it passes through. Copper IUDs have a typical first-year contraceptive success rate greater than 98 percent.

[0004] Most copper IUDs have a plastic T-shaped frame that is wound with pure electrolytic copper wire and/or has copper collars (sleeves). The arms of the frame hold the IUD in place near the top of the uterus. The Paragard® intrauterine copper contraceptive device (www.paragard.com) and the generic TCU 380A are currently the most common copper IUDs. Copper IUDs can typically be implanted for up to 10 years.

[0005] The mechanism of action of a copper IUD is essentially a predictable electrochemical process of corrosion, driven by the IUD's immersion in the uterine fluid. Over time, the copper element (wires, beads, tubes, etc.) corrodes and releases copper ions. Typically, the release rate is governed by the surface area and volume of copper, the chemistry (especially pH) of the uterine fluid, and the specific composition and surface properties of the copper elements. The frame of the IUD on which the copper is attached is typically made of a flexible, non-corrosive polymer. Since typical polymers are not electrochemically active, they do not influence the ion release rate of the copper elements. Therefore, the copper ion release characteristics of a typical plastic-frame IUD are strictly governed by the amount, preparation and configuration of the copper itself. One challenge with copper IUDs has been that increased effectiveness typically means increased amounts of copper on the IUD, and increased amounts of copper typically lead to increased side effects, primarily increased menstrual and intermenstrual bleeding, and increased pelvic pain. Balancing effectiveness with minimization of side effects has been a continuing challenge for making copper IUDs.

[0006] One advantage of the copper IUD is its ability to provide emergency contraception up to five days after unprotected sex. It is generally known as the most effective form of emergency contraception available. Another advantage is that it contains no hormones, so it can be used while breast feeding, and fertility returns quickly after removal. Lastly, copper IUDs have been shown to be clinically effective for up to 10 years of continuous use. Disadvantages include the possibility of heavier menstrual periods and more painful menstrual cramping in some women.

[0007] A hormonal IUD, such as the Mirena® Levonorgestrel-releasing intrauterine system (www.mirena-us.com), uses the controlled release of a hormonal contraceptive such as Levonorgestrel (a progestin). The hormonal contraceptive released from a hormonal IUD prevents ovulation from occurring. The hormone also thickens the cervical mucus so that sperm cannot reach the fallopian tubes. Hormonal IUDs can typically be implanted for up to 5 years.

[0008] Hormonal IUDs do not increase bleeding as copper-containing IUDs do. Instead, they can often reduce menstrual bleeding or prevent menstruation altogether, and thus they are sometimes used as a treatment for menorrhagia (heavy menstrual bleeding). Hormonal IUDs have common side effects, however. The most common side effects with levonorgestrel IUDs

are hormone-related effects, such as headaches, nausea, breast tenderness, depression and cyst formation.

[0009] Based on effectiveness and the types of side effects, copper IUDs are preferable for many women. Although currently available copper IUDs are very effective, it would still be advantageous to have improved copper IUDs. For example, it would be advantageous to have copper IUDs that were very effective but had minimal side effects.

BRIEF SUMMARY

[0010] Disclosed herein are various embodiments of an improved copper IUD. Generally, the described embodiments provide an IUD with a desirable (or “controlled”) release rate of copper ions. Different embodiments may be configured with different copper ion release rates. For example, a particular copper ion release rate may be identified to provide a desired balance between IUD effectiveness and reduced side effects, compared to currently available devices.

[0011] In one aspect, an intrauterine contraceptive device may include a frame comprising a first metal having a first galvanic potential and at least one metallic member coupled with the frame, the at least one metallic member comprising a second metal having a second galvanic potential different from the first galvanic potential. In some embodiments, the first galvanic potential may be more anodic than the second galvanic potential. In alternative embodiments, the first galvanic potential may be more cathodic than the second galvanic potential.

[0012] In some embodiments, the frame may be made entirely of metal. Alternatively, the frame may be made partially of metal and partially of a non-metallic substance. For example, the first metal may in some embodiments be Nitinol. The second metal may be copper. In some embodiments, for example, the metallic members are multiple copper sleeves disposed around the frame at various locations. Some embodiments include the combination of the first metal being Nitinol and the second metal being copper. In embodiments where the second metal is copper, the first galvanic potential and the second galvanic potential may be configured to achieve approximately a desired copper elution rate of the at least one metallic member. In all of these embodiments, the non-metallic substance may be a polymer, a silicone rubber or other

engineered polymer plastic, for example. Optionally, the device may further include a retrieval string attached to one end of the metal frame.

[0013] In another aspect, a method of preventing conception may involve advancing an intrauterine contraceptive device into a uterus, where the intrauterine device includes a frame comprising a first metal having a first galvanic potential, and at least one metallic member coupled with the frame, comprising a second metal having a second galvanic potential different from the first galvanic potential. In some embodiments, the second metal may be copper, and the first and second galvanic potentials may be configured to achieve approximately a desired copper ion elution rate. In some embodiments, the first metal may be Nitinol, and advancing the contraceptive device into the uterus may involve advancing a distal end of an introducer device through a cervix, into the uterus, and advancing the contraceptive device out of the distal end, thus allowing the Nitinol of the frame to expand to contact a wall of the uterus.

[0014] In another aspect, a method of manufacturing an intrauterine contraceptive device may involve coupling a frame comprising a first metal having a first galvanic potential with at least one metallic member, comprising a second metal having a second galvanic potential different from the first galvanic potential. The second metal may be copper, and the first and second galvanic potentials may be configured to achieve approximately a desired copper elution rate. The first metal may be Nitinol. In some embodiments, coupling the frame with the at least one metallic member may involve attaching multiple copper sleeves around an outside of the Nitinol frame at different locations along the frame.

[0015] These and other aspects and embodiments will be described in further detail below, in reference to the attached drawing figures.

BRIEF DESCRIPTION OF DRAWINGS

[0016] Figure 1 is a front view of a prior art, T-shaped, copper IUD with a plastic support structure;

[0017] Figure 2 is a bar graph illustrating a galvanic series for a number of common metals and alloys;

[0018] Figure 3 is a front view of a copper IUD with a metal frame, according to one embodiment;

[0019] Figure 4 illustrates potentiodynamic polarization curves for copper sleeves tested in simulated uterine fluid at 37°C, pH=7.1;

[0020] Figure 5 illustrates potentiodynamic polarization curves for bare Nitinol frames tested in simulated uterine fluid at 37°C, pH=7.1; and

[0021] Figure 6 illustrates potentiodynamic polarization curves for finished device assemblies (copper sleeves crimped onto Nitinol frames) tested in simulated uterine fluid at 37°C, pH=7.1.

DETAILED DESCRIPTION

[0022] The mechanism of action of a copper IUD is essentially a predictable electrochemical process of corrosion, driven by the IUD's immersion in the uterine fluid. Over time, the copper elements of the IUD (copper wires, beads, tubes, or the like) corrode and release copper ions. For a given IUD, the copper ion release rate can be measured using standard laboratory tests in simulated uterine fluid (SUF). Typically, the release rate is governed by the surface area and volume of copper, the chemistry (especially pH) of the SUF, and the specific composition and surface properties of the copper elements. In currently available IUDs, the primary driver influencing the copper release rate is the amount of exposed copper surface area. In other words, to achieve a higher copper ion release rate, an IUD would typically have an increased copper surface area, which generally means the IUD will contain more copper overall.

[0023] Referring now to Figure 1, a typical, prior art, T-shaped, copper IUD 10 is illustrated. The IUD 10 includes a frame 12, copper sleeves 14 disposed around the frame 12 in three areas, and a retrieval string 16. The frame 12 is typically made of a flexible polymer and is often T-shaped for positioning in the uterus. Since typical polymers are not electrochemically active, they do not influence the ion release rate of the copper elements 14. Therefore, the copper ion release characteristics are strictly governed by the amount of surface area of the copper sleeves 14 themselves.

[0024] Galvanic corrosion is an electrochemical process in which one metal corrodes preferentially to another when both metals are in electrical contact and immersed in an

electrolyte. The strength of this electrical potential between two metals or alloys is called the galvanic potential. The galvanic reaction can be exploited for positive benefit. For example, a galvanic potential between dissimilar metals can be used in primary batteries to generate an electrical voltage. The measured voltage is representative of the transfer of charged metal ions from one of the metals (the anode) to the other (the cathode). The stronger the galvanic effect between the two metals, the higher the transfer rate of ions from the anode to the cathode.

[0025] To determine the galvanic potential between two metals, we use a galvanic series, an example of which is illustrated in Figure 2. In a galvanic series, metals are ranked by the electrical potential they develop in a given electrolyte against a standard reference electrode—i.e., their galvanic potential versus the reference electrode. The relative position of two metals on such a series determines which metal will be the anode and which will be the cathode (if they are put in contact in an appropriate electrolyte). The magnitude of the distance between the two metals on the galvanic series will determine the strength of the galvanic potential between them. A specific galvanic series can be determined for any metals or alloys of interest, tested in a specific electrolyte (e.g., SUF) at an appropriate pH.

[0026] Referring now to Figure 3, in one embodiment, an IUD 20 may include a metal frame 22, multiple copper sleeves 24 (or “copper elements”), and a retrieval string 26. This embodiment of the IUD 20, as well as other, alternative embodiments, is described in further detail in pending U.S. Patent Application Serial Number 13/795,940, entitled “Intrauterine Contraceptive Device,” filed March 12, 2013, which is hereby incorporated by reference in its entirety. According to various embodiments, the galvanic effect can be exploited in the copper IUD 20 by coupling the copper elements 24 to the metal frame 22 or other metal structure. The material of the metal frame 22 or structure may be chosen to achieve a desired galvanic effect between itself and the copper elements 24. In one embodiment, for example, the frame 22 may be made of Nitinol (see Figure 3, on which Nitinol and copper are depicted).

[0027] For the sake of comparison, a “baseline” copper ion elution rate may be defined as one in which there is no galvanic effect present (e.g., copper on a polymer frame, as in prior art IUDs). If the metal frame 22 (or other metallic structure) has a galvanic potential more anodic than the galvanic potential of the copper sleeves 24 (lower on the galvanic series), then the

electrochemical driving force would be toward the copper sleeves 24, thereby reducing the copper ion release rate relative to the baseline. Alternatively, if the metal frame 22 or structure that has a galvanic potential more cathodic than the copper sleeves 24 (higher on the galvanic series), then the electrochemical driving force would be away from the copper sleeve 24, thereby increasing the copper ion release rate relative to the baseline. The greater the difference between the materials on the galvanic series, the more significant the decrease or increase in copper ion release rate. The galvanic potential is also related to the relative surface areas of the anode and the cathode, so the surface area ratio between the frame 22 and the copper sleeves 24 may also be selected to achieve a desired ion release rate.

[0028] In such a way, the material of the frame 22 and/or other elements in contact with the copper elements 24 may be selected to control the galvanic potential between the frame 22 and the copper 24, thereby allowing specificity, control and optimization of the ion release rate. This may have a number of advantages. In some embodiments, the IUD 20 may achieve a copper release rate comparable or identical to that of a currently available (i.e., prior art) IUD with a lower amount (i.e., less surface area) of copper, by coupling the copper 24 with the metal frame 22 that is more cathodic than the copper 24. The smaller surface area of the copper 24 may help reduce copper-related side effects, compared to prior art copper IUDs. Alternatively, in other embodiments, the IUD 20 may be configured to release copper ions at a rate similar or identical to that of a currently available copper IUD but for a longer period of time. This may be achieved by giving the copper sleeves 24 a greater exposed surface area than the copper element(s) of a currently available device, while coupling the sleeves 24 with the frame 22 made of a material that is more anodic than the copper elements 24. In this case, the greater amount of available copper is balanced by a slower release rate to achieve, overall, a similar ion release profile. However, in this case, the slower release rate with a larger copper reservoir allows the elution to happen over a potentially longer period of time, thereby extending the effectiveness of the IUD 20 beyond the typical 10 years of device life.

[0029] In still other embodiments, the IUD 20 may achieve a copper ion release rate whose release curve is more curvilinear or more linear in comparison to the standard commercial copper IUD release rate curve. In this manner, a metallic IUD with a controlled release rate may be chosen to avoid the burst release of copper ions typically associated with commercial copper

IUDs which implement a plastic core. The burst release of copper ions has been shown to be directly associated with the onset of clinical side effects of the standard commercial copper IUDs, including in particular, side effects experienced in the first 1 to 6 months of IUD use, including increased menstrual bleeding, intermenstrual bleeding, cramping and general pelvic pain. Such a reduction in clinical side effects without the need for ancillary medications would be a significant advantage.

[0030] In various embodiments, the metal frame 22 and/or other metal structure(s) may be made from any material with desired galvanic properties, including but not limited to Nitinol, stainless steel, titanium, cobalt-based alloys, tantalum, platinum, gold, silver, and MP35N. The frame 22 may be made from one material or multiple materials. In alternative embodiments, the frame 22 may be made entirely of metal or may have discrete active metallic portions or elements, some or all of which may be in contact with the copper elements 24, with non-metallic parts between the metallic portions or with no parts at all between the metallic portions. The copper elements 24 may take any suitable shape, size, form and number in various embodiments. In the embodiment illustrated in Figure 3, there are ten copper sleeves 24 disposed on the frame 22. Alternative embodiments may include more or fewer sleeves 24 and/or smaller or larger sleeves 24. In other alternative embodiments, the sleeves 24 may be replaced by, or used in combination with, other copper elements, including but not limited to wire, ribbon, coils, tubes, beads, and the like. Additionally, surface processing of the frame 22 and/or other metallic structure may be tailored to achieve a desired galvanic potential. For example, this may be accomplished through heat treatment, oxidation, electropolishing, passivation, and/or other chemical processing.

Description of Corrosion Testing

[0031] To determine the baseline corrosion behavior of a Nitinol frame and copper sleeves, such as those described above in reference to Figure 3 (together referred to below as the “ContraMed IUD”), and to evaluate the effects of different surface processing on the Nitinol frame, preliminary potentiodynamic polarization testing was conducted. Processing of the Nitinol surface was targeted to achieve a rest potential (“Erest”) similar to or higher than that of the copper sleeves, in order to both optimize the intentional corrosion (and ion release) of the

copper and minimize any deleterious galvanic corrosion effects on the Nitinol frame. A review of the literature of electropolished, etched, chemically-polished, and heat-treated (with oxide) Nitinol revealed that rest potentials can be of a wide range, from less than -420 mV to as high as +20 mV vs. SCE.

[0032] Potentiodynamic polarization testing was conducted according to ASTM F2129 on copper sleeves and Nitinol frames made from different starting wires and processed in different ways. This testing was conducted in phosphate buffered saline (PBS) at 37°C at a pH of 7.1. PBS was chosen for this testing for simplicity as well as to allow comparison of the Nitinol corrosion behavior with data from the literature. The testing was conducted using a Gamry Cyclic Polarization Corrosion Apparatus.

[0033] Testing was also conducted in simulated uterine fluid (SUF) per the following composition: NaHCO₃ 0.25; NaH₂PO₄ • 2H₂O 0.072; Glucose 0.50; CaCl₂ 0.167; KCl 0.224; NaCl 4.97. The Simulated Uterine Fluid solution was purged with nitrogen gas, and pH was adjusted to 7.1 before testing. The Rest Potential (“Er”) was monitored for one hour before the corrosion test began. Specimens were subjected to a scan from below the zero current potential to 1.0 V at a rate of 1 mV/s. No reverse scan was conducted, and the test was stopped after a scan of -1 mV/s to 0.8 V (vs. Er).

Results

[0034] As described previously, the ideal Nitinol surface processing scheme would achieve a rest potential (E_{rest}) that is similar to or higher than that of the copper sleeves (-286.1 mV), in order to both optimize the intentional corrosion (and ion release) of the copper and minimize any deleterious galvanic corrosion effects on the Nitinol frame. At the same time, the Nitinol surface should demonstrate excellent resistance to breakdown. Based on the work of Rosenbloom and Corbett, a Nitinol surface with an average breakdown potential in excess of 600 mV (as tested in PBS at 37°C) is generally considered to be in an optimum state for use as a medical implant.

[0035] Figures 4-6 illustrate plots of all the curves for a given sample group on the same axes. Figure 4 illustrates potentiodynamic polarization curves for copper sleeves tested in simulated uterine fluid at 37°C, pH=7.1. Figure 5 illustrates potentiodynamic polarization curves for bare Nitinol frames tested in simulated uterine fluid at 37°C, pH=7.1. Figure 6 illustrates

potentiodynamic polarization curves for finished device assemblies (copper sleeves crimped onto Nitinol frames) tested in simulated uterine fluid at 37°C, pH=7.1. As illustrated in Figures 4-6, the copper curves and the Nitinol curves are very different. Copper corrodes via generalized corrosion, while Nitinol, due to its formation of a protective surface oxide layer, corrodes via breakdown (i.e., pitting). As expected, the corrosion of the assembled devices is dominated by corrosion of the copper sleeves, and no breakdown behavior is observed in the potentiodynamic polarization curve.

[0036] Although various embodiments and features are described herein, the present invention extends beyond the specifically disclosed embodiments to other alternative embodiments and/or uses of the invention and obvious modifications and equivalents thereof. Thus, the scope of the present invention herein disclosed should not be limited by the particular disclosed embodiments described above.

CLAIMS

What is claimed is:

1. An intrauterine contraceptive device, comprising:
a frame comprising a first metal having a first galvanic potential; and
at least one metallic member coupled with the frame, the at least one metallic member comprising a second metal having a second galvanic potential different from the first galvanic potential.
2. A device as in claim 1, wherein the first galvanic potential is more anodic than the second galvanic potential.
3. A device as in claim 1, wherein the first galvanic potential is more cathodic than the second galvanic potential.
4. A device as in claim 1, wherein the frame is made entirely of metal.
5. A device as in claim 1, wherein the frame is made partially of metal and partially of a non-metallic substance.
6. A device as in claim 1, wherein the frame comprises a non-rigid material selected from the group consisting of a flexible polymer thread, a polyester thread, a nylon thread or other biocompatible fabric.
7. A device as in claim 1, wherein the first metal is Nitinol.
8. A device as in claim 1, wherein the second metal is copper.
9. A device as in claim 8, wherein the at least one metallic member comprises multiple Copper sleeves disposed around the frame at various locations.

10. A device as in claim 8, wherein the first galvanic potential and the second galvanic potential are configured to achieve approximately a desired copper elution rate of the at least one metallic member.

11. A device as in claim 1, wherein the first metal is Nitinol, and wherein the second metal is copper.

12. A device as in claim 1, further comprising a retrieval string attached to one end of the metal frame.

1/5

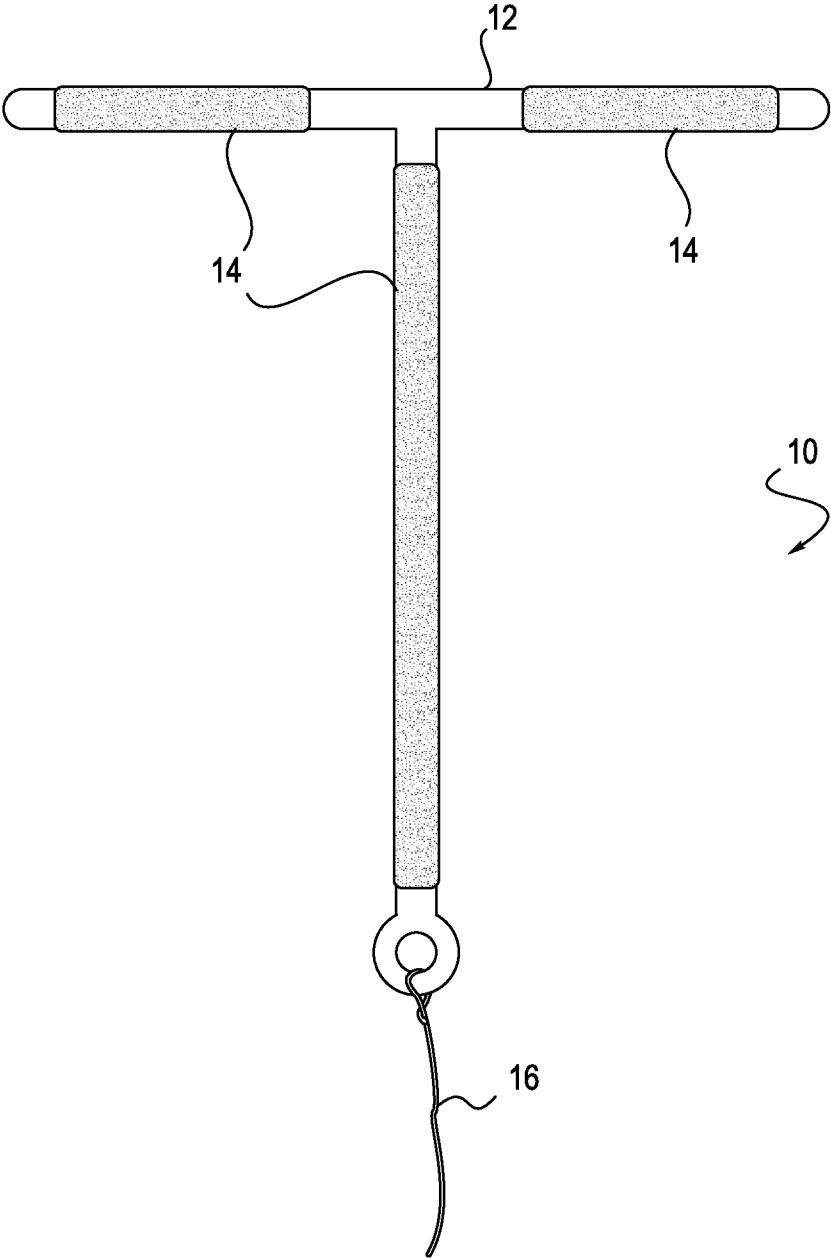


FIG. 1
(Prior Art)

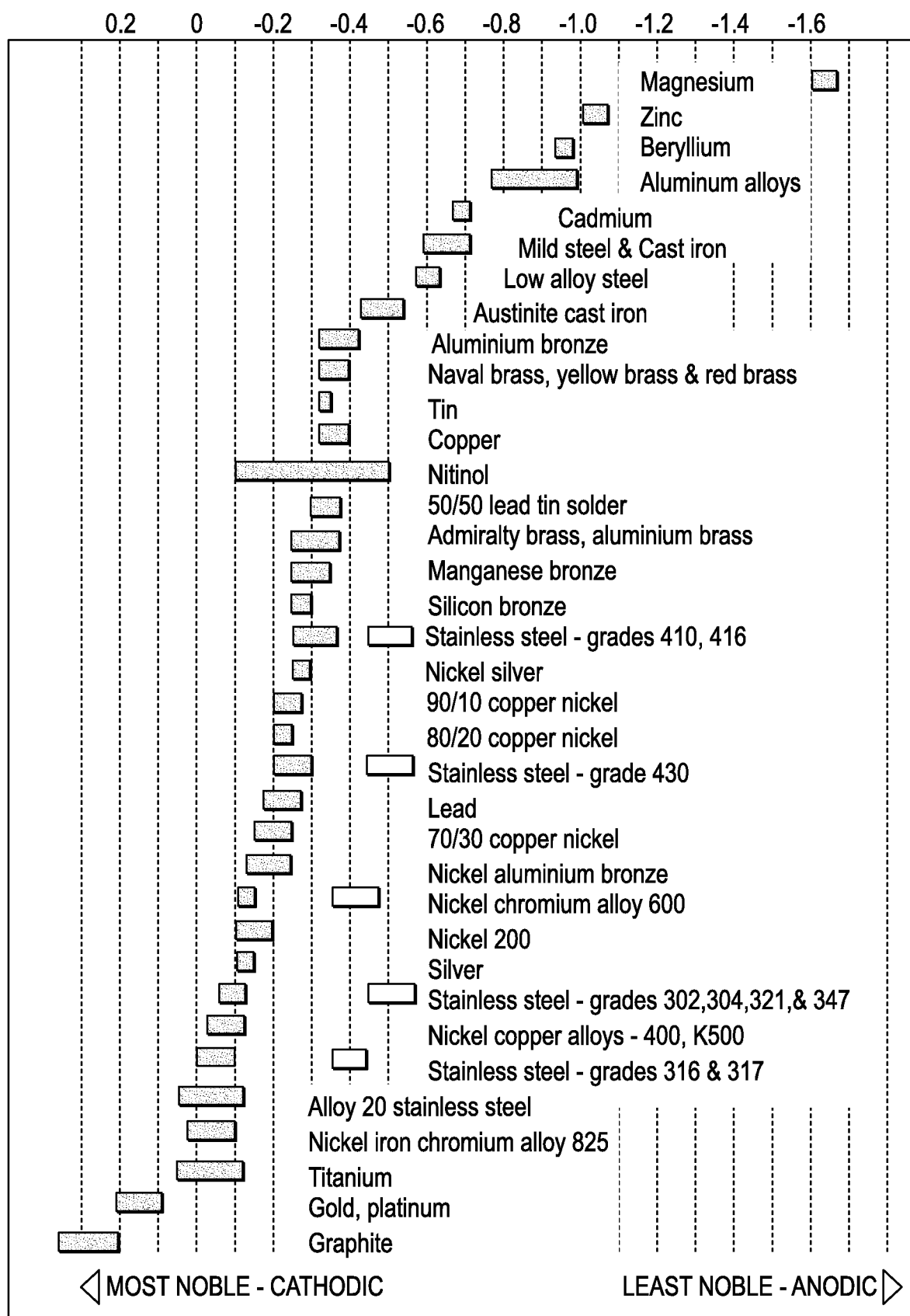


FIG. 2

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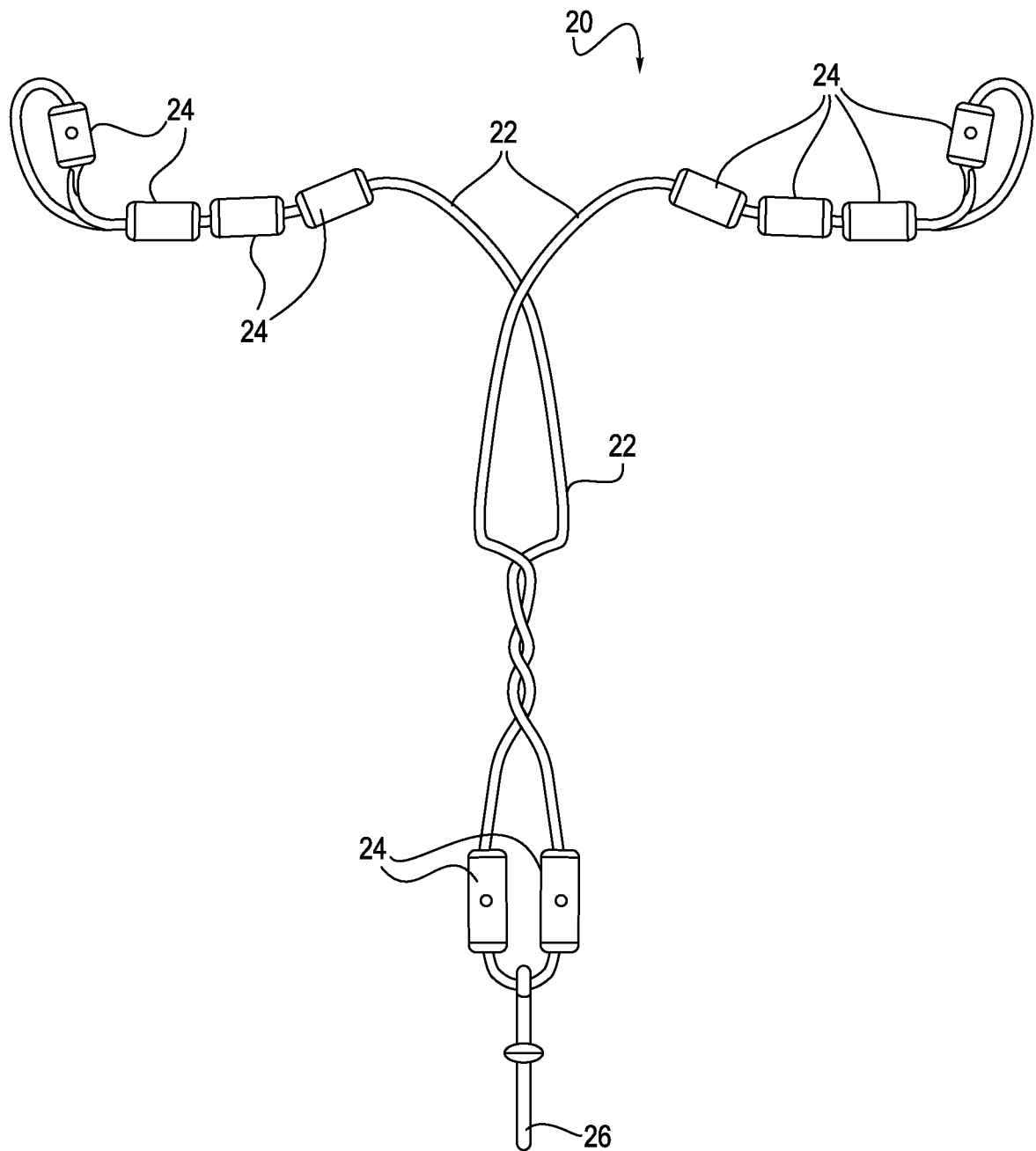


FIG. 3

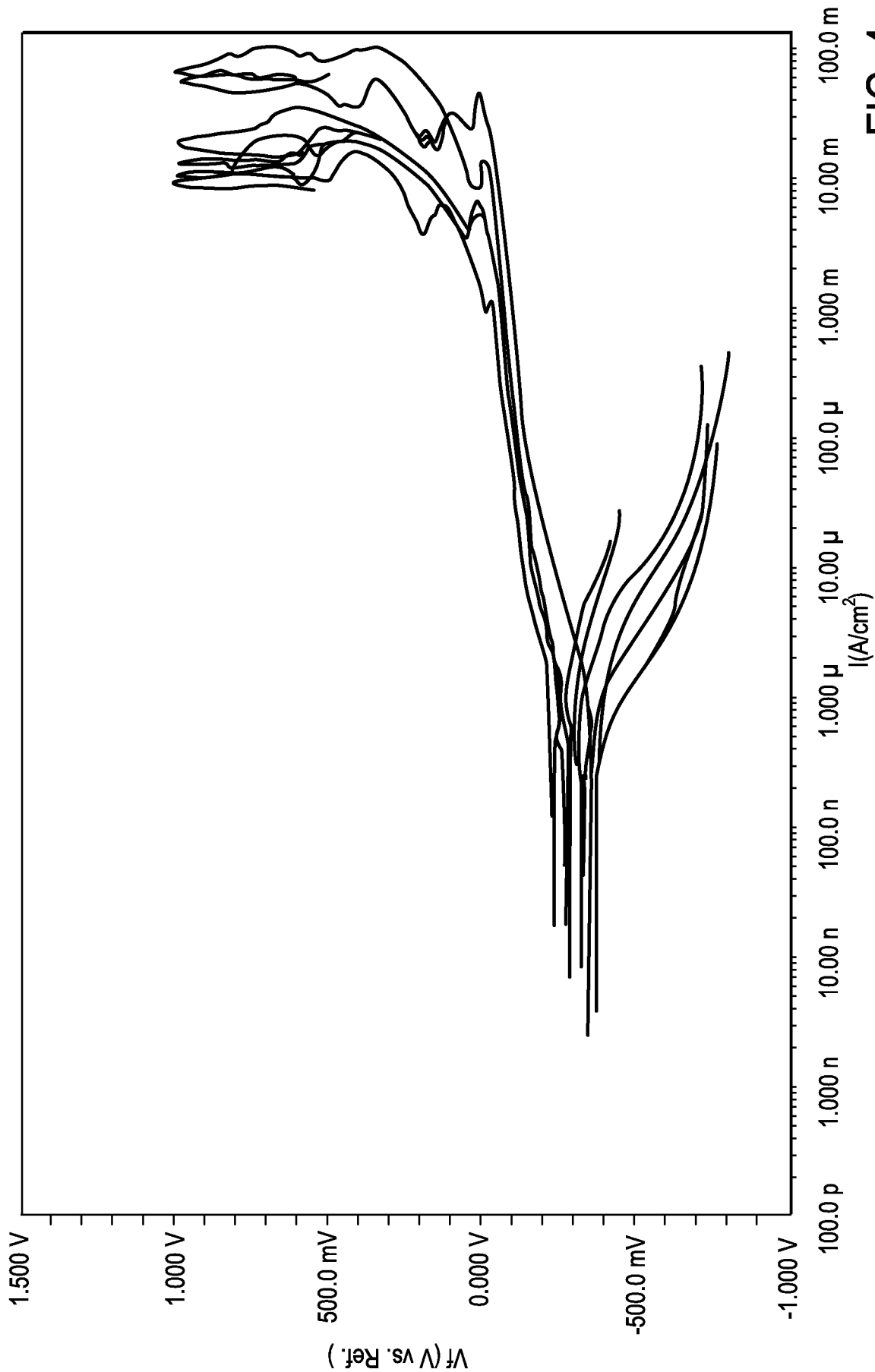


FIG. 4

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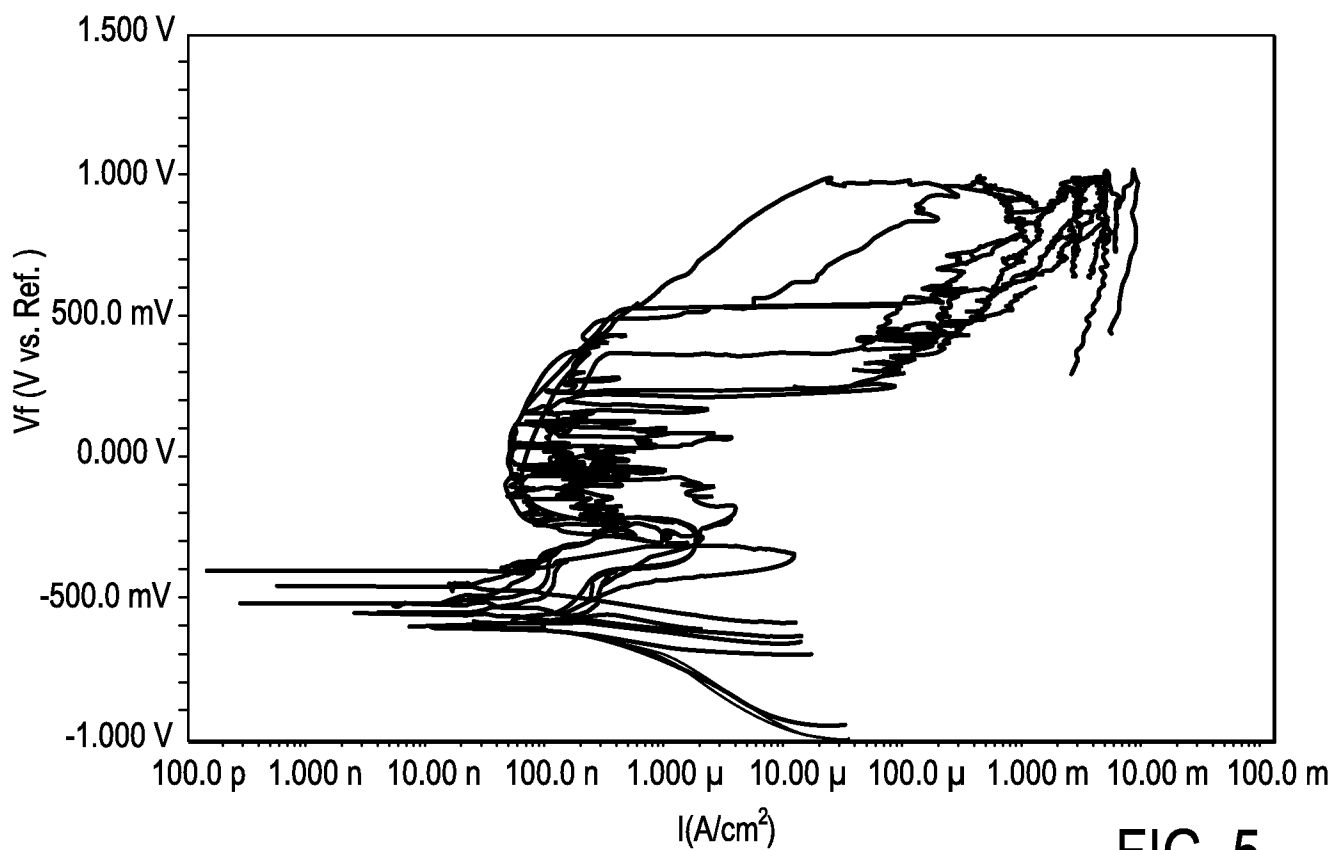


FIG. 5

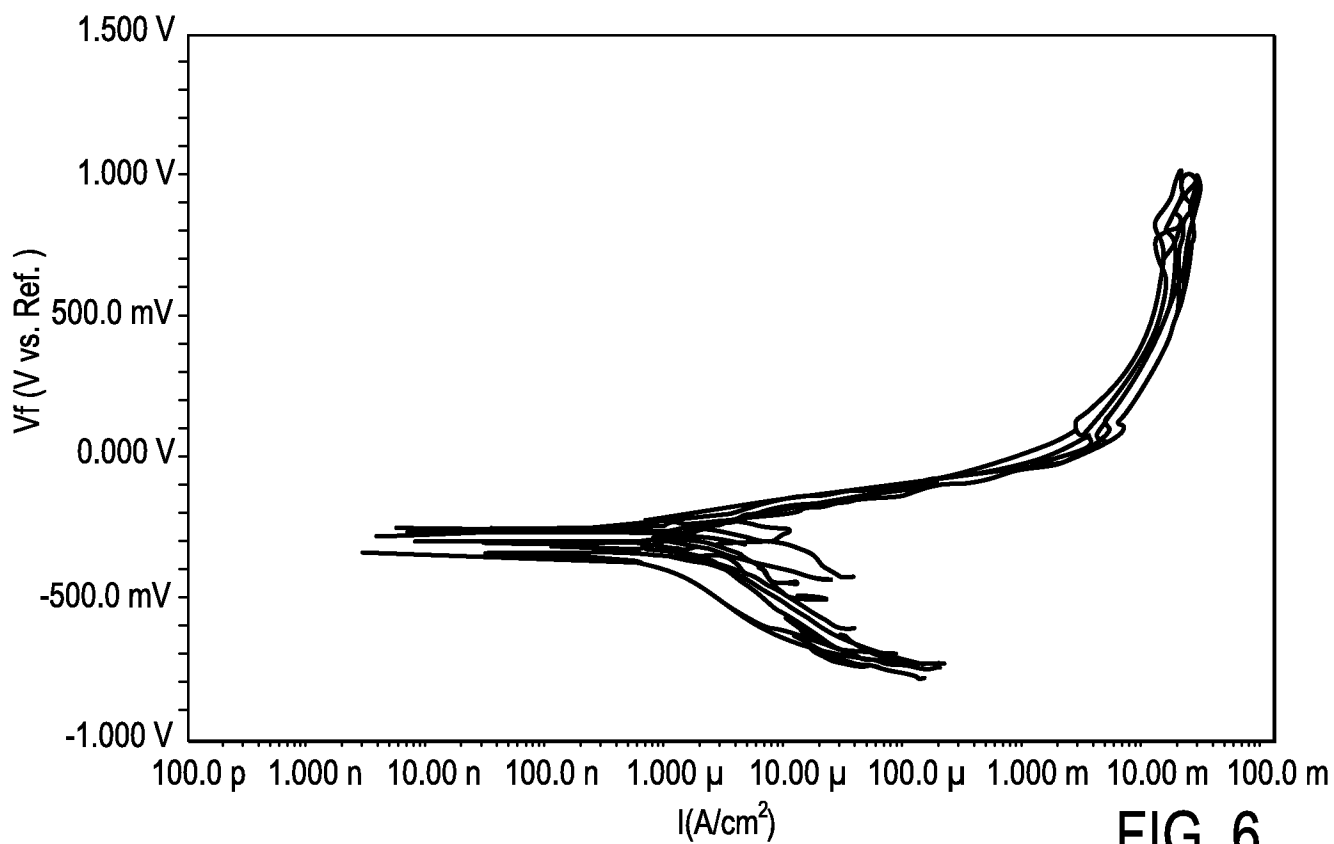


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/49392

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61F 6/14 (2014.01)

CPC - A61F 6/14

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)

IPC(8): A61F 6/06, 6/08, 6/14 (2014.01)

CPC: A61F 6/06, 6/14, 6/142, 6/144; USPC: 128/833, 839, 840

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

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

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C, B, DE-A, DE-T, DE-U, GB-A, FR-A); Espacenet; Google; Google Scholar; Google Patent; ProQuest; Medline/PubMed, IP.com; Search terms used: Intrauterin*, IUD, Contracept*, Birth, Control, Fertility, Control, Nitinol, Nickel, Titanium, Nickel, Alloy*, Copper*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 202096333 U (XUZHE, Z) January 4, 2012; figures 1-3; paragraphs [0028], [0050] (see Google Patents translation)	1-4, 7-12
-		-----
Y		5, 6
Y	US 2008/0047563 A1 (TAL, MG et al) February 28, 2008; figure 5; paragraph [0061]	5, 6
A	US 3789838 A (FOURNIER, EP et al) February 5, 1974; entire document	1

☐ Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search

29 October 2014 (29.10.2014)

Date of mailing of the international search report

31 MAR 2015

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