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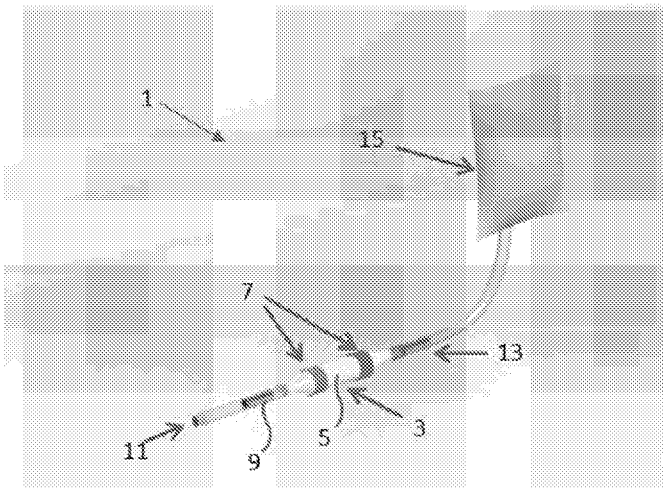

FIG. 5B

(57) Abstract: Electroactive pumps and methods of their use are disclosed herein. A pump can include a container having an initial volume. The container includes a passivated conductive film extending along at least a portion of the wall and an outlet valve. Application of a first voltage to the film in a physiological electrolyte solution causes a portion of the film to swell, thereby decreasing the volume of the container to a second volume. The transition from the initial volume to the second volume is capable to dispense a fluid housed within the container through the outlet valve. For example, in some embodiments, the interior void of the container is devoid of solid moving parts and is at least partially filled with a solution (e.g., a solution containing insulin). The solution can be dispensed upon the transition to the second volume.

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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PASSIVATED CONDUCTIVE FILMS, AND ELECTROACTUATORS CONTAINING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos. 62/634,403, filed February 23, 2018, and 62/634,413, filed February 23, 2018, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention is directed to passivated bilayered conductive films. The films are useful as biocompatible electroactuators, and can be used in implantable medical devices, including implantable pumps for delivering medicaments and other fluids *in vivo*.

BACKGROUND

Polymeric electroactuators have attracted considerable interests in their application as artificial muscles in robots. However, due to major concerns on biocompatibility and durability, existing high-performance polypyrrrole (PPy)-based electroactuators to date are unsuitable for devices designed to work in *in vivo* settings. Transformation of PPy electroactuators stems from ion exchanges between the polymer, doped with anions such as $CF_3SO_3^-$, dodecylbenzenesulfonate (DBS), or bis-(trifluoromethanesulfonyl)imide (TFSI), and the surrounding electrolyte. Unfortunately, these large dopant anions are inherently cytotoxic, precluding use in *in vivo* applications. Additionally, PPy electroactuators doped with such large anions achieve their best performance only when the electrolyte is enriched in assistive anions such as TFSI-, PF_6-, or ClO_4-, none of which are available in physiological fluids. To address this problem of biocompatibility, the dominant approach is to load the necessary anions into a gel and encapsulate the PPy-gel laminate using biocompatible coatings. Such designs also enable the actuators to work in air independently. Nonetheless, PPy electroactuators are often implemented as multi-layered laminates to work in an aqueous electrolyte, because a unilateral passivation is needed to block ion exchanges on one side of the PPy film in order to achieve differential stress generation. Otherwise, strain and stress produced at the opposing sides would counteract each other, thus significantly diminishing the overall performance of the actuator. However, such layered designs add a substantial amount of mechanical rigidness and load to the PPy film, impeding its electroactuation. Moreover, differential stresses generated at the layer

interface during electroactuation often cause ripples and cracks in the laminate, ultimately leading to delamination and breakdown of the actuator.

There remains a need for biocompatible, polymeric electroactuators that can be used to fabricate implantable medical devices. In particular, the field of drug delivery could find benefits from improved biocompatible electroactuators. For example, patients with Type 1 Diabetes (T1D) rely on external insulin treatment permanently. Much research is directed toward making this treatment easier on patients. Most patients use insulin subcutaneously, either as multiple daily injections (MDI) or as continuous subcutaneous insulin infusion (CSII). Alternatively, intraperitoneal (IP) administration of insulin with an implant can be used. Polymer implants, microencapsulation, micro-chip drug reservoirs, immunoisolating capsules, and diffusion chambers are some examples of "sustained released" implantable devices which have been commercialized. But the low capability of these approaches in mimicking the pancreatic insulin discharge profile stimulated the development of implantable micropumps to deliver the insulin in a predefined pattern. Utilizing controllable actuators coupled with a continuous glucose meter and a control algorithm, these pumping systems can be programmed for specific rates of release and also have an order of flexibility to play active (not only passive) roles in response to the different working conditions. Comparing to subcutaneous injections (MDI or CSII), advantages of continuous intraperitoneal insulin infusion (CIPII) using an implanted insulin pump include improved glycaemic regulation and decreased frequency of hypoglycaemia, as well as improved quality of life and treatment satisfaction (Van Dijk, P., *Diapedia*). These benefits led the way for several manufacturers (Accu-Chek, Animas, Debiotech, Deltec, Insulet, Medtronic and Sooil) around the world to develop implantable insulin pumps, such as the Infusaid M1000, Siemens ID1 / ID3 and Minimed PIMS/MIP (later Medtronic). However, clinical complications, including infection at the implantation site, catheter obstructions due to insulin aggregates, and fibrotic encapsulation of the tip of the catheter, have hindered the widespread adoption of CIPII with an implanted insulin pump. As a result, most insulin pump producers decided to cease the development of IP insulin pumps. Currently, only one implantable pump (MIP 2007C, Medtronic/Minimed, Northridge, CA, USA) is still available for clinical use in very few patients around the world. Thus, there is a critical need to continue developing the CIPII pumps to mitigate those clinical complications for T1D patients to ultimately benefit from the CIPII therapy.

An implantable insulin micropump is a critical component in CIPII. Additionally, a catheter is placed in the abdomen to deliver IP insulin. Implantation of the pump is performed under general anesthesia. Usually, the pump is located in a subcutaneous pocket in a lower

abdominal quadrant. From this pocket, the peritoneum is opened and the tip of the catheter is carefully inserted and directed towards the liver. After implantation, the pump reservoir is refilled at the outpatient clinic transcutaneously (Van Dijk, P., *Diapedia*). Currently there are several areas for micropump improvement in insulin delivery devices. First, conventional devices utilize bulky piston-plunger motors. Decreasing the size of the pump will result in fewer complications and higher comfort for the patient. Second, conventional piezoelectric actuators require a high actuation voltage, on the range of 100 Volts, introducing the risk of electric injury. Reducing the voltage requirement will thereby reduce the risk to the patient.

SUMMARY

Disclosed herein are high-performance polymeric electroactuators that are biocompatible. The electroactuators include passivated conductive films having an active face and an inactive face, the active face being substantially electrically conductive, and the inactive face being substantially electrically non-conductive. The films can include one or more electrically conductive polymers entangled with one or more hydrophilic, dynamic polymers. The films can be prepared using an iterative electropolymerization process.

Electroactive pumps and methods of their use are also disclosed herein. A pump can include a container having an initial volume. The container includes a passivated conductive film extending along at least a portion of the wall and an outlet valve. Application of a first voltage to the film in a physiological electrolyte solution causes a portion of the film to swell, thereby decreasing the volume of the container to a second volume. The transition from the initial volume to the second volume is capable to dispense a fluid housed within the container through the outlet valve. For example, in some embodiments, the interior void of the container is devoid of solid moving parts and is at least partially filled with a solution (e.g., a solution containing insulin). The solution can be dispensed upon the transition to the second volume.

Application of a second voltage to the film increases the volume of the container. Certain embodiments of the electroactive pump further include an inlet valve and a reservoir in fluid communication with the inlet valve. The increase in the volume of the container can cause fluid from the reservoir to travel through the inlet valve and into the interior void of the container.

In some embodiments, the container is an elongated balloon. The passivated conductive film can extend around a circumference of an outer surface of the balloon, or it can extend laterally along an outer surface of the balloon. In some embodiments, the passivated conductive film forms the wall of the balloon. In some embodiments, a physiological electrolyte solution bathes a portion of the passivated conductive film.

In some embodiments, the first voltage is less than 5 Volts. The passivated conductive film can be configured to respond to voltage that is applied wirelessly. The pump can, in some embodiments, be devoid of internal or external batteries.

Methods of dispensing fluids from a container are disclosed herein. The methods can include providing a container having an initial volume and a passivated conductive film extending along at least a portion of an outer surface of the container, applying a first voltage to the passivated conductive film in a physiological electrolyte solution, swelling a portion of a passivated conductive film, decreasing the volume of the container to a second volume, and dispensing a fluid from the container through an outlet. The step of swelling a portion of the passivated conductive film can include drawing ions from a surrounding physiological electrolyte solution into the passivated conductive film. In some embodiments, the first voltage is less than 5 Volts. The first voltage can be wirelessly applied. In some embodiments, the methods can further include applying a second voltage to the pump, deswelling a portion of the passivated conductive film, and increasing the volume of the container. Increasing the volume of the container can create a suction that pulls fluid into the container from an adjacent reservoir.

The details of one or more embodiments are set forth in the descriptions below. Other features, objects, and advantages will be apparent from the description and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-1D depict composition and properties of PPy/PEG-borate composite films. Samples were synthesized at a constant potential of 1.1 V for 90 min. (Figure 1A) Chemical composition. (Figure 1B) and (Figure 1C) Electroactivity difference between the two sides of a film in PBS. A piece of 3M XG6110 water-resistant tape was laminated to either the inactive (Figure 1B) or active (Figure 1C) side to block mass transport. The two specimens had the same dimensions. Left, no stimulation; right a -1 V was applied for 10 s. (Figure 1D) Photos and SEM images of the two sides respectively.

Figures 2A-2E depict observation and characterization of microspots on the inactive side. The sample was synthesized at 1.1 V for 120 min. (Figure 2A) Optical microscopic image. The circled region was selected for further investigations in (Figure 2B–2E). (Figure 2B) SEM image. (Figure 2C) AFM image. (Figure 2D) and (Figure 2E) In situ EDS maps of fluorine (Figure 2D) and oxygen (Figure 2E). Brighter pixels correlated to higher contents.

Figures 3A-3D depict electrochemical studies on nucleus growth. (Figure 3A) The first CV cycle of electropolymerization on a Pt electrode at a scan rate of 50 mV s-1. The oxidation peak at 1.86 V indicated the monomer oxidation potential for pyrrole on the emerging inactive

layer. (Figure 3B) Proposed electropolymerization process. (Figure 3C) Consecutive CV cycles, showing left shifting of the oxidation peaks as the PPy/PEG-borate nuclei were developing. The oxidation peak ultimately stabilized at 1.1 V. The peak at -0.6 V marked a full reduction of the oxidized PPy backbones. (Figure 3D) Current density under constant-potential (potentialstatic) electropolymerization of PPy/PEG-borate. 1.1 V was applied for 90 min.

Figures 4A-4C depict electroactuation of the PPy/PEG-borate actuator in PBS. (Figure 4A) Cross-sectional illustration of the electroactuation mechanism. (Figure 4B) Performance of the actuator at its maximum bending strain. Top, before stimulation; bottom, stimulated at -1 V for 10 s. (Figure 4C) Evolution of the electroactivity during the first 20 cycles, stimulated by a biphasic voltage of ±1 V for 10 s in each phase.

Figure 5A shows photo of an electroactive container—a looped ribbon of monolayered PPy/PEG-borate strip clipped by copper tape at ends—that served as electroactuator in the pump; and the electric-controllable squeezing effect in PBS.

Figure 5B shows a schematic of pump parts that includes a container actuated by a passivated conductive film positioned along its wall.

Figure 5C shows a photograph of a pump embodiment prior to be assembled into a case.

Figure 5D shows another example of how a passivated conductive film can be positioned along the wall of a balloon container.

Figure 6A shows a plan view of a pump housing case embodiment.

Figure 6B shows a side view of the pump housing case embodiment of Figure 6A.

Figure 6C shows a perspective view of the pump housing case embodiment of Figure 6A.

Figure 6D shows a plan perspective view of the pump housing case embodiment of Figure 6A.

Figure 6E shows a rendering of a lid of a pump housing case.

Figure 6F shows a prototype of the pump housing case of FIGS. 6A-6E.

Figure 7A shows a plan view of a pump housing case embodiment.

Figure 7B shows a side view of the pump housing case embodiment of Figure 7A.

Figure 7C shows a plan view of the pump housing case embodiment of Figure 7A, attached to a catheter and a butterfly needle and alongside a ruler for size reference.

Figure 7D shows an enlarged view of the pump housing case of Figure 7C.

Figures 8A-8C show photographs from an in-vitro flow rate test of the electroactuation assembly, with the PPy-coated balloon immersed in PBS. Two complete squeezing cycles are shown in each set of images, with the fluid level before (upper image) and after (lower) a squeeze. The fluid mimicking insulin here is deionized water colored by methylene blue. A ruler

in the unit of centimeter is placed on the top for scale reference. FIG. 8A) Reduction/squeeze phase at -1.8 V for 25 seconds and oxidation/recovery phase at 0.6 V for 40 seconds. FIG. 8B) Reduction/squeeze phase at -1.8 V for 40 seconds and oxidation/recovery phase at 0.6 V for 60 seconds. FIG. 8C) Reduction/squeeze phase at -1.8 V for 60 seconds and oxidation/recovery phase at 0.6 V for 90 seconds.

Figure 9 shows a graph of the volumetric outputs in a 60 second squeeze driven by a PPy balloon squeezer at -2 V (vs. Ag/AgCl electrode).

Figure 10 shows a graph of the blood glucose evolution of diabetic mice after insulin injection.

DETAILED DESCRIPTION

Before the present methods and systems are disclosed and described, it is to be understood that the methods and systems are not limited to specific synthetic methods, specific components, or to particular compositions. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes¬ from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps. "Exemplary" means "an example of" and is not intended to convey an indication of a preferred or ideal embodiment. "Such as" is not used in a restrictive sense, but for explanatory purposes.

As used herein, a material is considered biocompatible if it does not provoke an adverse event when contacted with mammalian tissue. Adverse events include severe inflammatory response and degradation into toxic byproducts.

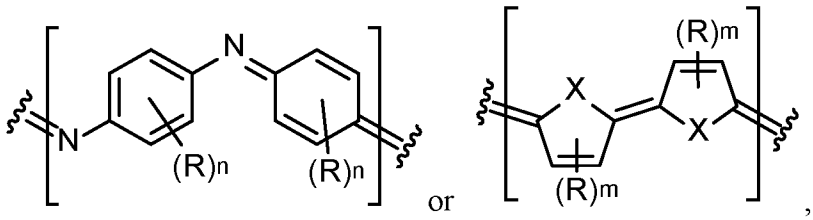
Disclosed are components that can be used to perform the disclosed methods and systems. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while specific reference of each various individual and collective combinations and permutation of these may not be explicitly disclosed, each is specifically contemplated and described herein, for all methods and systems. This applies to all aspects of this application including, but not limited to, steps in disclosed methods. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the disclosed methods.

Disclosed herein are films with bilayered electrical resistances. The first layer, which is exposed on the first face of the film, is electrically non-conductive (or low-conductive) while the second layer, which is exposed on the second face of the film (opposite the first face) is electrically conductive. The electrically non-conductive/low-conductive face may be designated "passivated" relative to the conductive face. The electrically conductive face can be designated the electro-active portion, and the non-conductive face can be designated the electro-inactive portion. A film having faces of uneven electrical resistance and conductivity may be designated a "passivated film." Generally, the electro-inactive portion can have a thickness that is no greater than about 10 microns, no greater than about 8 microns, no greater than about 6 microns, no greater than about 4 microns, no greater than about 2 microns, or no greater than about 1 micron. The total thickness of the film can be no greater than about 100 microns, no greater than about 50 microns, no greater than about 40 microns, no greater than about 35 microns, no greater than about 30 microns, no greater than about 25 microns, no greater than about 20 microns, or no greater than about 15 microns.

The two faces of the film are characterized by differing electrical conductivities. In some embodiments, the electrical conductivity of the electro-active portion can be at least 2x, at least 4x, at least 6x, at least 8x, at least 10x, at least 15x, at least 20x, at least 25x, at least 50x, or at least 100x greater than the electrical conductivity of the electro-inactive portion. For instance, the electro-active portion can have an electrical conductivity at 23° C. of at least 25 S/cm, at least 50 S/cm, at least 75 S/cm, at least 100 S/cm, at least 125 S/cm, or at least 150 S/cm. The electro-inactive portion can have an electrical conductivity at 23° C. of no greater than 25 S/cm, no

greater than 10 S/cm, no greater than 5 S/cm, no greater than 1 S/cm, no greater than 0.5 S/cm, or no greater than 0.1 S/cm.

The films include at least one electrically conductive polymer. Exemplary conductive polymers include polythiophenes, polyanilines, polyfurans, polypyrroles, and polycarbazoles. Such conductive polymers may be substituted by one or more groups. For instance, the term polythiophene includes substituted polythiophenes such as poly(3,4-propylenedioxythiophene) and poly(3,4-ethylenedioxythiophene). In certain embodiments, the conductive polymer may include a compound having either of have the following formulae:



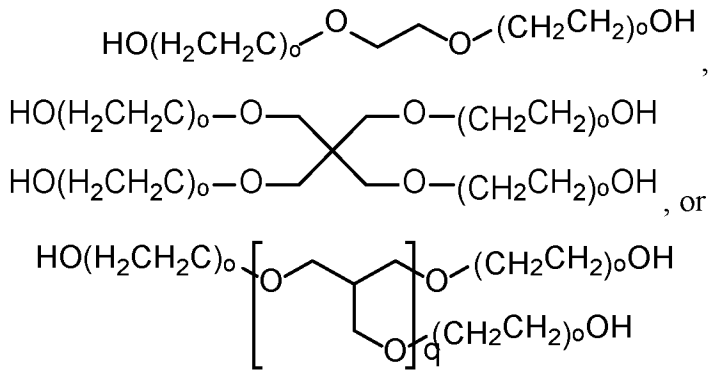
wherein R is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, F, Cl, Br, I, CN, NO_2, n is 0, 1, 2, 3 or 4, and m is 0, 1 or 2. In some embodiments, m can be 2 and the two R groups can together form a ring. Compounds in which X is NH are designated polypyrroles, when X is O are designated polyfuran, when X is S are designated polythiophene, and when X is Se are designated polyseleophene. In some embodiments, the conductive polymer can include compounds in which X is a mixture of O, S and/or NH. For instance, the conductive polymer can be a polyfuran wherein 1-5% of the X groups are N or S. In some embodiments it is preferred than n and m are both 0. In some embodiments, the electrically conductive polymer is not chemically doped with a non-polymeric dopant during its manufacture, i.e, is not reacted with a non-polymeric metal salt or acid.

The films also include at least one dynamic, hydrophilic polymer. As used herein, dynamic polymers are those which undergo reversible bond breaking and forming reactions. Although covalent bonds are a preferred bond type, the dynamic polymers may also incorporate ionic bonds as well. A preferred bond breaking process is hydrolysis, for instance as found in ester bonds, especially borate esters.

In certain embodiments, the dynamic, hydrophilic polymer can be a borate ester having the general formula: $(RO)_nB(Z)_m$, in which R is a hydrophilic polymer moiety, Z is halogen (F, Cl, Br, or I) or hydroxyl, and n+m together equal 3 or 4. The skilled person will appreciate that when n+m is 4, the boron atom will be negatively charged (i.e., a borate), and the polymer will be associated with a suitable counterion. In one aspect of the invention, the counterion is supplied by the electrically conductive polymer. Preferred hydrophilic polymers include polyethylene glycols, giving rise to PEG-borate esters having the formula

$H[(CH_2CH_2O)_o]_nB(Z)_m$, in which Z, n, and m are as defined above, and o is selected from 1-100, 2-50, 2-40, 2-30, 2-25, 2-20, 2-15, 2-10, 4-10, or 6-10. Preferred PEG moieties include those having an average molecular from 100-1,000, from 100-900, from 100-800, from 100-700, from 100-600, from 100-500, from 100-400, from 100-300, from 100-200, from 200-1,000, from 300-1,000, from 400-1,000, from 500-1,000, from 600-1,000, from 700-1,000, from 800-1,000, from 900-1,000, from 200-700, from 200-600, from 200-500, or from 300-500.

In some embodiments, the dynamic, hydrophilic polymer can be a multi-arm PEG, for instance having the formula $[(C^p\text{-}(CH_2CH_2)_oO]_nB(Z)_m$, wherein o, n, Z, and m are as defined above, and C^p represents a core. Suitable cores can be derived from polyols such as ethylene glycol, glycerol, pentaerythritol, sorbitol, mannitol, tetraglycol, hexaglycol, as well as other carbohydrates and carbohydrate derivatives. In some instances, the hydrophilic polymer can include a multi-arm PEG having the formula:



wherein o is defined above, and q is 1, 2, 3, 4, or 5. The multi-arm PEG compounds can have an average molecular from 100-1,000, from 100-900, from 100-800, from 100-700, from 100-600, from 100-500, from 100-400, from 100-300, from 100-200, from 200-1,000, from 300-1,000, from 400-1,000, from 500-1,000, from 600-1,000, from 700-1,000, from 800-1,000, from 900-1,000, from 200-700, from 200-600, from 200-500, or from 300-500.

The films can be prepared using an iterative electropolymerization reaction. For instance, the dynamic hydrophilic polymer can be combined with conductive polymer precursor (i.e., polymerizable monomer), in a solvent, and subjected to a series of electrochemical polymerizations. The electrochemical polymerization is conducted using a working electrode, counter electrode, and reference electrode, and the polymerized film is deposited onto the working electrode. As such, by varying the shape of the working electrode, films of different shapes can easily be obtained. The working electrode may be prepared by coating a glass template (e.g., slide, rod, etc) with metals such as titanium and platinum.

By applying a first voltage to the cell, the electro-inactive portion of the film is deposited onto the working electrode, e.g., a first polymerization. By applying a second, different voltage

subsequent to the first voltage, the electro-active portion of the film is deposited on top of the electro-inactive portion, e.g., a second polymerization. Because the electropolymerization is conducted in the presence of the hydrophilic, dynamic polymer, the formed polymers are entangled with the dynamic, hydrophilic polymer. For both polymerization steps, a constant current density from 0.6-1.4 mA cm^{-2}, from 0.7-1.2 mA cm^{-2}, from 0.8-1.2 mA cm^{-2}, from 0.8-1.1 mA cm^{-2}, or from 0.8-1.0 mA cm^{-2} can be applied.

Generally, the first polymerization is conducted using a voltage no greater than 1 V, no greater than 0.95 V, no greater than 0.9 V, no greater than 0.85 V, no greater than 0.8 V, or no greater than 0.75 V. Generally, the first polymerization is conducted for a period of no more than 5 minutes, no more than 4.5 minutes, no more than 4 minutes, no more than 3.5 minutes, no more than 3 minutes, or no more than 2.5 minutes.

Generally, the second polymerization is conducted using a voltage greater than 1 V, greater than 1.05 V, greater than 1.1 V, greater than 1.15 V, greater than 1.2 V, greater than 1.25 V, or greater than 1.3 V. Generally, the second polymerization is conducted for a period of at least 30 minutes, at least 45 minutes, at least 60 minutes, at least 75 minutes, at least 90 minutes, at least 120 minutes, or at least 150 minutes.

Borate esters of the formula: $(RO)_nB(Z)_m$ or $[(C^p\text{-}(CH_2CH_2)_oO]_nB(Z)_m$, (wherein C^p, R, Z, n, and m as defined above) may be prepared by combining a boron electrophile having the formula BZ^1_3 wherein Z^1 is a halogen (F, Cl, Br, or I) with a molar excess of an alcohol having the formula R-OH in an inert solvent. When the R-OH is a polyethylene glycol or a multi-arm polyethylene glycol, suitable inert solvents include secondary and tertiary alcohols such as isopropanol and tert-butanol, for example.

The dynamic, hydrophilic polymer may be prepared in the same reaction vessel in which the electropolymerization is conducted. A boron electrophile may be combined with a molar excess of a hydrophilic alcohol, e.g., a polyethylene glycol. The conductive polymer precursor may also be present in the initial reaction mixture, or it may be added after the polymer has formed. The dynamic, hydrophilic can spontaneously form, or the mixture can be heated in order to form the polymer. Once the dynamic, hydrophilic polymer has formed, the iterative electropolymerization process may be performed. Once the polymerization is complete, the film may be removed from the working electrode and rinsed with a solvent.

Turning now to the subject of biocompatible electroactuation devices, the film described above can be used to improve medical implants that include electroactuators. The field of insulin delivery is of particular interest, as described in the background section. As such, a pump capable of delivering insulin to a patient is described. The pump has utility as an insulin pump

due to, for example, the high biocompatibility of the passivated conductive film, low voltage requirements, and the small size requirements. However, the pump disclosed herein is not limited to use in diabetic care, medical devices, or even to medicine in general. The pump may have utility in other disciplines and this disclosure does not limit its field of use to medicine. Other possible fields of use include, but are not limited to, robotics, computers, appliances, microelectromechanical systems, and any field that may incorporate microelectromechanical systems or benefit from the use of a micropump.

Starting in the mid-1970s, a steadily growing and astonishing diversity of micropump principles, technical concepts and applications have emerged (Woias, P., *Sensors and Actuators B: Chemical)*. Two classes of micropump principles have been explored: reciprocating and continuous flow. The pump disclosed herein is a reciprocating micropump that uses the passivated conductive film described above as part of the pump. By comparison to conventional options, the disclosed pump is durable, small, lightweight, and can be wirelessly actuated to overcome the major disadvantages of current implantable pumps and advance the CIPII therapy to benefit T1D patients. For example, the passivated conductive film takes the place of a bulky piston-plunger motor that are used in commercially available implantable insulin pumps. Furthermore, the passivated conductive film supersedes piezoelectric actuators conventionally used in micropumps in that it utilizes a voltage on the range of 2 Volts, peak-to-peak, for a strong and fast electroactuation. In contrast, piezoelectric actuators require a high actuation voltage on the range of 100 Volts (Woias, P., *Sensors and Actuators B: Chemical*). The high power efficiency enabled by the pump disclosed herein allows for a battery-free embodiment that can use wireless induction for electroactuation (in contrast to conventional implantable pumps that require an internal battery). Moreover, with the low operating voltage, risks of electric injuries are significantly reduced.

FIG. 5B shows a schematic of one embodiment of the pump disclosed herein. The pump includes a container 3 that includes a wall 5 (which defines an interior void), a passivated conductive film 7 extending along at least a portion of the wall 5, and an outlet valve 9 in fluid communication with catheter 11. The embodiment shown includes an inlet valve 13 in fluid communication with a reservoir 15. As shown in FIG. 5B, the container 3 can be provided as a soft yet elastic elongated medical balloon. However, other types of containers 3 can also be utilized. In the embodiment shown in FIG. 5B, two separate passivated conductive films 7 extend fully around the circumference of the container 3. Alternatively, one or more passivated conductive films could extend laterally along the container 3. In some embodiments, such as the one shown in FIG. 5D, the conductive film 7 can extend circumferentially and laterally along the

container so as to form a spiral. The container 3 and the passivated conductive film 7 can be positioned in direct contact with each other, or a flexible intermediate structure can be positioned between the container 3 and the passivated conductive film 7. In some embodiments, the passivated conductive film 7 can be applied to the container 3 as a laminate. In some embodiments, the passivated conductive film 7 can form the wall 5 of the balloon or container 3, such that the film 7 is in direct contact with contents housed within the interior void of the container 3.

Application of a first voltage to the film 7 (or a portion thereof) in a physiological electrolyte solution causes a portion of the film 7 to swell. Particularly, application of the first voltage to the passivated conductive film 7 causes ions and water molecules from the electrolyte solution to be drawn into the polymer, inducing swelling. The swelling of the film 7 causes a decrease in the volume of the container 3 from an initial volume to a second, smaller volume. In the embodiment shown in FIG. 5B, the swelling film 7 places a pressure on the outer surface of the container 3, thereby causing a decrease in the volume of the interior void of the container. If the film 7 forms the wall 5 of the container 3, the swelling film 7 causes a decrease in the volume of the interior void of the container. Either way, the decrease in volume of the container 3 dispenses fluid (e.g., insulin) housed within the container 3 through the outlet valve 9. The outlet valve 9 can be, for example, a check valve that is opened by pressure exerted by a fluid within the container 3 when the container 3 decreases in volume. The outlet valve 9 allows the fluid to flow out of the container 3 directly into the surroundings, while preventing backflow. In some embodiments, as shown in FIG. 5B, the outlet valve can release the fluid into a catheter 11 that leads the fluid to a desired location.

As shown in FIG. 5B, the pump 1 can also include a check valve, or inlet valve 13. The inlet valve 13 remains closed when the passivated conductive film 7 is in the swollen state. Application of a second voltage to film 7 causes a deswelling of the film 7, which causes the container 3 to recover its initial volume. In some instances, the recovery of the initial volume of the container may not be fully complete, but at least the application of the second voltage to film 7 causes the container to recover to a larger volume than the second volume. The increase in volume of the container 3, in the absence of the dispensed liquid, causes a suction that opens the inlet valve 13. The inlet valve 13 can be in fluid communication with a reservoir 15 that contains additional fluid (e.g., insulin), such that when the inlet valve 13 is opened, the container 3 is refilled with fluid for the next cycle while the outlet valve 9 is closed.

Advantageously, the interior void of the container 3 is devoid of moving parts. In contrast to conventional insulin pumps, the pump disclosed herein does not require a piston-

plunger motor, therefore decreasing the size for implantation. The simplicity of the design, by comparison, lowers the risk of malfunction due to fewer mechanical parts.

The passivated conductive film 7 is biocompatible, and may be implanted with no further chemical treatments. For example, the passivated conductive film 7 can comprise biocompatible poly(ethylene glycol) (PEG, such as the PPy/PEG-borate composite described above). Since macromolecular PEG-borate counterions are incorporated and immobilized in PPy matrix, the film generates deformation primarily via exchange of Na+ with electrolyte solutions. The physiological electrolyte solution can be any biocompatible, non-toxic, solution existing at physiological pH. The physiological electrolyte solution has ions and water molecules that can be drawn into or repulsed out of the passivated conductive polymer film 7 when the various voltages are applied to cause swelling and deswelling of the film. The ions contained in the physiological electrolyte can include, for example, sodium, chloride, potassium, phosphate, bicarbonate, magnesium, and/or calcium. Examples include, but are not limited to, saline, phosphate buffered saline, Ringer's solution, and the patient's blood.

By contrast, for example, existing high-performance polypyrrrole (PPy)-based electroactuators to date are unsuitable for devices designed to work in in vivo settings. Transformation of conventional PPy electroactuators stems from ion exchanges between the polymer, doped with anions such as $CF_3SO_3^-$, dodecylbenzenesulfonate (DBS), or bis-(trifluoromethanesulfonyl)imide (TFSI), and the surrounding electrolyte. Unfortunately, these large dopant anions are inherently cytotoxic, precluding use in in vivo applications. By contrast, the passivated conductive films 7 disclosed herein are devoid of dopant anions. Additionally, PPy electroactuators doped with such large anions achieve their best performance only when the electrolyte is enriched in assistive anions such as $TFSI^-$, PF_6^-, or ClO_4^-, none of which are available in non-toxic, physiological fluids.

In some embodiments, the voltage that causes the passivated conductive film 7 to enlarge can be less than 5 Volts. By contrast to conventional micropumps that utilize piezoelectric actuators, this voltage is much lower. For example, a typical piezoelectric actuator can require an actuation voltage in the range of 100 Volts. By contrast, the required actuation voltage for the pump disclosed herein is less than 5 Volts peak-to-peak (including less than 4 Volts, less than 3 Volts, less than 2 Volts, and less than 1 Volt peak-to-peak). This low operating voltage reduces the risk of electric damage to the user, patient, or surrounding device. Furthermore, the low voltage/high power efficiency enables the actuation voltage to be applied wirelessly. Some embodiments are completely devoid of internal or external batteries, and can use wireless

induction for electroactuation. By contrast, conventional implantable pumps require an internal battery.

In some embodiments, after the first voltage is applied to cause the passivated conductive film 7 to take the first, enlarged configuration, application of a second can cause the passivated conductive film to shrink, taking a second configuration. In other words, the volume of the first configuration of the passivated conductive film is larger than the volume of the second configuration of the passivated conductive film. Cycling of voltages causes a continuous pumping of the container 3 to cause the fluid retained in the container 3 to be expelled from the outlet valve 9 and refilled from reservoir 15.

As discussed above, the passivated conductive film 7 is a monolayer polymer material formed of an electrically conductive and electroactive polymer entangled with a flexible and inactive polymer of limited conductivity and electroactivity. The passivated conductive film has a first face and a second face. The first face has a higher proportion of electroactive polymer than the second face, enabling it to swell to a greater extent than the second face in order to achieve differential stress generation. The second, more passivated face has a higher proportion of the inactive polymer than the first face, and swells less than the first face. The differential swelling is an important feature – without it, strain and stress produced at the opposing faces would counteract each other, significantly diminishing the overall performance of the actuator. Conventional electroactuating designs use layers or laminates to achieve unilateral passivation. Such layered designs add a substantial amount of mechanical rigidness and load to the film, impeding its electroactuation and compromising its deformation output. Moreover, differential stresses generated at the layer interface during electroactuation often cause ripples and cracks in the laminate, ultimately leading to delamination and breakdown of the actuator.

Methods of dispensing a fluid from a container are disclosed herein. The methods providing a container having an initial volume and a passivated conductive film extending along at least a portion of an outer surface of the container, applying a first voltage to the film in a physiological electrolyte solution, swelling a portion of a film, decreasing the volume of the container to a second volume, and dispensing the fluid from the container through an outlet. Swelling a portion of the passivated conductive film can, in some embodiments, include drawing ions from a surrounding physiological electrolyte solution into the passivated conductive film. The first voltage can be less than 5 Volts peak-to-peak, as described above (including less than 5 Volts, less than 4 Volts, less than 3 Volts, less than 2 Volts, and less than 1 Volt peak-to-peak). The first voltage can be wirelessly applied. Some embodiments of the method can include applying a second voltage to the pump, deswelling a portion of the passivated conductive film,

and increasing the volume of the container. The increase in volume creates a suction that pulls fluid into the container from an adjacent reservoir.

Benefits of the pumps and methods disclosed herein include its battery- and plunge-free design, which notably reduces weight and size comparing to conventional implantable pumps. The lower operating voltage (about 1-2 V, in some embodiments) also minimizes potential risks for electric injuries. Compact double-sided wireless powering units can be employed which output a power of about 1-2 mW and a voltage up to about 1.8 V, which is sufficient to drive the PPy actuators. As described in the Examples below, the established linear correlation between solution output and squeezing duration can facilitate the control of insulin delivery at a flow rate resolution of about 0.3-0.5 μL/s.

EXAMPLES

The following examples are for the purpose of illustration of the invention only and are not intended to limit the scope of the present invention in any manner whatsoever.

Example 1 – Formation of a passivated conductive film

All chemicals were purchased from Sigma-Aldrich unless otherwise indicated. Pyrrole (> 98%) and PEG with an average M_n of 400 were used. Preparation of the organic synthesis solution started with dissolving 6 g PEG in 45 mL 2-proponal (anhydrous, 99.5%) at room temperature. 18 mL boron trifluoride diethyl etherate (≥46.5 % BFEE basis) was then slowly added, while cooling the flask down in icy water. After degassing the mixture on a rotary evaporator (IKA, RV10) for 3 minutes at 150 mbar, 220 μL pyrrole was added. Electropolymerization was performed on an electrochemical workstation (CHI 660F, CH instrument) using a three-electrode cell: A microscopy glass slide (50 mm × 75 mm × 1 mm, VWR) pre-coated with 10 nm titanium (Ti) and 20 nm platinum (Pt) in an e-beam evaporator (Denton DV-502A) was used as the working electrode; an Ag/AgCl wire (4 cm long, 2 mm in diameter) was used as the quasi reference electrode; and a Pt sheet (30 cm^2) served as the counter electrode. The optimal monolayered PPy/PEG-borate electroactuator was synthesized by a two-phase electropolymerization process at 0° C: the synthesis started at 1 V (*vs.* Ag/AgCl) anodic potential for 5 min to generate the inactive layer, followed by a 90 min growth process at 1.1 V with a constant current density of 0.8–1 mA cm^{-2}. The obtained PPy/PEG-borate film was rinsed by isopropanol and deionized water, then peeled off and dried in air overnight.

Microstructure Characterizations: An AFM (Icon AFM, Bruker) was used on the air tapping mode with an NSC-15 cantilever at 1 Hz scan rate. An SEM (Helios Nanolab 600, FEI)

equipped with energy dispersive x-ray spectroscopy was used for imaging and *in situ* chemical analysis. An XPS (Axis Ultra, Kratos) equipped with an argon ion gun was used for depth-profiling elemental composition analysis on both sides of the actuator.

Electroactivity Tests: Electroactivity tests were conducted on the same electrochemical workstation (CHI 660F, CH instrument) using a similar three-electrode cell with the PPy/PEG-borate electroactuator as the working electrode, a stainless steel plate as the counter electrode, and an Ag/AgCl wire as the reference electrode. PBS (Thermo Fisher Scientific) was used as the electrolyte.

Example 2 – Design of electroactive actuator and pump housing case

With its power density being only 4.5 mW cm^{-2}, this actuator is promising for application in numerous biomedical devices. Figure 5A demonstrates a simple electroactive actuator formed by the passivated conductive film. The actuator is submerged in phosphate buffered saline (PBS). The actuator comprises a looped ribbon with the active side facing outward. Under repetitive electrical stimulation, this device rapidly closes its loop creating a squeezing action in the reduction phase and then reset in the oxidation phase. Unlike PPy actuators previously reported, this intrinsically passivated, monolayered actuator requires no coatings for unilateral passivation or accommodating counterions, which enables a straightforward and reliable design of an implantable insulin pump. The pump shown in FIG. 5B includes a container 3 (also referred to herein as a balloon container or a squeezer), an insulin reservoir 15, an inlet valve 13 for unidirectional gating, and a wireless powering unit (not shown). When fully loaded with insulin solution, the assembly comprising a container 3, a reservoir 15, and intermediate tubing parts all together provides total volumetric capacity of 1.4 mL. FIG. 5C shows a photograph of some of these components and also including a butterfly needle 17, pictured alongside a ruler for reference. Capacity of the reservoir 15 (0.5 mL at current) could be enlarged to accommodate more solution, or inversely, the case could be shrunk for a more compact design if that is preferred. The miniature metallic inlet valve 13 advantageously regulates one-way solution flow from the reservoir 15 to the container 3 and eventually to the tip of catheter 11. The inlet and outlet valves 13, 9 have diameters of 2.5 mm and are readily inserted into the size-matched silicone tubing and then placed at each end of the container 3. Note that valves chosen have a critical pressure of 0 Pa, which means they add little fluid resistance for the permeated flow direction. Heat-shrinkable tubing provides a good connection at all joints, and no leaks were found during the experimentation phase.

In FIG. 5C, a tubing extends from the right side of the reservoir 15. This tubing is temporarily reserved for this study due to the convenience of easily refilling the reservoir 15 for extensive in vitro studies, but will be removed in the final assembled device. A coated silver wire 14 is used to connect the container 3 and a radio-frequency (RF) harvester mounted backside, through a hole reserved at the bottom of the case (hole 29 can be seen in FIG. 6D). A hole 30 in the side of the case is used to access the catheter 11. The pre-coated silver wire is selected because it doesn't induce hydrolysis even at actuation voltage over 1 V owing to its insulative coating. The container used in this example is urethane medical balloon, medium durometer, 10 mm long, 6 mm in diameter. The container 3 and the reservoir 15 integrated with an inlet valve 13 can be sourced from Vention Medical Inc (Chattanooga, TN). FIG. 5D shows an alternative positioning of the passivated conductive film 7, wrapped in a spiral around the balloon container 3.

FIGS. 6A-6F show a first pump housing case embodiment 20 designed to accommodate a pump such as the one shown in FIG. 5B. The placement of these components in the housing case 20 is shown in FIG. 6A. The pump housing case 20 includes a container compartment 21, a reservoir compartment 23, an inlet/check valve compartment 25, and a wireless unit compartment 27. FIGS. 6A-6D show additional renderings of the housing case 20, and FIG. 6E shows a rendering of a lid 35 for the housing case. A photograph of a 3D printed prototype is shown in FIG. 6F. This particular embodiment has a width w of 15 millimeters, a length l of 25 millimeters, a height h of 5 millimeters, an outer wall 31 thickness of 1.5 mm and a 2 mm diameter hole 29 in the wireless unit chamber (for threading leads to the actuators and wireless harvester). Bars 33 extend between compartments to partially separate them. Lid 35 can be placed on top of the housing to seal it.

FIGS. 7A-7D show an additional pump housing case embodiment 37 designed to accommodate a pump such as the one shown in FIG. 5B. Housing case 37 includes a reservoir compartment 41 and a container compartment 43. Bottom holes 38, 40 shown in FIG. 7A allow for the wiring from the RF-harvester, which is attached to the back surface of the case (one hole for the anode and one for the cathode to prevent the wires from tangling). Side hole 42 shown in FIG. 7B is used to access the catheter. The compartment 44 on in the upper right hand corner of the case in FIGS. 6A and 7A is reserved for the bending tubing. FIGS. 7C and 7D show a photograph of an exemplary pump positioned within pump housing case 37 in FIGS. 7C and 7D. Catheter 11 extends out of housing case 37 to butterfly needle 45. Housing case 37 has a lid 39 that can tightly cover the entire the PBS-filled base, as shown in FIG. 7C (right behind the assembled pump). An enlarged photo of the pump housing case 37 is shown in FIG. 7D.

Example 3 – Characterization of flow rate

The RF-harvester used in this example has a maximum voltage output of ±1.8 V. As such, the reduction potential was set to -1.8 V and the volumetric output was controlled by varying the reduction duration. Following the principle above, to maximize power efficiency and device longevity, a small oxidation voltage of +0.6 V is used with a relatively longer oxidation duration. The whole actuation assembly was tested using PBS as the electrolyte and methylene blue to enhance visualization of the fluid flow during actuation. The aim of this example was to determine the flow rate and maximum volumetric output at the RF-deliverable power. FIGS. 8A-8C show video snapshots of real-time evolution of the fluid level through 20 cycles. Only two cycles are shown, because starting from the third cycle the solution is squeezed into regions covered by the tape, but data recording continues.

The maximum output is realized as shown in FIG. 8C: each reduction/squeeze phase lasts for 60 seconds at -1.8 V, giving a fluid displacement of 8.5 mm in a catheter of 2 mm inner diameter. As such, a volumetric output of 26.7 μL is achieved after each squeeze. An oxidation/recovery phase (0.6 V, 90 s) is followed to compensate charges in PPy and restore the squeezer to the original state. Comparing to the reduction phase under -1.8 V, the oxidation phase needs longer time because of the smaller voltage.

When the total squeezing duration is reduced to 25 seconds (FIG. 8A), a small output of 6.3 μL per squeeze is observed. The container again takes 10–12 seconds to initiate the fluid flow in the catheter, thus the average flow rate in the last 13 seconds is about 0.48–0.50 μL/second. Squeezing duration in FIG. 8B is increased to 40 seconds, and it gives an output of 14.8 μL in the last 30 seconds for each squeeze. The flow rate in a squeezing phase is not constant, but smaller at the beginning and gradually increasing to a stable plateau as the reduction process progresses. Specifically, the first 10 seconds in a 60 second squeeze doesn't give a notable output, however, during the subsequent 50 seconds, an average flow rate of 0.53 μL/second is observed from the first container, and this value is well repeated throughout 20 squeezes. In further cycles, a notable degradation on flow-rate is observed at the driving voltage. For example, the flow rate at the same voltage of -1.8 V decreases to 0.36 μL/second for the 30th cycle due to aging of the electroactuators. For the purpose of device longevity, reducing voltage to -0.6 V can achieve a consistent flow rate of 0.12 μL/second through up to 50 cycles, but this requires longer squeezing duration to achieve the same solution output and the longer procedure time may cause diabetic mice to be over-anesthetized. In the animal studies, -1 V was thus

chosen for all squeezes, and a flow-rate of 0.21 μL/second is consistently achieved at this driving voltage, giving ~10 μL/min when excluding the initialization delay.

FIG. 9 plots the real-time flow rate of a 60 second squeeze for the first two squeezes shown in FIG. 8C, from which a nearly linear correlation is seen between the output and squeezing duration after the initialization period. Interestingly, at a given reduction/squeezing voltage, the flow rate always is constant, so that the volumetric output can be precisely controlled by the actuation duration. This result suggests that as the reduction begins, PPy first expels small free anions (mostly Cl-) causing minimum shrinking and then absorbs large hydrated cations (mostly Na+) generating a significant volumetric swelling. Meanwhile, absorption of more cations makes the film more porous, thus generating room for further absorption to sustain the volumetric expansion during a squeeze.

Example 4 – Blood glucose testing in diabetic mice

Having validated that the flow rate and output capacity can be precisely controlled by the actuation voltage and duration in Example 3, Example 4 reviews the functionality of the pump for subcutaneous insulin injection. A pump injection protocol developed in vitro on diabetic mice is employed for the pilot animal study. The blood glucose response is monitored with syringe injection as control.

Diabetic mice carrying a high initial blood glucose level (over 600 mg/dl) are used for the subcutaneous injection protocol. During the test, glucose level is monitored every 10 minutes to a full period of 130 minutes by collecting a small droplet of blood from the intentionally injured tail end. As shown in FIG. 10, after injecting a dose of 0.5 IU to the mice via syringe, the first readable data below 600 mg/dl shows up 20 minutes later, and a minimum glucose concentration of 328 mg/dl is observed at 100 minutes, but thereafter glucose gradually increases back to the initial level. Thus, a dose of 0.5 IU proves insufficient to reduce the blood glucose to a normal range below 200 mg/dl. When the insulin dose is increased to 1 IU, the desired minimum of 177 mg/dl is eventually observed at 120 minutes after syringe injection. Therefore, aiming to give an insulin dose of 1 IU, the pump is pre-filled with 20 IU/mL solution and run using a 50 μL injection protocol pre-established in in-vitro study (five cycles at -1 V, 60 s and 0.6 V, 60 s; average power 1.7 mW). The outcome shows good agreement with the syringe-injection case: the blood glucose declines to 169 mg/dl after 120 minutes. The experiment is repeated on another diabetic mouse receiving a 0.5 IU via pump, and the result again demonstrates qualitative consistency with that of the syringe delivery (curve only recorded for 60 minutes and

thus not compared in FIG. 10). From these results, it is confirmed that the actuation protocol developed in vitro is transferable to subcutaneous injection.

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CLAIMS

What is claimed is:

1. A pump comprising:

a container having an initial volume, the container comprising,

a passivated conductive film extending along at least a portion of a wall of the container, and

an outlet valve;

wherein application of a first voltage to the film in a physiological electrolyte solution causes a portion of the film to swell, thereby decreasing the volume of the container to a second volume;

wherein the transition from the initial volume to the second volume is capable to dispense a fluid housed within the container through the outlet valve; and

wherein application of a second voltage to the film increases the volume of the container,

wherein the passivated conductive film includes having a first face and a second face, the film comprising an electrically conductive polymer and a dynamic, hydrophilic polymer, wherein the electrically conductive polymer and dynamic hydrophilic polymer are entangled together, wherein the first face comprises an electro-active portion and the second face comprises an electro-inactive portion.

2. The pump of claim 1, wherein the container further comprises an inlet valve.

3. The pump of claim 2, further comprising a reservoir in fluid communication with the inlet valve.

4. The pump of any one of claims 1-3, wherein the container further comprises an interior void, wherein the interior void of the container is devoid of solid moving parts.

5. The pump of any one of claims 1-4, wherein the container further comprises an interior void, and wherein the interior void of the container is at least partially filled with a solution containing insulin.

6. The pump of any one of claims 1-5, wherein the electrically conductive polymer comprises a poly(thiophene), poly(aniline), poly(pyrrole), or poly(carbozole) polymer.

7. The pump of any one of claims 1-6, wherein the electrically conductive polymer comprises a poly(pyrrole).

8. The pump of any one of claims 1-7, wherein the dynamic, hydrophilic polymer comprises a multi-arm poly(ethylene glycol).

9. The pump of any one of claims 1-7, wherein the passivated conductive film comprises poly(ethylene glycol).

10. The pump of any one of claims 1-9, wherein the total thickness of the passivated conductive film is no greater than about 100 microns, no greater than about 50 microns, no greater than about 40 microns, no greater than about 35 microns, no greater than about 30 microns, no greater than about 25 microns, no greater than about 20 microns, or no greater than about 15 microns.

11. The pump of any one of claims 1-10, wherein the electro-inactive portion has a maximum thickness no greater than about 10 microns, no greater than about 8 microns, no greater than about 6 microns, no greater than about 4 microns, no greater than about 2 microns, or no greater than about 1 micron

12. The pump of any of claims 1-11, wherein the passivated conductive film is prepared by a process comprising the steps:

a) providing a solution comprising a dynamic hydrophilic polymer and conductive polymer precursor monomer; wherein the solution is in contact with a working electrode, counter electrode, and reference electrode;
b) applying a first voltage of no greater than 1 V for a period of 5 minutes or less;
c) applying a second voltage of greater than 1 V; and
d) separating the conductive film from the working electrode.

13. The pump of any one of claims 1-12, wherein the passivated conductive film is devoid of dopant anions.

14. The pump of any one of claims 1-13, further comprising a physiological electrolyte solution bathing a portion of the passivated conductive film.

15. The pump of any one of claims 1-14, wherein the first voltage is less than 5 Volts.

16. The pump of claim 1-15, wherein the passivated conductive film is configured to respond to a wirelessly applied first voltage.

17. The pump of claim 1-16, wherein the pump is devoid of internal or external batteries.

18. The pump of any one of claims 1-17, wherein the container is an elongated balloon.

19. The pump of claim 18, wherein the passivated conductive film extends around a circumference of an outer surface of the balloon.

20. The pump of claim 18, wherein the passivated conductive film extends laterally along an outer surface of the balloon.

21. The pump of claim 18, wherein the passivated conductive film forms the wall of the balloon.

22. A method of dispensing a fluid from a container, the method comprising:

providing a container having an initial volume and a passivated conductive film extending along at least a portion of a wall of the container;

applying a first voltage to the passivated conductive film in a physiological electrolyte solution;

swelling a portion of a passivated conductive film;

decreasing the volume of the container to a second volume;

dispensing a fluid from the container through an outlet.

23. The method of claim 22, wherein swelling a portion of the passivated conductive film comprises drawing ions from a surrounding physiological electrolyte solution into the passivated conductive film.

24. The method of claim 22 or 23, wherein the first voltage is less than 5 Volts.

25. The method of any one of claims 22-24, wherein the first voltage is wirelessly applied.

26. The method of any one of claims 22-25, further comprising
applying a second voltage to the pump,
deswelling a portion of the passivated conductive film, and
increasing the volume of the container,
wherein increasing the volume of the container creates a suction that pulls fluid into the container from an adjacent reservoir.

27. A passivated film having a first face and a second face, the film comprising an electrically conductive polymer and a dynamic, hydrophilic polymer, wherein the electrically conductive polymer and dynamic hydrophilic polymer are entangled together, wherein the first face comprises an electro-active portion and the second face comprises an electro-inactive portion.

28. The passivated film according to claim 27, wherein the film has a thickness comprising the electro-active portion and the electro-inactive portion.

29. The passivated film according to claim 27 or claim 28, wherein the electro-inactive portion has a maximum thickness no greater than about 10 microns, no greater than about 8 microns, no greater than about 6 microns, no greater than about 4 microns, no greater than about 2 microns, or no greater than about 1 micron.

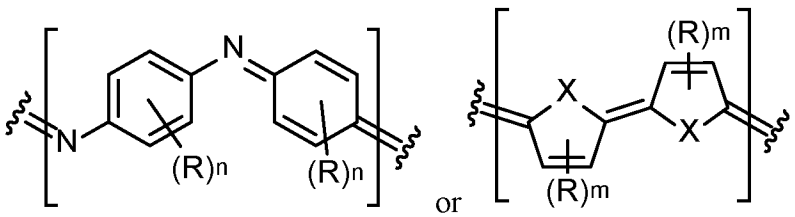
30. The passivated film of any of claims 27-29, wherein the total thickness of the film is no greater than about 100 microns, no greater than about 50 microns, no greater than about 40 microns, no greater than about 35 microns, no greater than about 30 microns, no greater than about 25 microns, no greater than about 20 microns, or no greater than about 15 microns.

31. The passivated film according to any of claims 27-30, wherein the electro-active portion has an electrical conductivity at 23° C. of at least 25 S/cm, at least 50 S/cm, at least 75 S/cm, at least 100 S/cm, at least 125 S/cm, or at least 150 S/cm.

32. The passivated film according to any of claims 27-31, wherein the electro-inactive portion has an electrical conductivity at 23° C. of no greater than 25 S/cm, no greater than 10 S/cm, no greater than 5 S/cm, no greater than 1 S/cm, no greater than 0.5 S/cm, or no greater than 0.1 S/cm.

33. The passivated film according to any of claims 27-32, wherein the electrically conductive polymer comprises a poly(thiophene), poly(aniline), poly(pyrrole), or poly(carbozole) polymer.

34. The passivated film according to any of claims 27-33, wherein the electrically conductive polymer comprises:



wherein R is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{1-6}haloalkoxy, F, Cl, Br, I, CN, NO_2, n is 0, 1, 2, 3 or 4, and m is 0, 1 or 2.

35. The passivated film according to any of claims 27-34, wherein the electrically conductive polymer comprises a poly(pyrrole) polymer.

36. The passivated film according to any of claims 27-35, wherein the dynamic, hydrophilic polymer comprises reversibly hydrolyzable bonds.

37. The passivated film according to any of claims 27-36, wherein the dynamic, hydrophilic polymer comprises a borate ester.

38. The passivated film according to any of claims 27-37, wherein the dynamic, hydrophilic polymer comprises a borate-polyol ester.

39. The passivated film according to any of claims 27-38, wherein the dynamic, hydrophilic polymer comprises a borate ester having the formula:

$$(RO)_nB(Z)_m,$$

wherein R is a hydrophilic polymer moiety, Z is halogen (F, Cl, Br, or I) or hydroxyl, and n+m together equal 3 or 4.

40. The passivated film according to any of claims 27-39, wherein the dynamic, hydrophilic polymer comprises a borate ester having the formula:

$$H[(CH_2CH_2O)_o]_nB(Z)_m,$$

wherein Z is halogen (F, Cl, Br, or I) or hydroxyl, n+m together equal 3 or 4, and o is selected from 1-100, 2-50, 2-40, 2-30, 2-25, 2-20, 2-15, 2-10, 4-10, or 6-10.

41. The passivated film according to any of claims 27-39, wherein the dynamic, hydrophilic polymer comprises a borate ester having the formula:

$$[(C^p\text{-}(CH_2CH_2)_oO]_nB(Z)_m,$$

wherein Z is halogen (F, Cl, Br, or I) or hydroxyl, n+m together equal 3 or 4, and o is selected from 1-100, 2-50, 2-40, 2-30, 2-25, 2-20, 2-15, 2-10, 4-10, or 6-10.

and C^p represents a core.

42. The passivated film according to any of claims 27-39, wherein the dynamic, hydrophilic polymer comprises a poly(ethylene glycol)-borate ester.

43. A method for preparing the passivated film according to any of claims 27-42, comprising the steps:

a) providing a solution comprising a dynamic hydrophilic polymer and conductive polymer precursor monomer; wherein the solution is in contact with a working electrode, counter electrode, and reference electrode;

b) applying a first voltage of no greater than 1 V for a period of 5 minutes or less;

c) applying a second voltage of greater than 1 V; and

d) separating the passivated film from the working electrode.

44. The method according to claim 43, comprising the step of combining an alcohol and electrophilic boron compound to give the dynamic hydrophilic polymer.

45. A passivated conductive film prepared by the process of claim 43 or 44.

46. An implantable pump, comprising the passivated film according to any of claims 27-42 or claim 45.

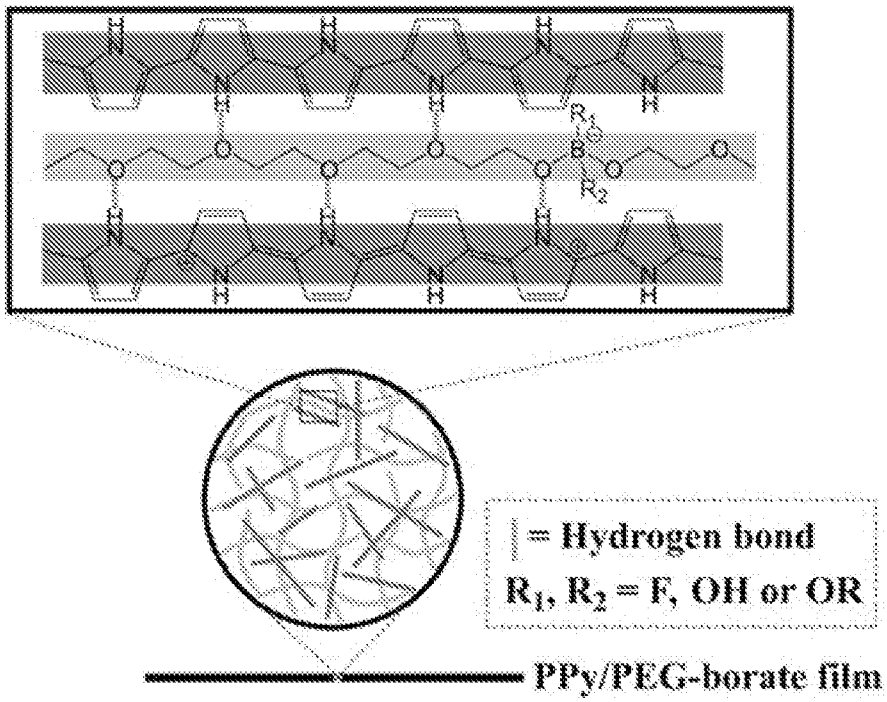


FIG. 1A

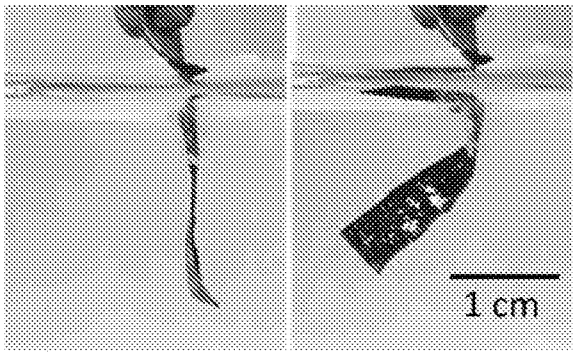


FIG. 1B

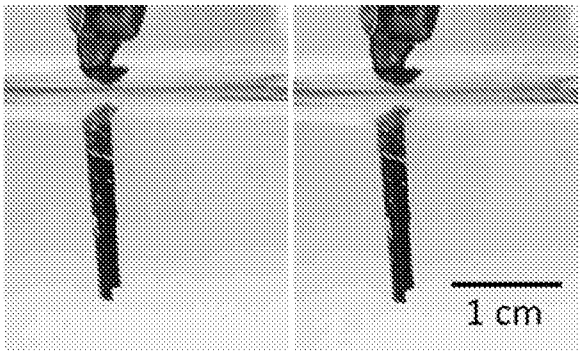


FIG. 1C

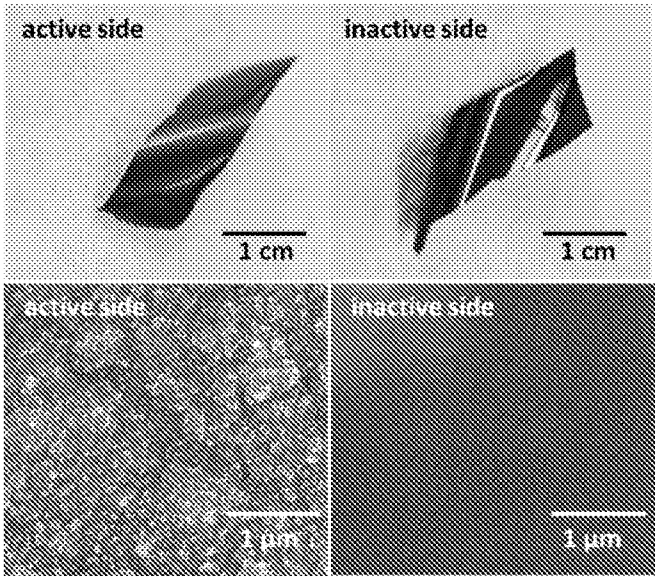


FIG. 1D

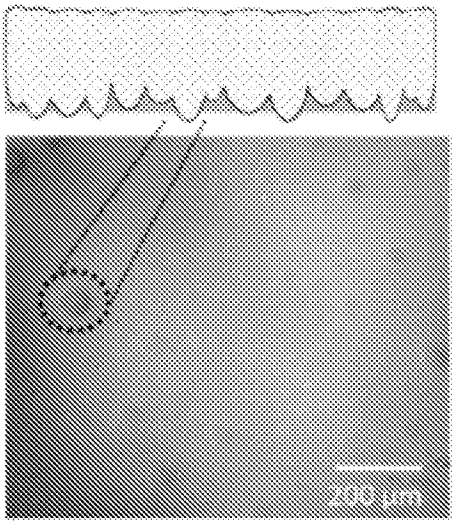


FIG. 2A

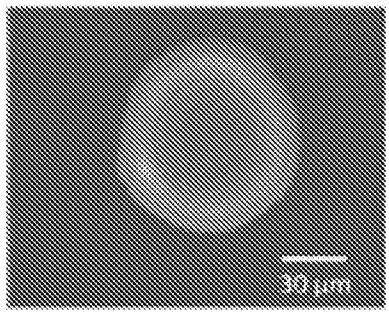


FIG. 2B

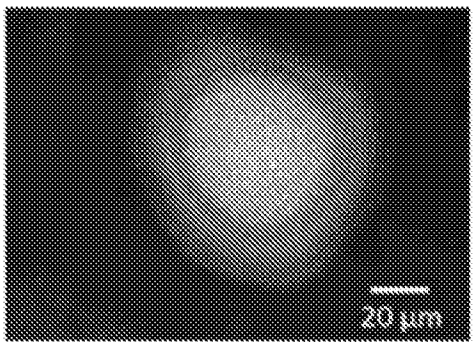
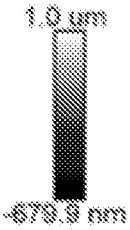


FIG. 2C



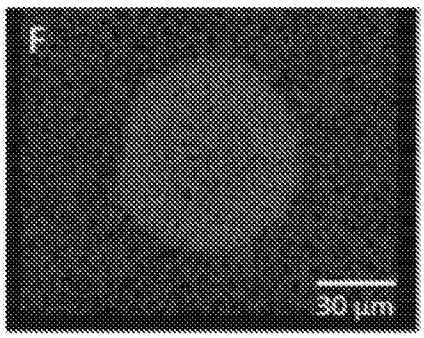


FIG. 2D

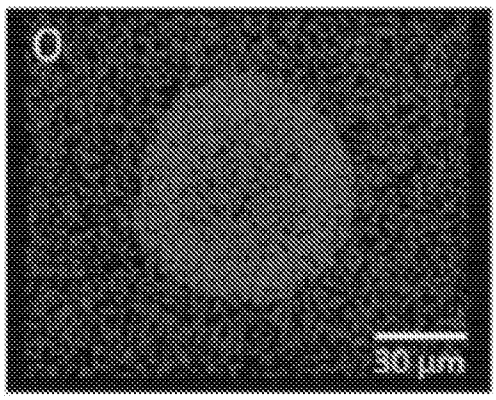


FIG. 2E

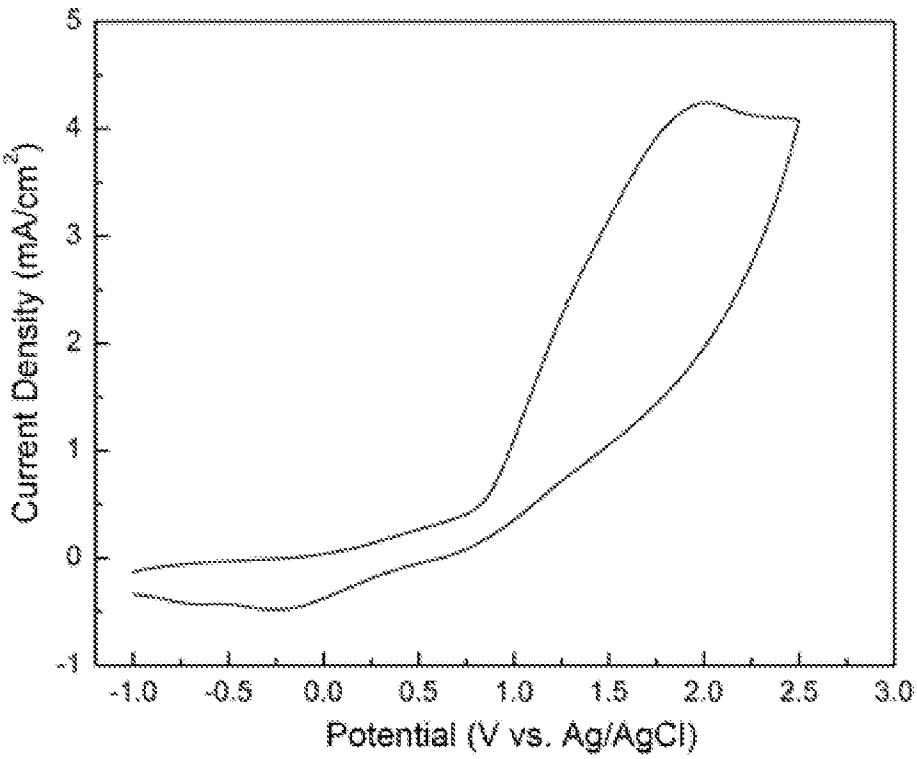

Current Density (mA/cm^2)
5
4
3
2
1
0
-1
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Potential (V vs. Ag/AgCl)

FIG. 3A

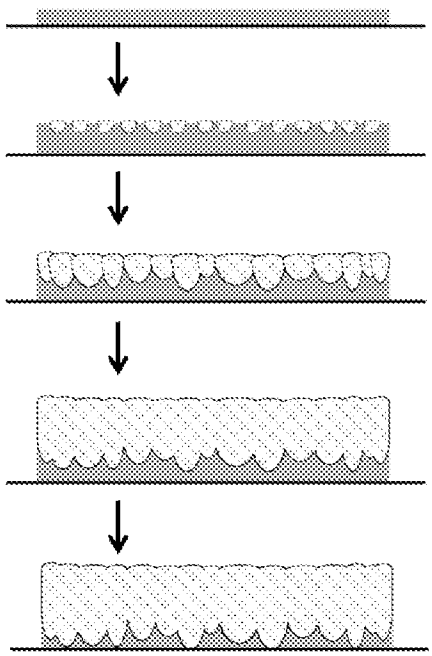


FIG. 3B

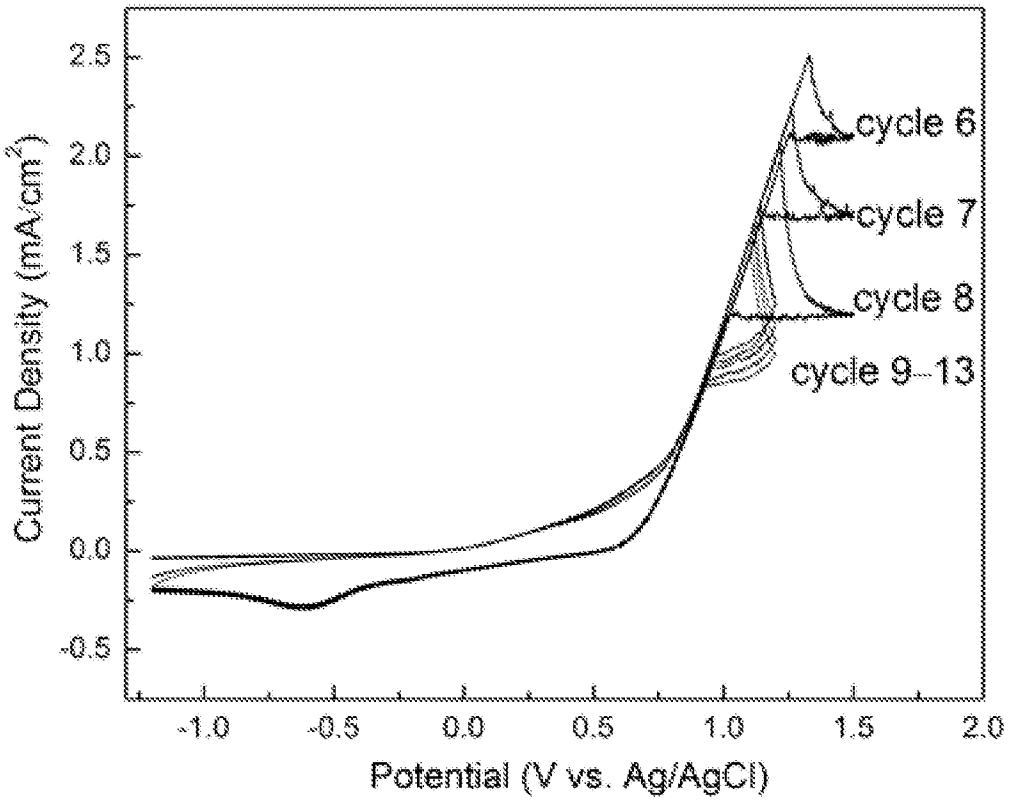

Current Density (mA/cm^2)
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
Potential (V vs. Ag/AgCl)
cycle 6
cycle 7
cycle 8
cycle 9–13

FIG. 3C

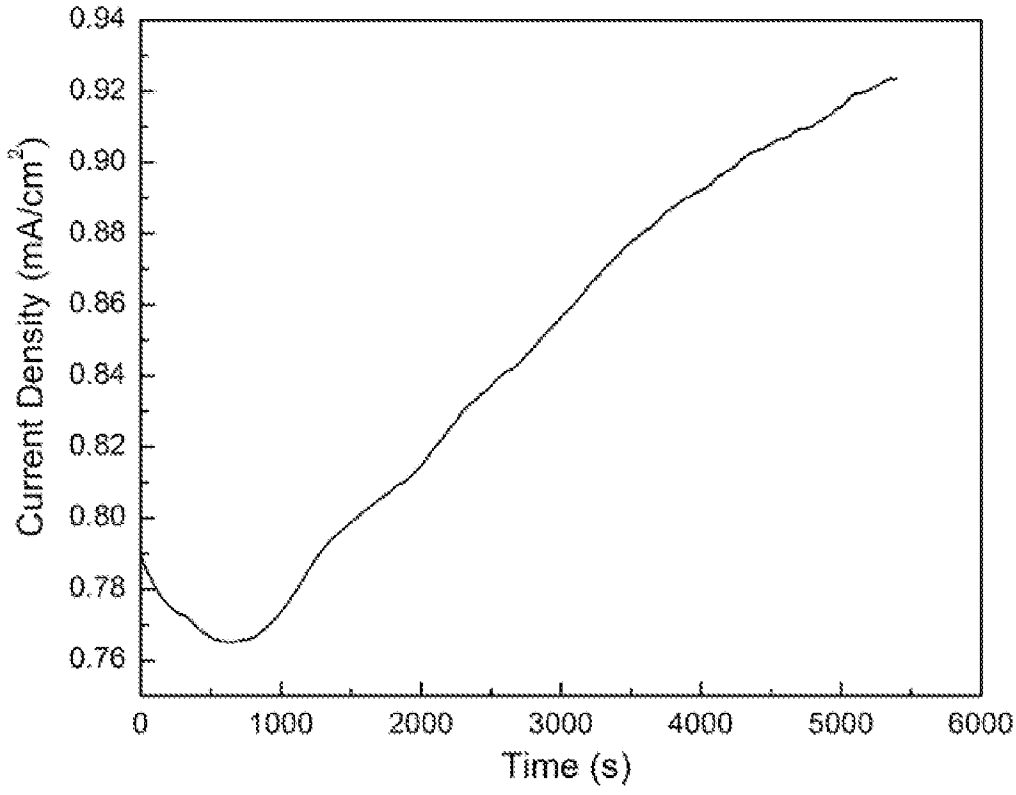

Current Density (mA/cm^2)
0.94
0.92
0.90
0.88
0.86
0.84
0.82
0.80
0.78
0.76
0
1000
2000
3000
4000
5000
6000
Time (s)

FIG. 3D

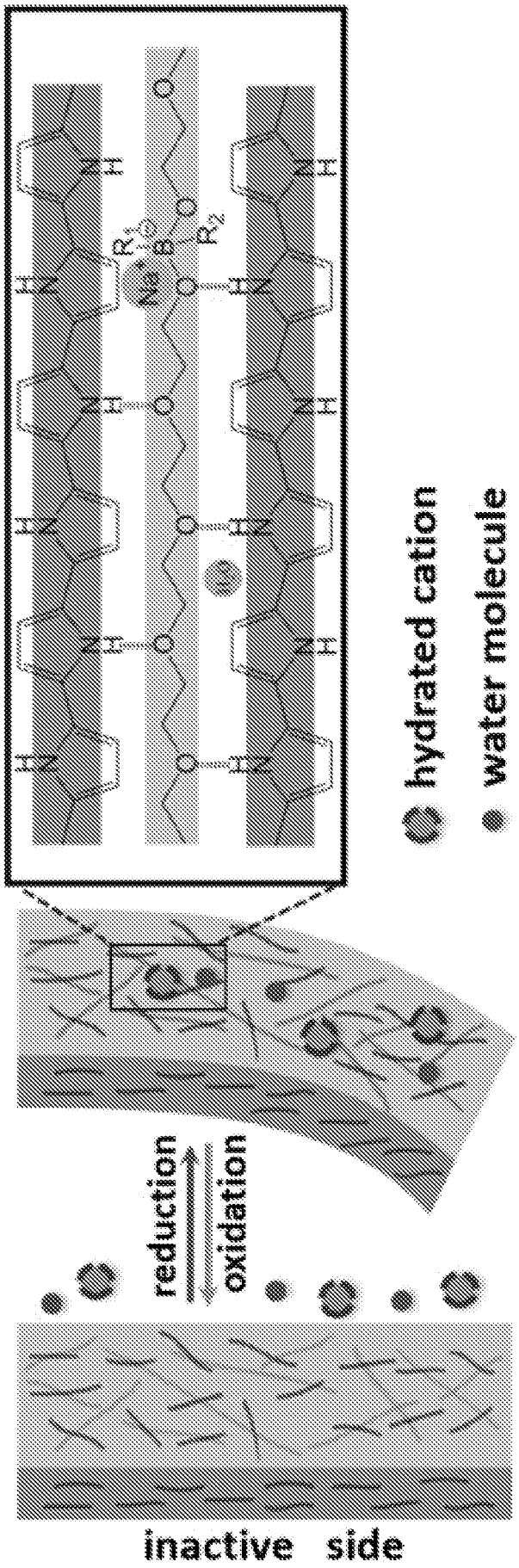

hydrated cation
water molecule
reduction
oxidation
inactive side

FIG. 4A

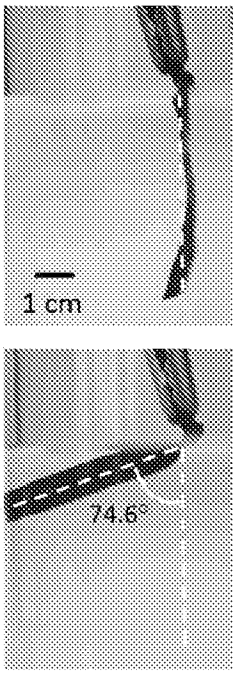

1 cm
74.6°

FIG. 4B

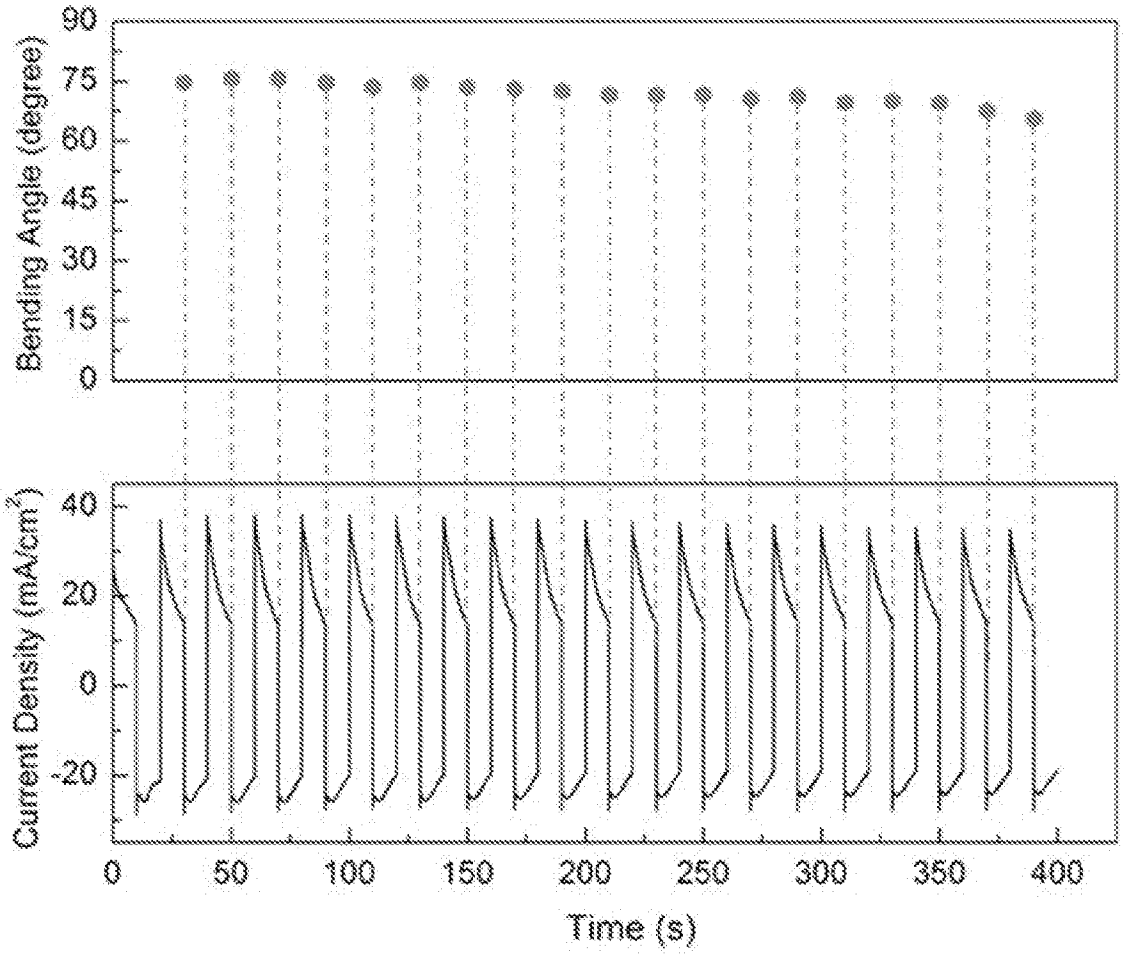

Bending Angle (degree)
90
75
60
45
30
15
0
Current Density (mA/cm²)
40
20
0
-20
0
50
100
150
200
250
300
350
400
Time (s)

FIG. 4C

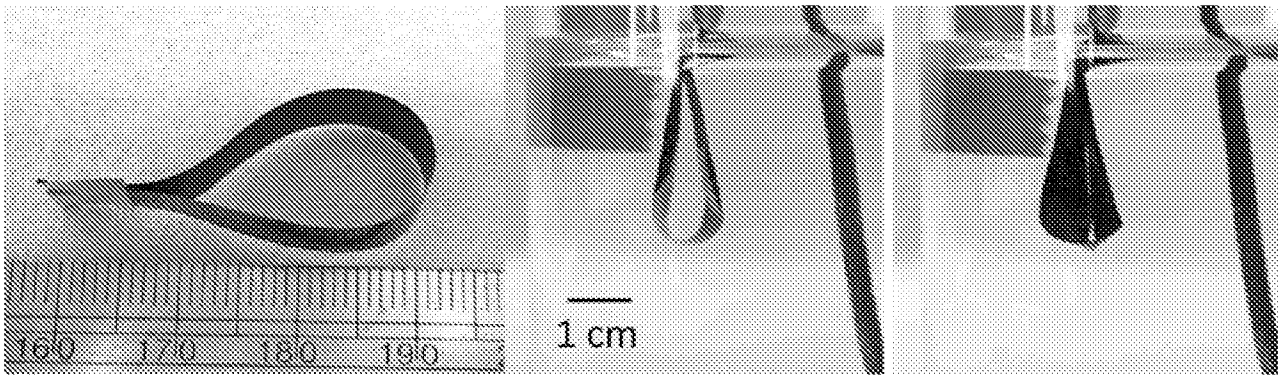


FIG. 5A

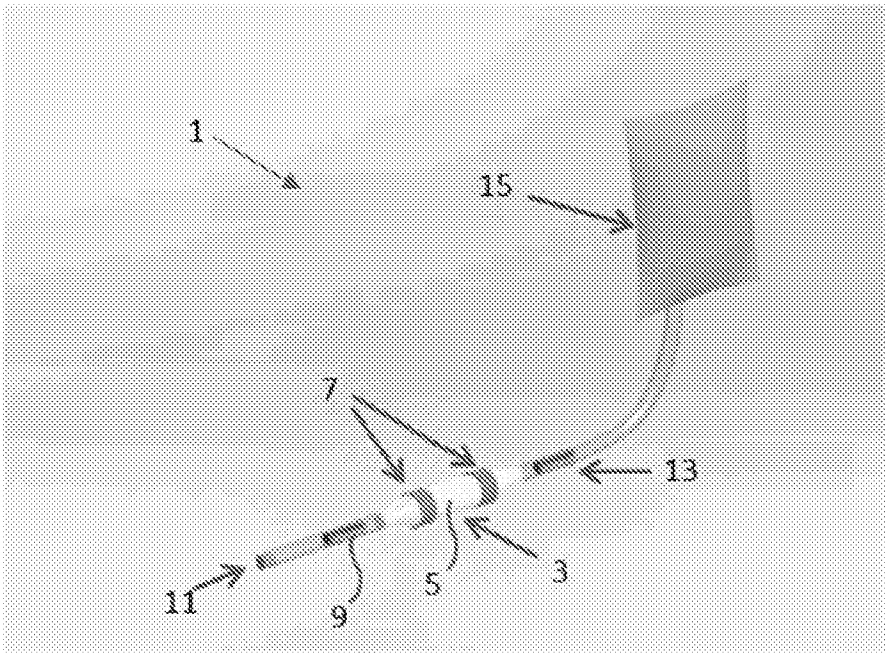


FIG. 5B

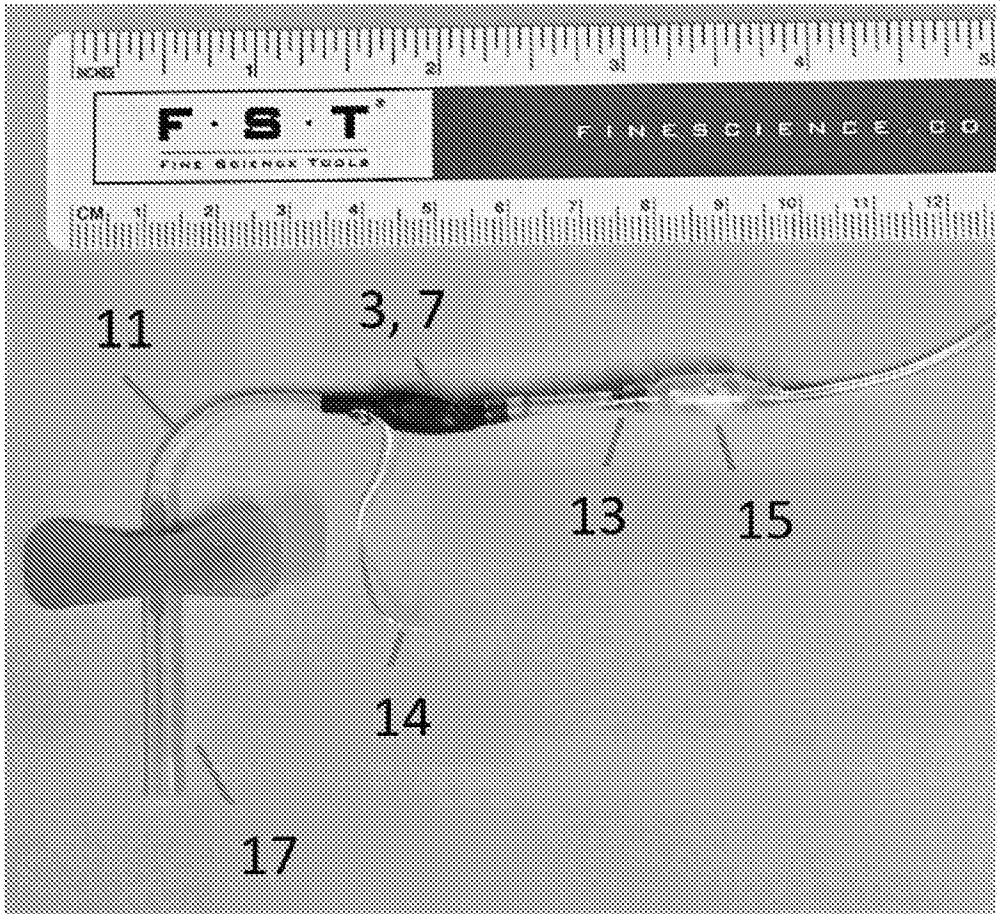


FIG. 5C

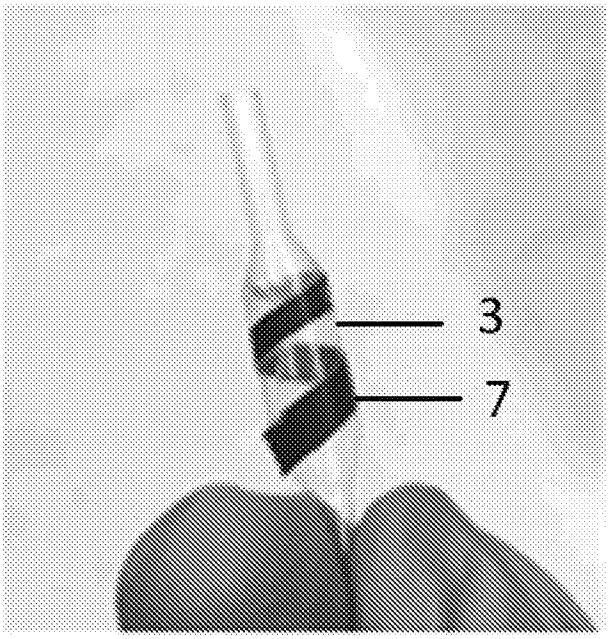


FIG. 5D

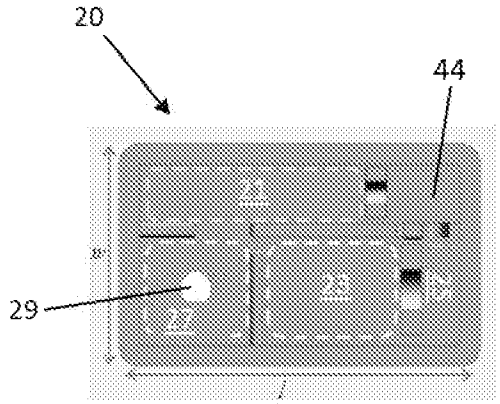


FIG. 6A

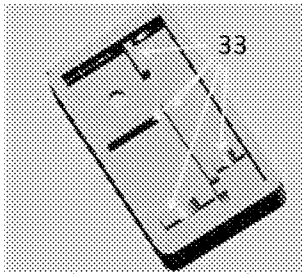


FIG. 6C

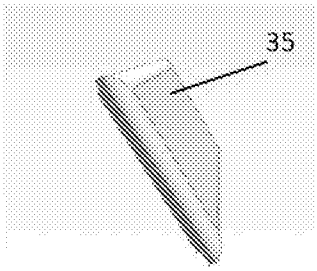


FIG. 6E

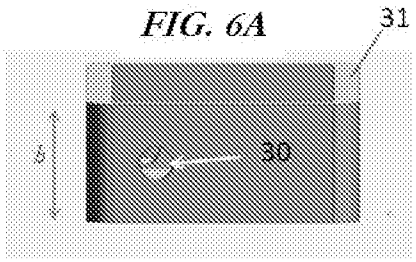


FIG. 6B

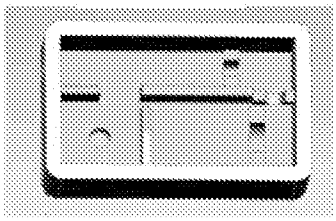


FIG. 6D

FIG. 6F

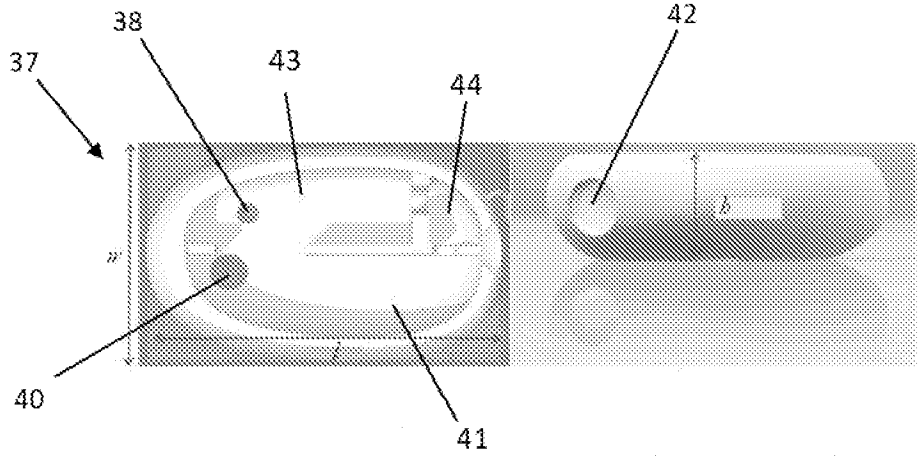


FIG. 7A

FIG. 7B

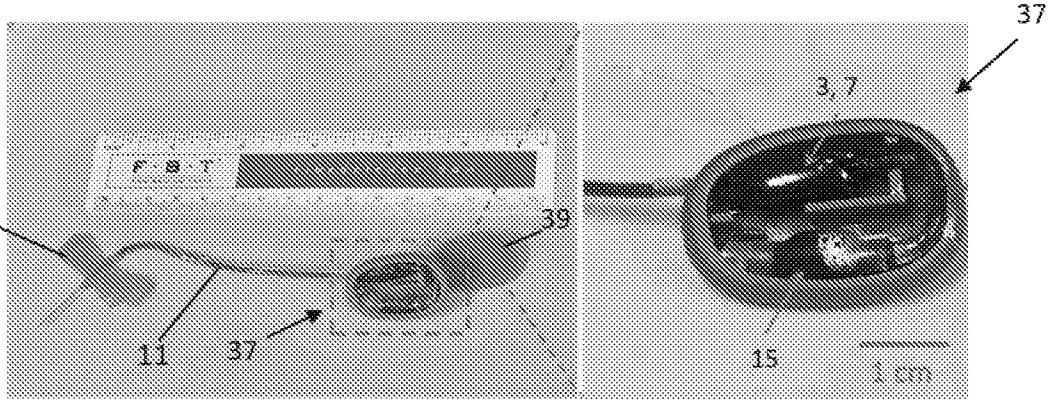


FIG. 7C

FIG. 7D

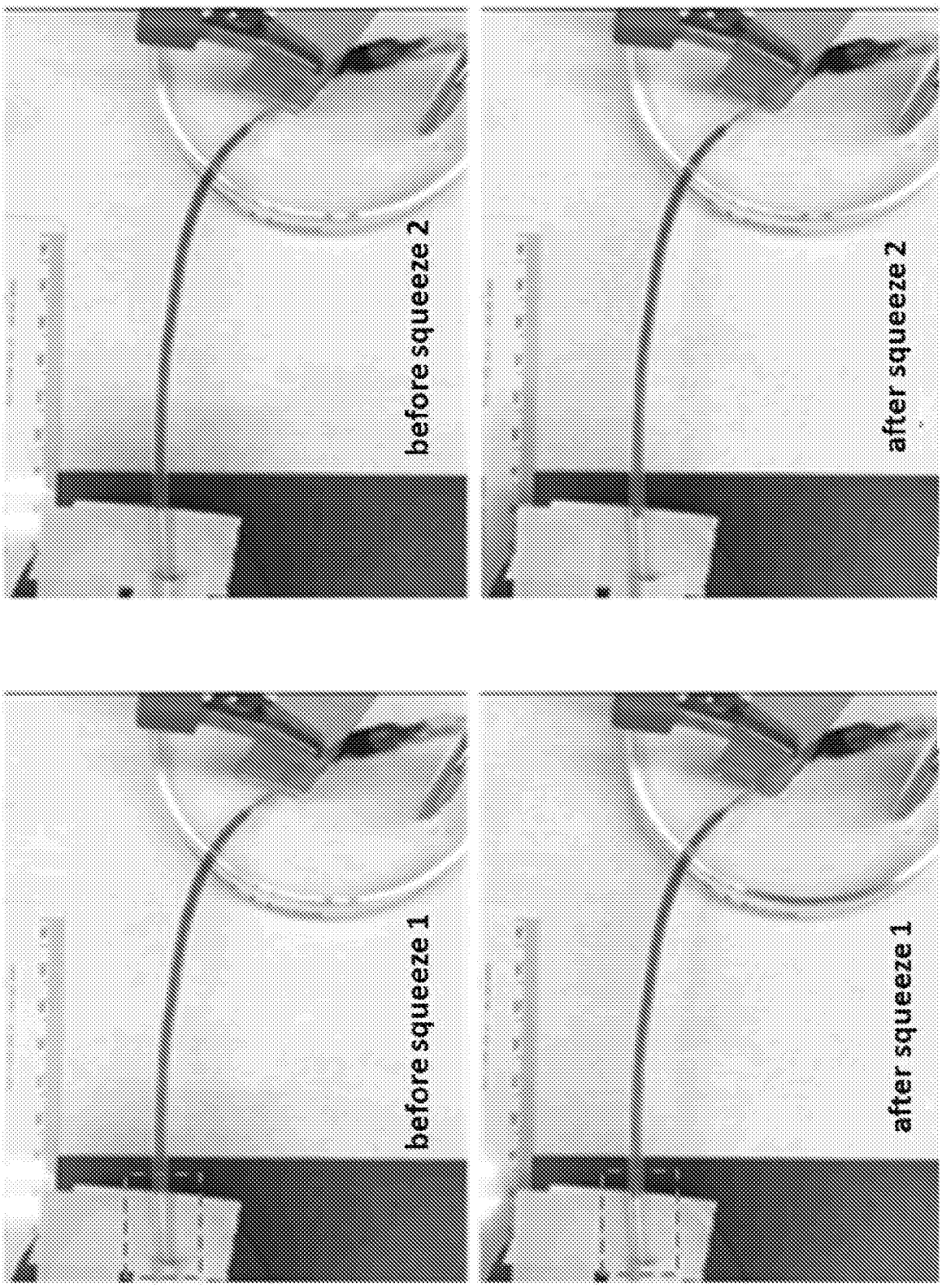

before squeeze 2
after squeeze 2
before squeeze 1
after squeeze 1

FIG. 8A

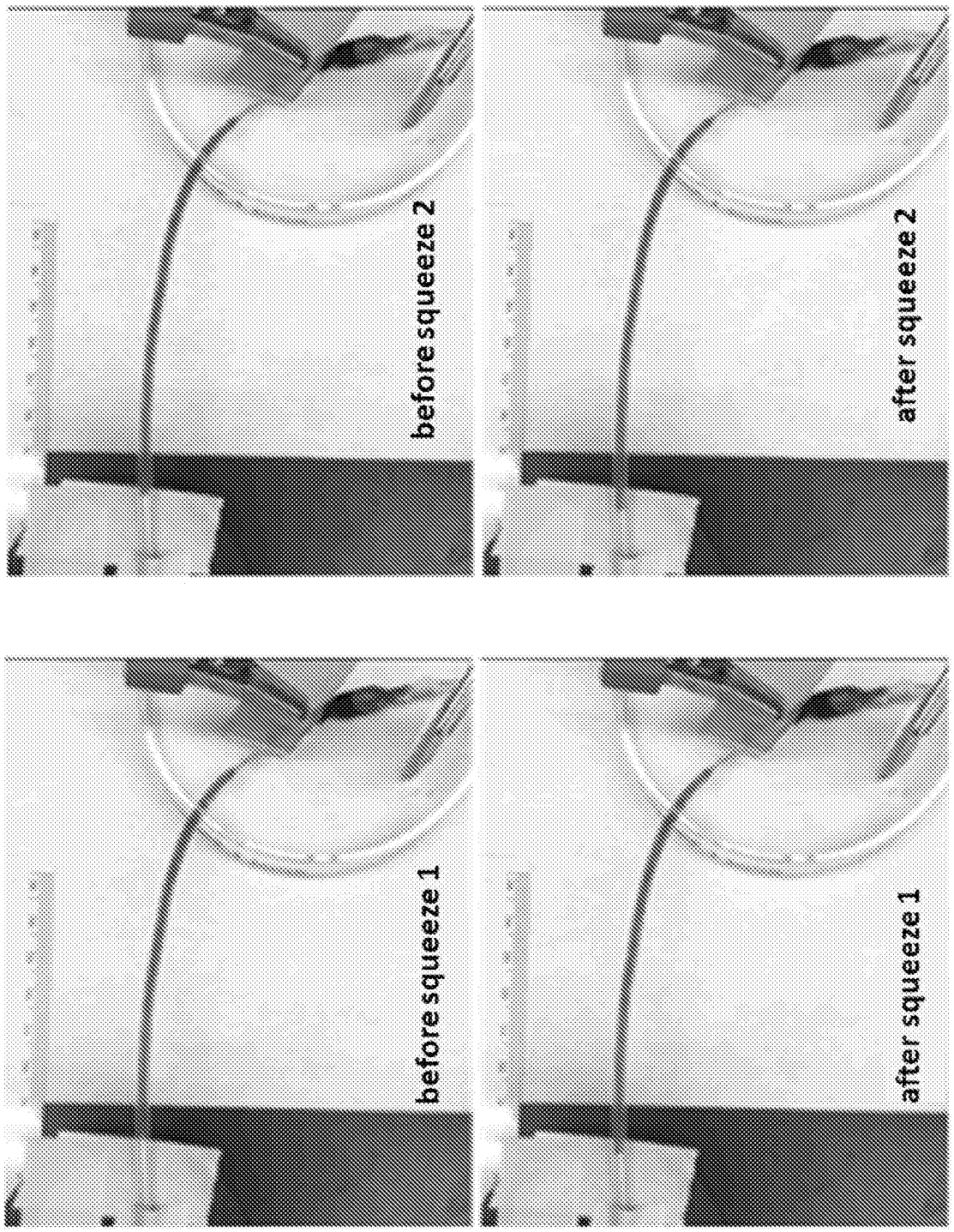

before squeeze 2
after squeeze 2
before squeeze 1
after squeeze 1

FIG. 8B

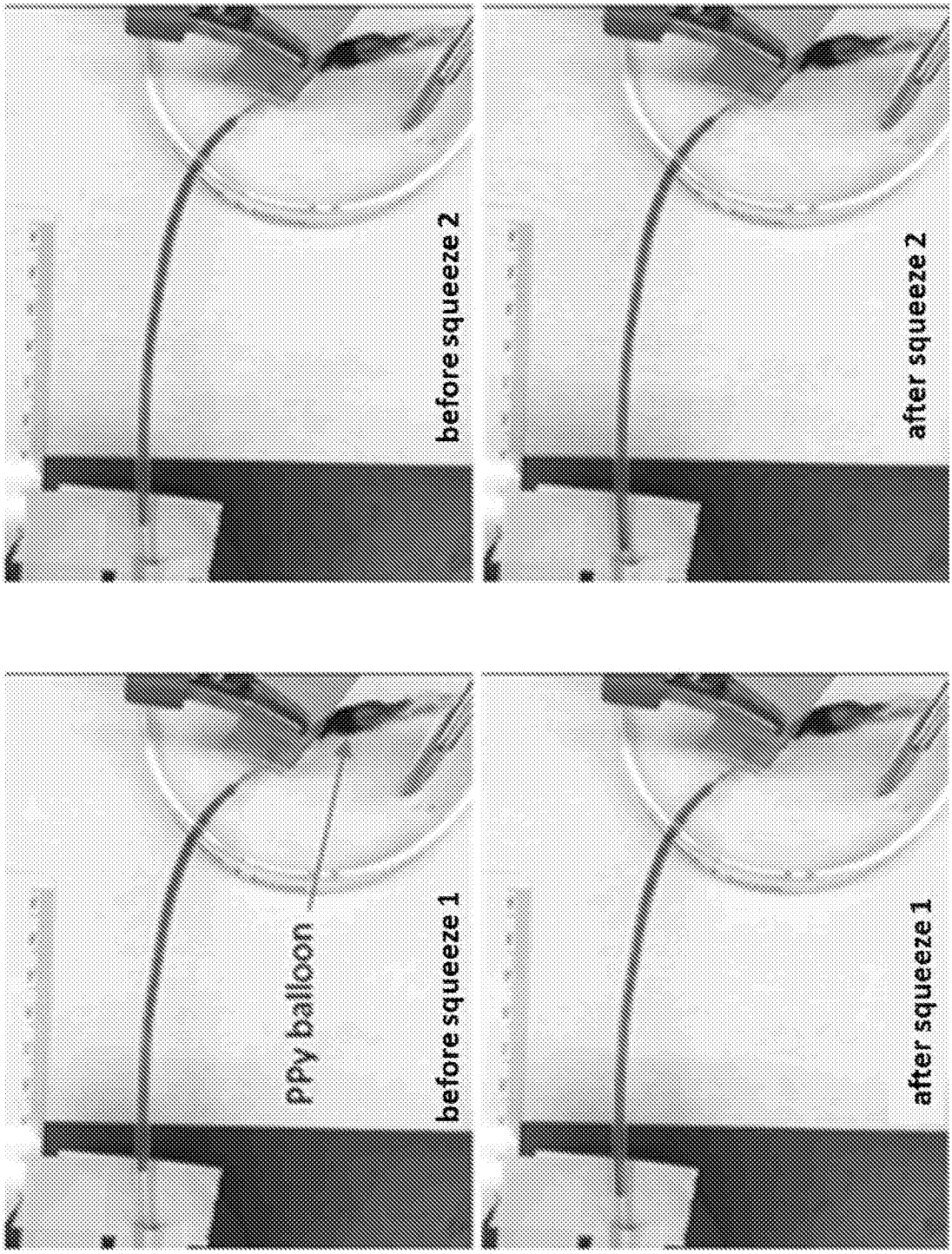

before squeeze 2
after squeeze 2
PPy balloon
before squeeze 1
after squeeze 1

FIG. 8C

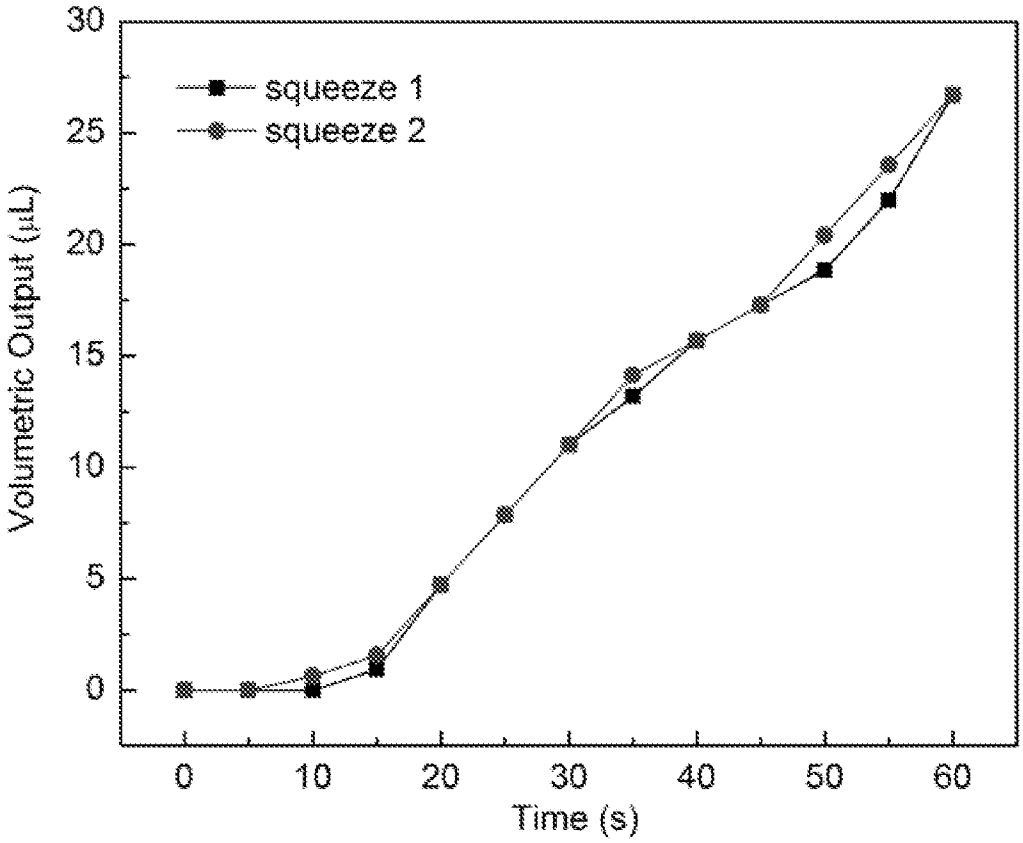

squeeze 1
squeeze 2
Volumetric Output (μL)
Time (s)
0
5
10
15
20
25
30
0
10
20
30
40
50
60

FIG. 9

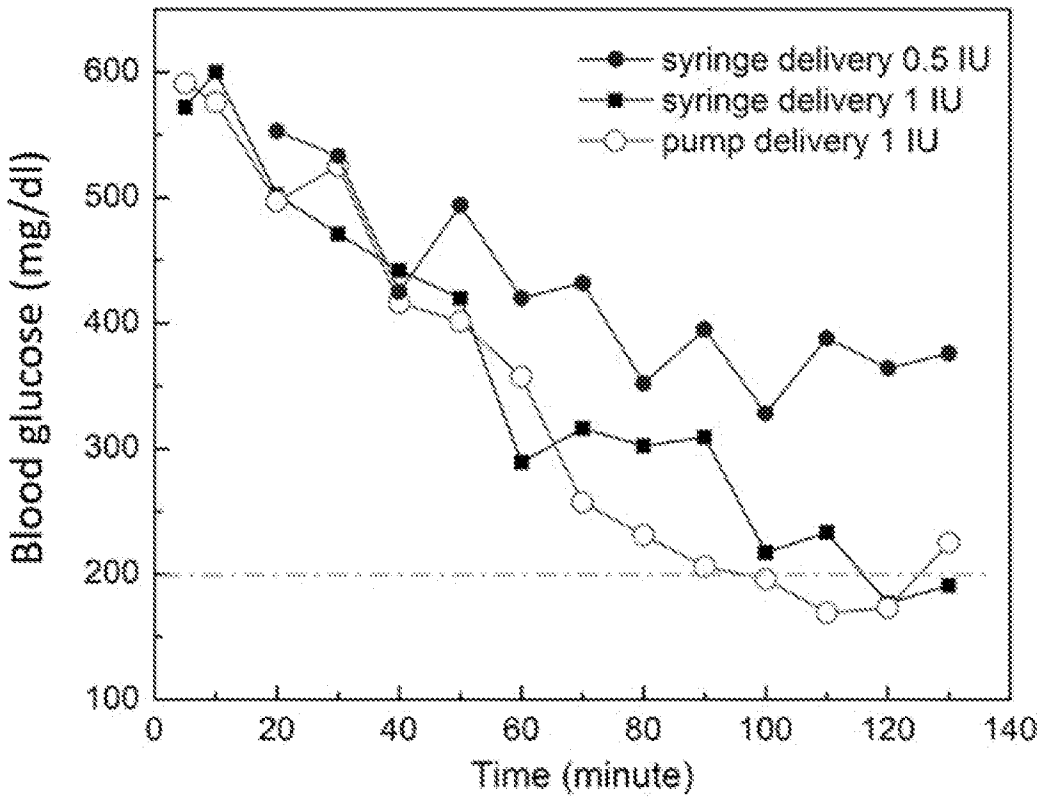

syringe delivery 0.5 IU
syringe delivery 1 IU
pump delivery 1 IU
Blood glucose (mg/dl)
Time (minute)
100
200
300
400
500
600
0
20
40
60
80
100
120
140

FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/19188

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 17/072, G01B 7/24, G01L 1/12 (2019.01)
CPC - A61B 17/00, A61B 17/072, A61B 17/0720

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)
See Search History Document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0068224 A1 (COUVILLON, JR et al.) 08 April 2004 (08.04.2004), abstract; FIG. 3; paras [0041], [0043], [0045-0046], [0047]-[0049], [0051]	1-4, 22-24
A	US 2005/0034755 A1 (OKADA et al.) 17 February 2005 (17.02.2005), abstract	1-4, 22-24
A	US 2006/0219983 A1 (ASAI et al.) 05 October 2006 (05.10.2006), abstract	1-4, 27-29
A	US 2011/0261430 A1 (MAZURKIEWICZ et al.) 27 October 2011 (27.10.2011), abstract; para [0002]	1-4, 27-29
A	US 2012/0055547 A1 (SCHULTZ-WITTMANN et al.) 08 March 2012 (08.03.2012)	22-24, 27-29

☐ 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
16 April 2019	15 MAY 2019
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/19188

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: 5-21, 25-26, 30-46
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.