



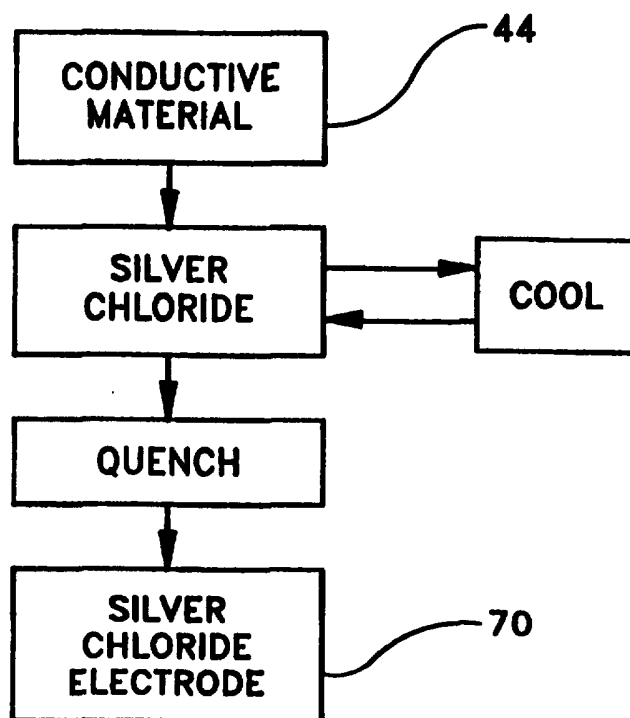
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(54) Title: METHOD OF PREPARING SILVER CHLORIDE ELECTRODES FOR IONTOPHORETIC DRUG DELIVERY DEVICES

## (57) Abstract

A method for preparing a silver chloride electrode suitable to use as a cathode for an iontophoretic device includes a conductive matrix having a surface to serve as an electrode, and silver chloride. The method further includes placing the conductive matrix into the silver chloride for a sufficient residence time, generally only a few seconds, to allow the conductive matrix to acquire a coating of silver chloride. The matrix is then withdrawn from the silver chloride and quenched, hardening the silver chloride. The matrix with the hardened silver chloride on its surface is then ready for placement in an iontophoretic device as a cathode. Preferably, the method includes dipping the conductive matrix into molten silver chloride forming a layer of silver chloride on its surface. The dipping process may be repeated to increase the thickness of the silver chloride coating when there is a requirement for more silver chloride than can be acquired in a single pass through the silver chloride. Results show that an electrode prepared on a silver plated copper matrix compares favorably with a pure silver matrix.



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## UNITED STATES PATENT APPLICATION

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### Method of Preparing Silver Chloride Electrodes for Iontophoretic Drug Delivery Devices

#### Field of the Invention

15       The present invention relates to iontophoresis and more particularly to a method of preparing a low cost manufacturable silver chloride electrode suitable for use as a cathode in iontophoretic drug delivery devices.

#### Background of the Invention

20

Delivery of medicaments into the body is accomplished by a variety of techniques. Oral ingestion and hypodermic delivery are the most common. Recently, transdermal delivery systems have become an increasingly important means of administering drugs. Such systems offer advantages clearly not achievable by other modes of delivery such as: controlled programmable sustained delivery, reduced side effects, non  
25       invasive to name a few.

Presently there are two types of transdermal drug delivery systems, i.e., "passive" and "active." In passive transdermal systems chemical potential gradients provide the dominant driving force to deliver the drug through the skin. For these drugs, a patch containing the drug is applied to the surface of the body and the drug moves into the body predominantly driven by diffusion controlled transport. Some examples of  
30       passive transdermal systems include: delivery of nicotine, nitroglycerine, scopolamine, application of topical anesthetic to provide localized pain relief.

In active transdermal systems, additional user assisted driving forces, either electrical (iontophoresis) or ultrasound (phonophoresis), are used to control the delivery of the drugs through the skin. Iontophoretic  
35       devices for delivering *ionized* drugs through the skin have been known since the early 1900's. Iontophoresis, according to Stedman's Medical Dictionary, is defined as "the introduction into the tissues, by means of an electric current, of the ions of a chosen medicament." In iontophoretic transdermal systems electric potential gradients provide the dominant driving force to deliver the ionized drug through the skin. For these  
40       drugs, an iontophoretic patch containing the drug is applied to the surface of the body, controlled current is driven through the patch via electrodes in contact with the patch and the drug moves into the body predominantly driven by migration controlled transport due to electric fields setup in the iontophoretic patch

by the applied current. Some examples of iontophoretic transdermal systems include: delivery of pilocarpine in diagnosing cystic fibrosis, delivery of topical anesthetic to name a few.

5 The iontophoretic patch primarily consists at a minimum of two compartments, an anode and a cathode, each of which are individually in contact with the body. The electrode compartments house the electrodes in contact with the ionic media and are disposed to be in intimate ionic contact with some portion of the body through the skin, to complete the internal electrical circuit. The electrodes are connected externally to a power supply to complete the external electrical circuit. During operation the entire system, power source, electrode, electrolyte, the skin and the body, forms one integrated electrochemical cell.

10

The electrode connected to the positive pole of the power supply is called the anode and the electrode connected to the negative pole of the power supply is called the cathode. When the current is turned on at the power supply, current flows from the anode to the cathode in the system controlled externally (to the patch) by electron transport and internally (inside the patch between the electrodes) by ion transport. This is possible because the electrodes act as transducers converting electron transport to ion transport via an electron transfer reaction (electrochemical reaction) at the electrode.

15 In general positive ions (cations) will tend to carry portion of the current and move towards the cathode and the negative (anions) ions will tend to carry portion of the current and move towards the anode. Hence by loading cationic drugs in the anode compartment and/or anionic drugs in the cathode compartment, iontophoresis can be used to deliver the ionized drug across the skin separator into the body.

20 The most commonly used cathode in iontophoretic systems is the Ag/AgCl cathode. The standard thermodynamic reduction equilibrium potential for the Ag/AgCl couple is 0.222V vs NHE (Normal Hydrogen Electrode). The desired electrochemical reaction at the cathode during iontophoresis is the reduction of AgCl to Ag:

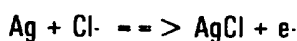


25 It is obvious to one of skill in the art, from the equation that only in regions where the following three minimum conditions are met will the cathodic reaction proceed: (i) accessibility to reactant AgCl, (ii) accessibility to an electron conductor for reactant electrons, and (iii) accessibility to an ion conductor for product chloride ions to carry the current into solution. Hence the desired cathode must contain the required AgCl reactant in contact with an electronic conductor and an ionic conductor. The theoretical minimum amount of AgCl required to support the electrochemical reaction at the cathode can be calculated from the current density and time using Faraday's law. Thus for example, to support current density of 0.5 mA/cm<sup>2</sup> for 24 hours, one would need a minimum of 64 mg/cm<sup>2</sup> of AgCl loading. Additional factors that would increase the AgCl loading requirements will include utilization of active mass and over design for safety.

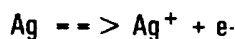
30 The scientific and patent literature abounds in articles on preparation and study of Ag/AgCl electrodes. Thomas, in Ion-Sensitive Intracellular Microelectrodes, Academic Press, 1984, describes chloriding of silver wires for use as microelectrodes by dipping them into molten silver chloride. Additionally, Souto et al., J. Appl. Electrochem., 15 (1985) pp.727-735 and Souto, Bull. Electrochem. 6(7) July 1990, pp. 691-693 describe the preparation of silver/silver chloride electrodes by heating a mixture of silver oxide and silver

chlorate molded around a silver wire. SU 1132210 teaches preparing a silver chloride electrode on a silver matrix by treating the silver base with a hydrogen peroxide solution containing chloride. GB 2215844 discloses a silver/silver chloride electrode prepared by vigorously stirring fine silver particles suspended in an aqueous chloride salt solution, slowly adding an aqueous silver salt solution while maintaining the suspension so that particles at nucleation sites form silver chloride particles, and, recovering the silver/silver chloride particles. The resulting silver particles coated with silver chloride are then formed into an electrode. In the above cited reports from the literature, the silver/silver chloride electrodes were intended to be used as reference electrodes, with no functional requirement of supporting a current being driven through them as is required of a cathode for iontophoresis.

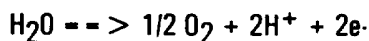
The most common technique for preparing iontophoretic AgCl cathodes involves electrolytic oxidation of Ag to AgCl in acid chloride environment. The desired electrochemical reaction is:



Other parasitic side reactions include silver dissolution:



and oxygen evolution:



United States Patent No. 5,084,006 discloses a cathode from a silver/silver chloride couple. United States Patent No. 5,057,072 also discloses a silver/silver chloride cathode. In both of these disclosures, herein incorporated by reference, there are teachings that the silver/silver chloride couple is generated electrolytically.

But the electrolytic production of AgCl cathodes suffers from several problems. The process is time consuming. The typical operating current density at 100% current efficiency for oxidation of Ag to AgCl is 1 mA/cm<sup>2</sup>. Preparation of an electrode at this current density to operate at 0.5mA/cm<sup>2</sup> for 24 hours would take a minimum of 12 hours. Since the processing time is high the processing cost of the electrode would also be high. If the operating current density is increased to reduce the processing time, the current efficient decreases due to the parasitic side reactions at the electrode.

Further, evolution of oxygen at the electrode will result in non adherent cracked AgCl films with less than desirable mechanical properties. Electrolytic chloriding also demands use of pure silver as feed stock for the conversion process. However during the conversion process less than 50% is typically chlorided to satisfy electron conduction requirements resulting in use of pure silver as a current collector in the electrode. It must be pointed out that the cathodic reaction does not require Ag as reactant and in fact pure silver is produced as a product of the cathodic reaction. The use of pure Ag as current collector in electrolytic AgCl cathodes adds to the material cost of the cathode. Further in the electrolytic process the uniformity of AgCl laydown is controlled by the current distribution on the electrode in the conversion cell. Any non uniform current

distribution on the electrode surface (including edge effects) will result in selective chloriding weakening the mechanical integrity and reducing the reliability of the electrodes.

Hence there is a need for a method to produce reliable, inexpensive and manufacturable AgCl cathodes for iontophoretic use. Such a method is disclosed herein below and will help advance the art and availability of iontophoretic devices.

#### Summary of the Invention

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As iontophoretic delivery of drugs becomes more widely utilized, the demand for silver chloride electrodes for use as cathodes will accordingly increase. The conventional method for preparing silver chloride electrodes by electrolytically chloriding silver electrodes suffers from performance, manufacturing and cost related problems. The lack of low cost, easily and rapidly prepared reliable silver chloride electrodes limits the availability of iontophoretic devices. The present invention of a method for preparing an active silver chloride electrode provides an easily manufactured, reliable, low cost, high capacity cathode (more than 2 mA hr/cm<sup>2</sup>) which will facilitate the use of iontophoresis as a drug delivery technique.

An active silver chloride electrode suitable for long duration use as a cathode in an iontophoretic drug delivery system may be prepared in a few seconds using the method of the present invention from low cost materials. The currently available preparative methods for active silver chloride electrodes require hours and high cost materials to provide an electrode with similar or deficient functional properties to electrodes prepared by the method of the present invention.

A method for preparing a silver chloride electrode suitable for use as a cathode for an iontophoretic device includes an electrically conductive matrix which has a surface to serve as an electrode. Preferably, the conductive matrix is placed in molten silver chloride. The method for preparing a silver chloride electrode preferably then includes allowing the conductive matrix sufficient residence time in the silver chloride melt to produce a substantially continuous silver chloride coating having a thickness on at least a portion of the conductive matrix. Preferably the method then includes withdrawing the conductive matrix from the molten silver chloride. After withdrawal of the conductive matrix from the silver chloride the method preferably includes cooling / quenching the conductive matrix and allowing a sufficient time to cool and harden the silver chloride coating.

Suitable materials for the conductive matrix include but are not limited to, silver, copper plated with silver, platinum, zinc plated with silver, tin plated with silver, carbon, carbon plated with silver, carbon impregnated with a binding agent and plated with silver.

In the silver chloride application, the conductive matrix is preferably dipped in a vessel with molten silver chloride. Alternatively, the silver chloride application may either include electrolytically coating a silver / silver-plated matrix with silver chloride at a temperature below the melting point of silver chloride or applying a finely divided powder of silver chloride to the surface of the conductive matrix. Both of the alternative methods of application result in formation of a discontinuous coating of silver chloride on the

surface of the conductive matrix. In these alternatives, the method then includes heating the applied discontinuous silver chloride coating above the melting temperature of silver chloride, thus, fusing the silver chloride into a continuous coating and then hardening the now continuous coating by cooling/quenching.

5 **Brief Description of the Drawings**

Fig. 1 is a schematic representation of an iontophoretic drug delivery device having a cathode formed by the method of the present invention;

10 Fig. 2a is a schematic representation of a conductive matrix before applying a silver chloride coating in accordance with the method of the present invention, wherein the conductive matrix a solid conductive matrix;

15 Fig. 2b is a schematic representation of the solid conductive matrix illustrated in Fig. 2a with a silver chloride coating applied thereon in accordance with the method of the present invention;

Fig. 2c is a schematic representation of a silver chloride electrode of the present invention after a period of use as a cathode in an iontophoretic device;

20 Fig. 2d is a schematic representation of a conductive matrix before applying a silver chloride coating in accordance with the method of the present invention, wherein the conductive matrix is a porous conductive matrix;

25 Fig. 2e is a schematic representation of the porous conductive matrix illustrated in Fig. 2d with a silver chloride coating applied to both sides of the matrix with the method of the present invention; and

Fig. 3 is a process flow diagram for the method of the present invention for preparing a silver chloride cathode.

30 Fig. 4a is a graph depicting single electrode potential data for a AgCl coated Ag mesh cathode prepared by the method of the present invention as described in Example 1.

Fig. 4b is a graph depicting single electrode potential data for a AgCl coated Ag plated Cu mesh cathode prepared by the method of the present invention as described in Example 2.

35

**Detailed Description of the Preferred Embodiments**

40 While this invention is satisfied by embodiments in many different forms, there is illustrated in the drawings and will herein be described in detail preferred embodiments of the invention with the understanding that the present disclosure is to be considered as exemplary of the principles of the invention and is not intended to limit the invention to the embodiments illustrated.

As shown in Fig. 1, generally an iontophoretic device 10 includes a power source 20, a controller 22, an anode assembly 30 and a cathode assembly 40 which are electrically interconnected with electrical conductors 45 to form a complete electrical circuit 60 when device 10 is mounted on a skin surface 50 of a patient and activated. Device 10 further includes a reservoir 31 and an anode conductive matrix 34 as part of anode assembly 30 and a reservoir 41 and a cathode conductive matrix 44 as part of cathode assembly 40 as well as a housing 100 (schematically shown in phantom), for holding the anode and cathode assemblies to the skin, to the power source, to the controller, and to each other.

In order for electrical current to flow through the device and the skin, electrons must move between anode assembly 30 and cathode assembly 40 through power source 20 and controller 22 through conductors 45, with an ionic flow between anode assembly 30 and cathode assembly 40 through the body of the patient. The function of power source 20 is to provide a source of required current and voltage to operate the iontophoretic device. Current conduction inside the anode/cathode reservoir is via ion transport and is utilized to deliver a medicament having a charge from one or both reservoirs into the patient through skin surface 50.

When the current is turned on in a typical operating iontophoretic device with Ag/AgCl electrode system electrochemical reactions take place at the electrodes. The result of these reactions is an electron current through the circuit and an ion flow to and from the body between the cathode and anode. Many therapeutically useful drugs are ionized to a positive ion and thus will be transported in an iontophoretic process from the anode. A typical anode contains a positively ionizable drug molecule D, water and an electrolyte with chloride as anion, preferably sodium chloride. The cathode reservoir may contain just an electrolyte, preferably sodium chloride.

The electrochemical reaction occurring at the anode is:



The drug and anolyte cations will be transported from the anode patch into the body while the chloride anions from the body will be transported into the anolyte.

The electrochemical reaction at the cathode is:



The catholyte anions and the chloride anions produced at the electrode will be transported into the body whereas the sodium cations from the body will be transported into the catholyte.

In order for drug delivery to progress satisfactorily, there generally must be substantially more equivalent silver chloride molecules in the cathode than equivalent drug molecules to be delivered from the anode. The reason for the excess silver chloride is that the ion current due to drug molecule delivery from the anode assembly is generally less than ten percent of the total ion current from the anode, the balance of the ion current being carried by smaller electrolyte ions. This directly places a greater demand on the active mass

requirement at the electrodes (Ag at anode and AgCl at cathode). Thus, for the longer duration of delivery required for many drugs, where milligram quantities of the drug are required for the desired therapeutic effect, substantial quantities of silver chloride must be available at the cathode.

5 In most of the commonly used iontophoretic cathodes, a silver mesh or silver foil matrix is electrolytically chlorided, i.e., an electric current is applied to the silver matrix in a solution containing chloride ion, so that silver is oxidized to silver chloride forming a coating on the silver matrix. Since a silver matrix is required, the initial cost of the electrode is significant, and since the generation of silver chloride is done electrolytically, the deposition of silver chloride will likely be discontinuous and not uniform and generally is not physically durable. This is especially true when making high capacity electrodes or those electrodes  
10 suitable for long duration use. Generation of milligram quantities of silver chloride electrolytically requires considerable time, considerable silver and, such a process is not easily automated. As was shown above, silver is not even required for the cathode reaction, it is generated by reduction of silver chloride during the iontophoresis.

15 The preferred method for forming silver chloride electrodes by the present invention is schematically demonstrated in Figs. 2a-2c and the process flow diagram in Fig. 3. Fig. 2b schematically shows a silver chloride electrode 70 prepared by the preferred method suitable for use in a cathode assembly in an iontophoretic delivery device. The preferred method includes providing a conductive matrix 44 having a surface 42 with a means for connecting 43 the conductive matrix 44 to device 10. These means 43 may be an uncoated extension of the conductive matrix, a wire, a printed circuit conductor to which the conductive matrix is electrically connected and the like. Preferably, the method then includes providing a station which includes silver chloride. The station preferably includes a vessel containing molten silver chloride, and the matrix is preferably dipped into the melt. The preferred method then provides a quenching bath, preferably  
25 water. For a small scale manufacture of electrodes following the method of the present invention, the elements for manipulating the conductive matrix may simply be forceps or tongs. Preferably, the conductive matrix is then engaged with the manipulating elements and placed into the silver chloride station for a sufficient amount of time to allow the matrix to acquire a substantially continuous coating of the silver chloride on at least a portion of the surface of the conductive matrix. The conductive matrix having the  
30 coating of silver chloride on its surface is then preferably withdrawn from the silver chloride station and transferred to the quenching station. In the quenching station, the matrix with the silver chloride on its surface preferably is allowed to remain for sufficient time for the silver chloride coating on the surface of the conductive matrix to cool to a hardened state. In a preferred embodiment of the method of the present invention the quenching station includes a water bath in which the conductive matrix is placed and allowed  
35 sufficient time for the silver chloride to cool to a hardened state. The conductive matrix preferably is then removed from the quenching station and disengaged from the manipulative elements providing completed silver chloride electrode 70 suitable for use in a cathode assembly in an iontophoretic device.

40 Suitable materials for forming the conductive matrix include, but are not limited to, silver, copper plated with silver, zinc plated with silver, platinum, tin plated with silver, carbon, carbon plated with silver, carbon with a suitable binder and carbon with a suitable binder plated with silver. The purpose of the silver plating on the copper, tin and the zinc matrices, is to prevent reaction of the copper, tin or the zinc with molten silver chloride. Since the silver serves only to render the conductive copper, tin or zinc inert to the

molten silver chloride, the actual amount of silver required is very small. A suitable binder for carbon includes inorganic materials such as clay or organic resins commonly used as fluxes in the semiconductor industry mixed with carbon in a range between about thirty percent to about ninety percent carbon. In this description carbon is intended to include forming a suitable matrix from carbon fibers, including woven materials, non  
5 woven materials and the like.

As is shown in Fig. 2b, preferred conductive matrix 44 acquires a substantially continuous coating of silver chloride 46 when passed through the preferred molten silver chloride. As is shown schematically in Fig. 2b, preferred electrode 70 prepared by the method of the present invention is suitable to be installed in  
10 cathode assembly 40 in iontophoretic device 10 of Fig. 1. When electrode 70 of the present invention is placed in a cathode assembly 40 as shown in Fig. 1 and an iontophoretic drug delivery process is initiated by driving current through the iontophoretic device, electrode 70 undergoes an electrochemical reaction according to equation (2) and develops the structure shown in Fig. 2c. In this application, the current flow reduces silver chloride to silver forming a silver layer 48 at an interface 47 between the silver chloride layer  
15 46 and the conductive matrix 44. In the preferred embodiment shown in Fig. 2d, the conductive matrix is a porous conductive matrix and as shown in Fig. 2e the silver chloride may be coated on both sides of the porous matrix. An example of a porous matrix is a metal or metallic mesh. The conductive matrix on which the silver chloride is coated on both sides is porous so that the electrons may pass through the matrix to reach and utilize the silver chloride on the other side.

20 In many prior cathodes used in iontophoretic devices, the conductive matrix is all silver. As is seen from the drawings and with the review of the electrochemistry occurring at the electrodes during iontophoresis, it is apparent that it is not even necessary that silver be present in the cathode, except for the small amount used as plating during the present coating process to prevent undesirable reactions between the  
25 non-silver conductive matrix and the molten silver chloride. Silver is formed by the reduction of silver chloride at the cathode by acquisition of an electron during iontophoresis. By elimination of the need for substantial quantities of silver, the cost of the electrode is greatly reduced, and by elimination of the need for electrolytic generation and deposition of silver chloride on the silver conductive matrix for formation of a silver chloride electrode, the silver chloride electrode becomes much more easily and rapidly manufactured.

30 However, it should be appreciated that the present method is suitable for preparing an electrode with silver or other non-silver conductive materials as the conductive matrix. A silver chloride electrode where silver is used as the conductive matrix prepared by the instant method is physically more durable and uniform than one prepared electrolytically. Additionally, the electrode of the present invention may be loaded with  
35 sufficient silver chloride to meet duration of use and quantity requirements as applicable for intended use of each electrode manufactured. Furthermore, the time required for preparation of a silver chloride electrode by the method of the present invention is measured in seconds using silver as the conductive matrix compared to hours for an silver chloride electrode of comparable capacity prepared by electrolytic deposition.

40 A copper or other non-silver conductive matrix plated with silver is suitable for forming a silver chloride electrode by the method of the present invention. A copper matrix by itself may not be satisfactory for some applications. If a copper matrix plated with silver is used to form a silver chloride electrode by the common electrolytic generation method, there would need to be sufficient silver plated on the matrix to form

the desired amount of silver chloride. A comparable capacity silver chloride electrode produced with a copper conductive matrix by the method of the present invention needs only sufficient silver plated onto the copper matrix to prevent undesirable side reactions between the copper and the molten silver chloride. All of the silver chloride needed to provide the same functional capability as the silver/silver chloride electrode, for use as a cathode in an iontophoretic device, is coated onto the conductive matrix using the same method as would be used for a pure silver matrix, thereby providing the same cathode functional capability at a greatly reduced cost.

For a silver chloride cathode to be effective in an iontophoretic device, there must be sufficient silver chloride available to sustain the reaction, as shown in equation (2) above, which provides chloride ion for the ion current from the cathode, for the time necessary to complete the desired drug dosage delivery. For example, if it was desired to operate the device 10, as shown in Fig. 1, at four tenths of a milliamp per  $\text{cm}^2$  for twenty four hours, 51.4 milligrams or 0.358 milliequivalents of silver chloride would be required per  $\text{cm}^2$ . Deposition of this quantity electrolytically requires the equivalent amount of coulombs for this current and will require several hours at typical operating current densities presuming 100% current efficiency. The silver chloride layer formed by this method would likely not be uniform, would lack physical integrity and would be discontinuous. The delivery of electrons can be done at a higher current for a shorter time, however, the silver chloride layer formed would surely not be uniform, be discontinuous and would not have the physical integrity of an electrode prepared by the method of the present invention.

In the present method, where a single pass of the conductive matrix through the preferred molten silver chloride does not provide a sufficient amount of silver chloride coating for the intended application, the preferred method may include an intermediate cooling step followed by a return to the molten silver chloride for additional loading of silver chloride. The first pass through the molten silver chloride provides a coating of silver chloride having an initial thickness, with each subsequent pass adding additional thickness and additional mass. Each pass of the conductive matrix through the preferred molten silver chloride requires only seconds. Thus, the total time required, even for high loadings of silver chloride, is small compared to the time required for electrolytic deposition of equivalent amounts. When the desired loading or thickness of silver chloride has been achieved, the matrix with the silver chloride coating is preferably then quenched, providing a glassy, hard and durable silver chloride surface. In the preferred method, the silver chloride is a vessel having molten silver chloride therein, and the matrix is dipped into the molten silver chloride for the coating step, preferably the intermediate cooling step may simply be a withdrawal from the molten silver chloride for a brief period of time followed by a replicate dipping, or it may include cooling by air or an inert gas.

In addition to the preferred method of coating the conductive matrix by dipping it into a melt of silver chloride, the method of the present invention also includes applying a coating of silver chloride to the conductive matrix at a temperature below the melting point of silver chloride followed by heating the silver chloride coating above its melting point to fuse it, and then quenching it to form a hard glassy surface. The application of silver chloride below the melting point includes, but is not limited to, powder coating, vacuum deposition, or in the case where the conductive matrix is silver, electrolytic generation of silver chloride. These below melting point applications of the present method followed by heating the coating to fuse it and form a continuous layer of AgCl, offer the opportunity to automate the formation of the electrodes on a flexible backing such as carbon fiber fabrics or films. The instant method may also include automated

localized heating for fusing of the silver chloride coating preferably followed by rapid quenching that would allow the use of flexible web as a carrier in an automated process. The present use of controlled localized heating followed by rapid quenching would allow the use of a carrier web which otherwise is unable to directly withstand the melting point of silver chloride (455° C.) and enable the backing to be utilized as part of the reservoir for the cathode as well as the electrode itself, further simplifying the construction of the iontophoretic device.

The silver chloride application and the quenching preferably includes inert atmosphere gas blanket on the molten pool to avoid incorporation of impurities into the silver chloride coating. Additionally, while the quenching preferably includes deionized water as the heat transfer agent, it may also include non-reactive gases such as nitrogen, argon, helium and the like as heat transfer agents.

Two examples are given below for preparation of silver chloride electrodes illustrating the method described in this invention. Example 1 describes the preparation of a silver chloride electrode on a silver mesh matrix. Example 2 describes the preparation of a silver chloride electrode on a copper mesh matrix plated with about 0.1mil of silver. Test results are shown in Table 1 comparing the electrode of example 1 with the electrode of Example 2 in a functional model for use as an iontophoretic cathode. The results show that the performance of a silver chloride electrode formed on the silver plated copper matrix is not different than the performance of the silver chloride electrode formed on the all silver matrix.

#### Example 1

Materials: a) Silver Mesh coupon 1 cm x 4 cm (Delker Corp., Branford, CT; #4Ag6.5031) with a surface substantially free from impurities; b) Silver Chloride (Baxter #2142-4).

Procedure: a) Place about 25 gm silver chloride (Melting Point = 455° C) in a ceramic crucible and heat to a temperature about 525° C.

b) Grasp the silver coupon with tongs and vertically dip the coupon into the molten silver chloride for about 5 seconds.

c) Vertically withdraw the coupon from the molten silver chloride and vertically dip into an ambient temperature deionized water quenching bath for about 5 seconds.

d) Remove the coupon from the quenching bath and release from the tongs. A substantially transparent glassy coating of silver chloride is visible on the surface of the coupon.

Figure 4a presents the single electrode potential data (versus AgCl wire reference electrode) for the cathode and the anode during the dechloriding test conducted as described in the experimental setup section. The cathode was 2.5cm square Ag mesh (4Ag6.5031) thermally coated with approximately 53mg of AgCl melt. The anode was 2.5cm square Ag mesh (6AgI-77); the electrolyte was 150mM saline solution at room temperature with no agitation; and the current density was 0.4mA/sq.cm.

The polarization on the cathode at 0.4 mA/sq.cm. is 20mV initially and increases to 50mV at the end of the experiment. The signal stays relatively stable throughout the life of the experiment. The increase in polarization from 20mV to 50mV is due to concentration overpotential effects at the electrode. The low and stable electrode polarization is very encouraging suggesting good electrode performance and a stable electrode structure with easily accessible AgCl reactant and electrolyte. After approximately 24 hours, the

cathode overpotential increases rapidly exceeding 50mV indicating a change in the electrochemistry at the electrode from silver chloride to water electrolysis. At this time, the electrode is practically "dead" for iontophoretic application since the electrolysis of water at the cathode will lead to detrimental pH effects.

5        The coulombic experimental specific capacity of the electrode for AgCl reduction from the above data is calculated to be 9.72 mA-hr/sq.cm. Using Faraday's law and the specific weight of AgCl loading, the theoretical specific capacity calculated is 9.9 mA-hr/sq.cm. The percent utilization of AgCl is determined based on the ratio of the experimental specific capacity to the theoretical specific capacity is then calculated to be 98.2%.

10

#### Example 2

Materials: a) Copper Mesh coupon 1 cm x 4 cm (Delker Corp., Branford, CT; #4Cu7100) plated with 0.1mm silver with a surface substantially free from impurities; b) Silver Chloride (Baxter #2142-4).

15        Procedure: a) Place about 25 gm silver chloride (Melting Point = 455° C) in a ceramic crucible and heat to a temperature about 525° C.

b) Grasp the silver plated copper coupon with tongs and vertically dip the coupon into the molten silver chloride for about 5 seconds.

20        c) Vertically withdraw the coupon from the molten silver chloride and vertically dip into an ambient temperature deionized water quenching bath for about 5 seconds.

d) Remove the coupon from the quenching bath and release from the tongs. A substantially transparent glassy coating of silver chloride is visible on the surface of the coupon.

25        Figure 4b presents the single electrode potential data (versus AgCl wire reference electrode) for the cathode and the anode during the dechloriding test conducted as described in the experimental setup section. The cathode was 1.0cm square Ag/Cu mesh "0.1mil" Ag coated 4Cu7-100) thermally coated with approximately 80mg of AgCl melt. The anode was 1.0cm square Ag mesh (6AgI0077); the electrolyte was 150mM saline solution at room temperature with no agitation; and the current density was 0.4mA/sq.cm.

30        The polarization on the cathode at 0.4 mA/sq.cm is 20mV initially and increases to 51mV at the end of the experiment. The signal stays relatively stable throughout the life of the experiment. The increase in polarization from 20mV to 51mV is due to concentration overpotential effects at the electrode. The low and stable electrode polarization is very encouraging suggesting good electrode performance and a stable electrode structure with easily accessible AgCl reactant and electrolyte. After approximately 35.75 hours,  
35        the cathode overpotential increases rapidly exceeding 60mV indicating a change in the electrochemistry at the electrode from silver chloride to water electrolysis. At this time, the electrode is practically "dead" for iontophoretic application since the electrolysis of water at the cathode will lead to detrimental pH effects.

40        The coulombic experimental capacity of the electrode for AgCl reduction from the above data is calculated to be 14.3 mA-hr/sq.cm. Using Faraday's law and the specific weight of AgCl loading, the theoretical specific capacity calculated is 14.84 mA-hr/sq.cm. The percent utilization of AgCl is determined based on the ratio of the experimental specific capacity to the theoretical specific capacity is then calculated to be 96.3%.

Table 1 presents a comparison of the electrodes of example 1 and example 2 in a functional evaluation of electrochemically accessible silver chloride for the reaction:



- 5 Electrodes prepared according to Examples 1 and 2 were each installed as a cathode versus a silver mesh anode in test cells containing aqueous 150 millimolar sodium chloride solution. Exposed cathode area was  $1\text{ cm}^2$  varied from  $1\text{--}2.5\text{ cm}^2$ . Testing was done under constant current control and the operating current density was  $0.4\text{ mA/cm}^2$ . The cathode potential was monitored with a Ag/AgCl reference electrode and the testing was stopped when the electrode reaction switched from AgCl reduction to hydrogen evolution (as  
10 observed from the change in the cathode polarization). The experimentally available coulombic capacity of the electrode was determined from the current density and the lifetime of the electrode for AgCl reduction electrochemistry. From the weight loading of AgCl the theoretical coulombic capacity of the electrode was also calculated from Faradays Law. The utilization of the active mass was then calculated as the ratio between the experimental and theoretical specific capacities. In general, low polarizations ( $< 100\text{ mV}$ ) and  
15 utilizations approaching 100% indicate good electrode performance.

**Table 1**

**Comparison of AgCl electrodes formed on a Silver and a Silver Plated Copper Substrate**

Sample	Silver chloride on Silver (Example 1)	Silver chloride on Silver plated copper (Example 2)
Time to prepare coating	$< 1\text{ min}$	$< 1\text{ min}$
Substrate Specific Weight $\text{gms/cm}^2$	0.0992	0.0284
Active mass specific weight $\text{gms/cm}^2$ (AgCl)	0.053	0.0795
Test Current Density $(\text{mA/cm}^2)$	0.4	0.4
Polarization (mV)		
at 5.0 hours	20	20
10.0	23	22
15.0	51	24
Theoretical specific capacity $(\text{mA hours/cm}^2)$	9.9	14.84
Experimental specific capacity $(\text{mA hours/cm}^2)$	9.72	14.3
Percent of theory utilized	98.2	96.3

- 20 The results shown in the table describe the performance of the example electrodes (for reduction of AgCl to Ag) when a current of 0.4 milliamps per  $\text{cm}^2$  is maintained in the test cell for a period in excess of 24 hours. The test simulates the use of the electrodes as a cathode in an iontophoretic drug delivery system.

In the table the silver conductive matrix has a higher substrate specific weight because it is a less open and thicker mesh than silver plated copper. The silver plated copper conductive matrix acquired a higher loading of silver chloride than the pure silver because of the different mesh dimensions. This data suggests that the mesh design can be effectively used to vary and control AgCl loading onto the substrate.

5

The specific capacity of the cathodes tested was in excess of 10 mA.hr/cm<sup>2</sup>. This implies that at 0.4 mA/cm<sup>2</sup> current density the cathodes can be safely operated with AgCl reduction electrochemistry in excess of 24 hrs. Also the utilization of the AgCl active mass (as calculated from the experimental and theoretical specific capacities) in the electrodes tested was in excess of 90% suggesting good electrode structure (ionic and electronic) and efficient use of the active electrode material.

10

It is noteworthy to observe that the processing time to prepare the high specific capacity electrodes on inexpensive substrates with good mechanical properties and with good utilization and performance as described above with the current disclosed method is typically less than a minute.

15

Preparation of a silver chloride electrode of similar capacity by electrolytic deposition of silver chloride on a silver substrate would require several hours of electrolytic deposition. Additionally, the electrolytically prepared electrode, since it would likely not be as uniform and is not mechanically as strong would likely not be as suitable for use in an iontophoretic device and most certainly would be more costly.

20

What is claimed is:

1. A method for preparing a silver chloride electrode suitable to use as a cathode an iontophoretic device, the method comprising:
  - placing a conductive matrix into silver chloride;
  - allowing said conductive matrix sufficient residence time in said silver chloride for said conductive matrix to acquire a substantially continuous coating of said silver chloride having a thickness on at least a portion said surface of said conductive matrix;
  - quenching said conductive matrix and allowing a sufficient time for cooling said coating of silver chloride to a hardened state; and
  - removing said conductive matrix having said hardened silver chloride coating thereon from said quenching bath.
2. The method of claim 1 wherein said conductive matrix comprises a conductive matrix selected from the group consisting of silver, silver plated copper, platinum, silver plated zinc, silver plated tin, carbon, silver plated carbon, carbon impregnated with a binding agent and carbon impregnated with a binding agent plated with silver.
3. The method of claim 2 wherein said conductive matrix includes a matrix formed and sized to fit an iontophoretic device.
4. The method of claim 2 wherein said step of providing said conductive matrix includes providing a preshaped conductive matrix for an iontophoretic device on a flexible material substantially resistant to said placing and said allowing steps and wherein said steps for said placing, said allowing and said quenching comprises a mechanized process.
5. The method of claim 2 wherein said silver chloride comprises a vessel having molten silver chloride therein and said placing step comprises dipping said conductive matrix into said molten silver chloride.
6. The method of claim 5 wherein said silver chloride further includes an inert gas atmosphere.
7. The method of claim 5 wherein said quenching includes a heat transfer medium selected from the group selected from the group consisting of water, nitrogen, argon and helium.
8. The method of claim 7 wherein said heat transfer medium comprises water and said quenching step comprises placing said conductive matrix having said silver chloride on said surface in said water for a sufficient time for said silver chloride to become a solid.
9. The method of claim 1 wherein said steps of said placing said conductive matrix into said silver chloride, said allowing and said quenching includes an intermediate cooling step before said quenching step and further includes said placing step and said allowing steps being sequentially repeated at least one time

before said quenching step thereby increasing said thickness of said coating of said silver chloride on said surface of said conductive matrix.

10. The method of claim 1 wherein said steps comprising placing, allowing, and quenching further include  
5 applying said silver chloride to said surface of said conductive matrix at a temperature below the melting temperature of said silver chloride thereby forming a discontinuous coating on said surface of said silver matrix, followed by heating said silver chloride above the melting temperature of said silver chloride thereby fusing said silver chloride and forming a continuous coating of said silver chloride on said matrix, said continuous coating being hardened by cooling in said quenching step.

10

11. The method of claim 10 wherein said applying said silver chloride to said surface of said conductive matrix at a temperature below the fusion temperature comprises application of a finely divided powder of silver chloride to said surface.

15 12. A method for preparing a silver chloride electrode from a silver matrix suitable to use as a cathode for an iontophoretic device comprising:

placing a silver matrix having a surface into silver chloride;

allowing said silver matrix sufficient residence time in said silver chloride for said silver matrix to  
20 acquire a substantially continuous coating of said silver chloride having a thickness on at least a portion said surface of said silver matrix; and

quenching said silver matrix for a sufficient time to cool said coating of silver chloride to a hardened state.

13. The method of claim 12 wherein said silver matrix for said electrode includes a material selected from  
25 the group consisting of silver wire, silver mesh and silver sheet, said surface of said silver matrix being substantially free of impurities.

14. The method of claim 13 wherein said silver matrix includes a matrix formed from silver mesh and sized to fit an iontophoretic device.

30

15. The method of claim 13 wherein silver matrix includes providing said silver preshaped for an iontophoretic device cathode on a flexible material substantially resistant to said placing and said allowing steps and said allowing, said withdrawing, said quenching and said removing steps comprises a mechanized process.

35

16. The method of claim 12 wherein said silver chloride comprises a vessel having molten silver chloride therein and said placing step comprises dipping said silver matrix into said molten silver chloride.

17. The method of claim 16 wherein said silver chloride further comprises an inert gas atmosphere.

40

18. The method of claim 12 wherein said steps of said placing, said allowing and quenching include an intermediate cooling step before said quenching and further includes said placing step and said allowing step

being sequentially repeated at least one time before said quenching step thereby increasing said thickness of said coating of said silver chloride on said surface of said silver matrix.

19. The method of claim 12 wherein said steps comprising placing, allowing, and quenching further  
5 include applying said silver chloride to said surface of said silver matrix at a temperature below the melting point temperature of said silver chloride thereby forming a discontinuous coating on said surface of said silver matrix, followed by heating said silver chloride above the melting temperature of said silver chloride thereby fusing said silver chloride and forming a continuous coating of said silver chloride on said matrix, said continuous coating being hardened by cooling in said quenching step.

10

20. The method of claim 19 wherein said applying said silver chloride to said surface of said silver matrix at a temperature below the melting point temperature of said silver chloride thereby forming a discontinuous coating on said surface comprises an aqueous electrochemical chloridation process.

15

21. The method of claim 19 wherein said applying said silver chloride to said surface of said silver matrix at a temperature below the fusion temperature comprises application of a finely divided powder of silver chloride to said surface.

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FIG-1

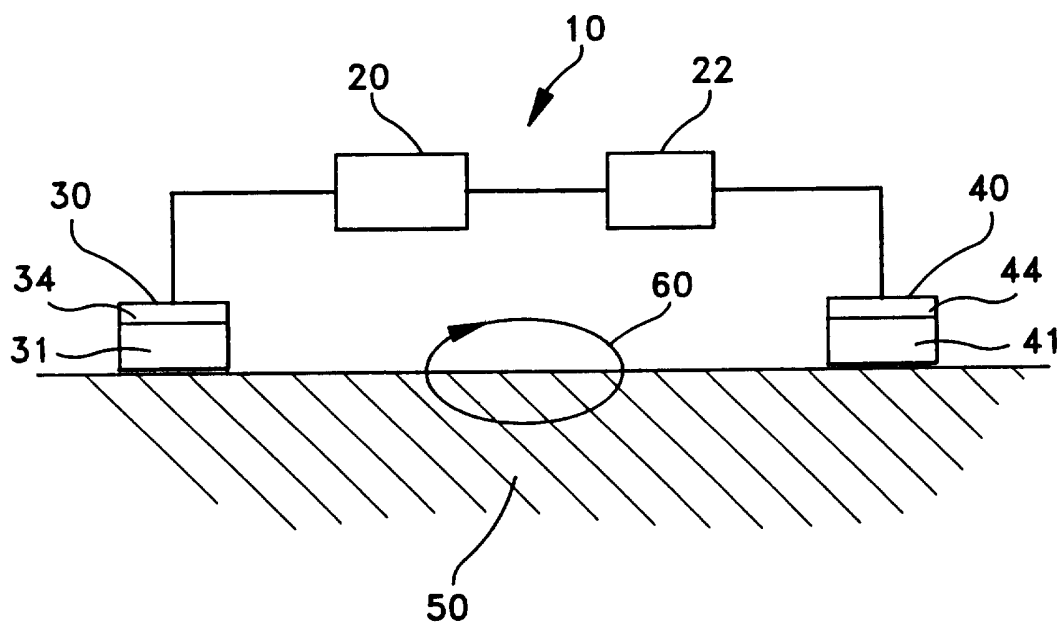
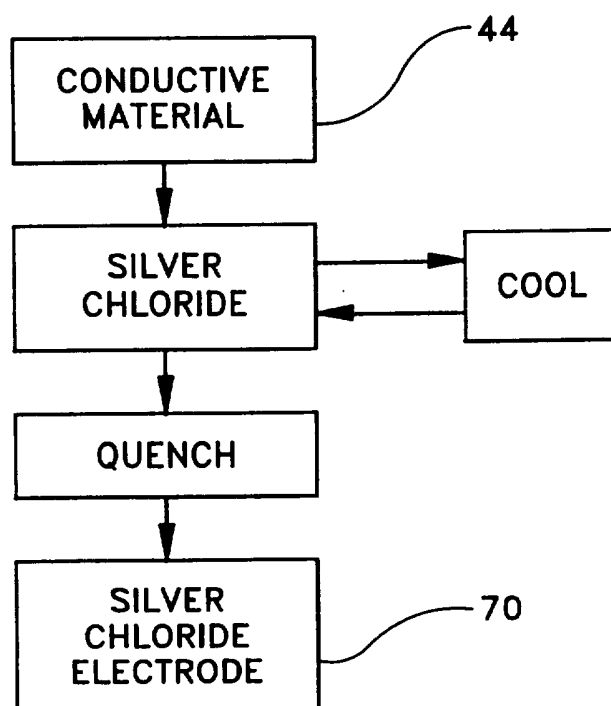


FIG-3



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FIG-2a

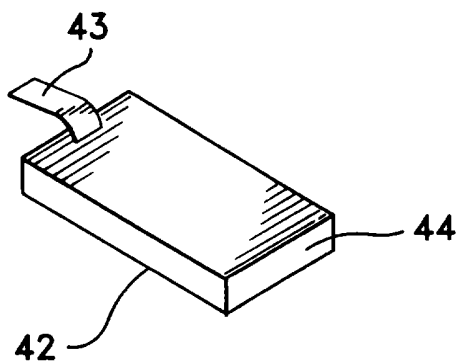


FIG-2b

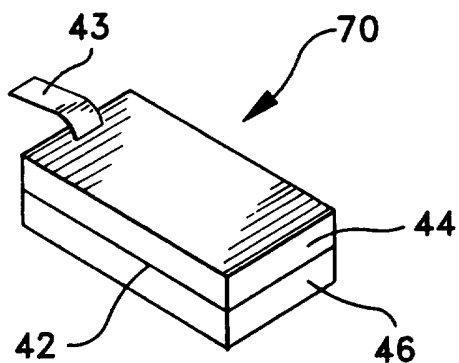


FIG-2c

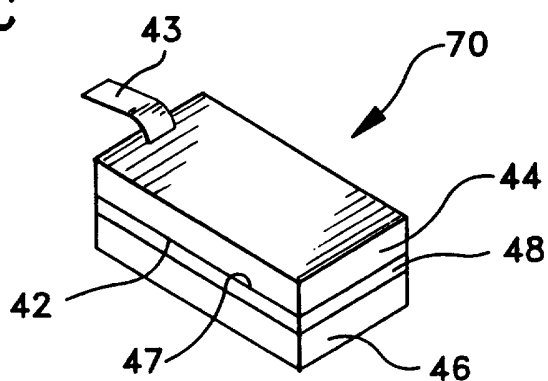


FIG-2d

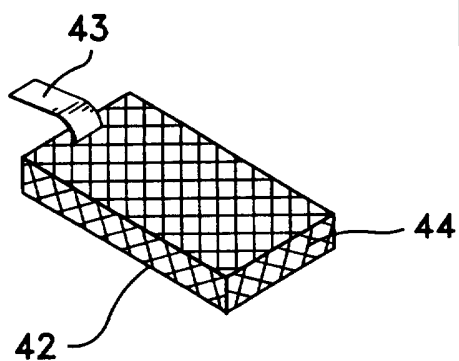
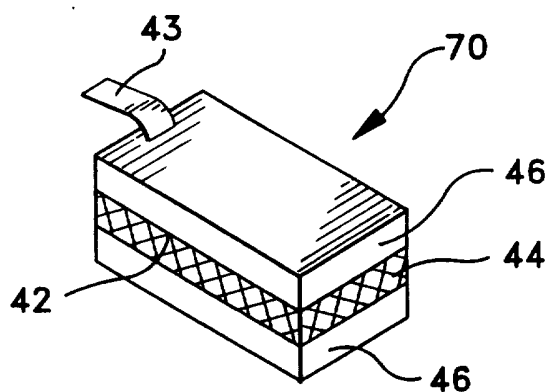
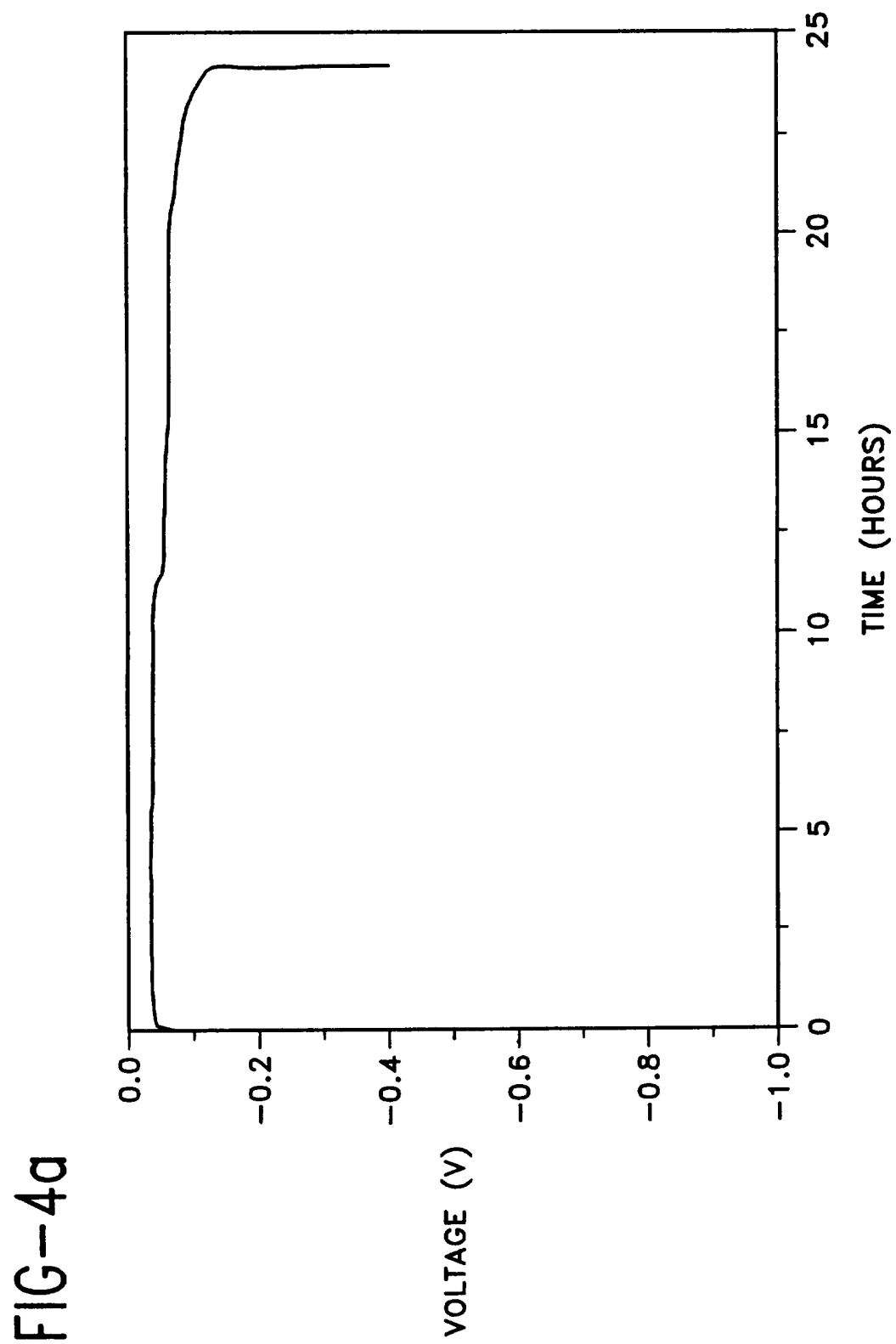


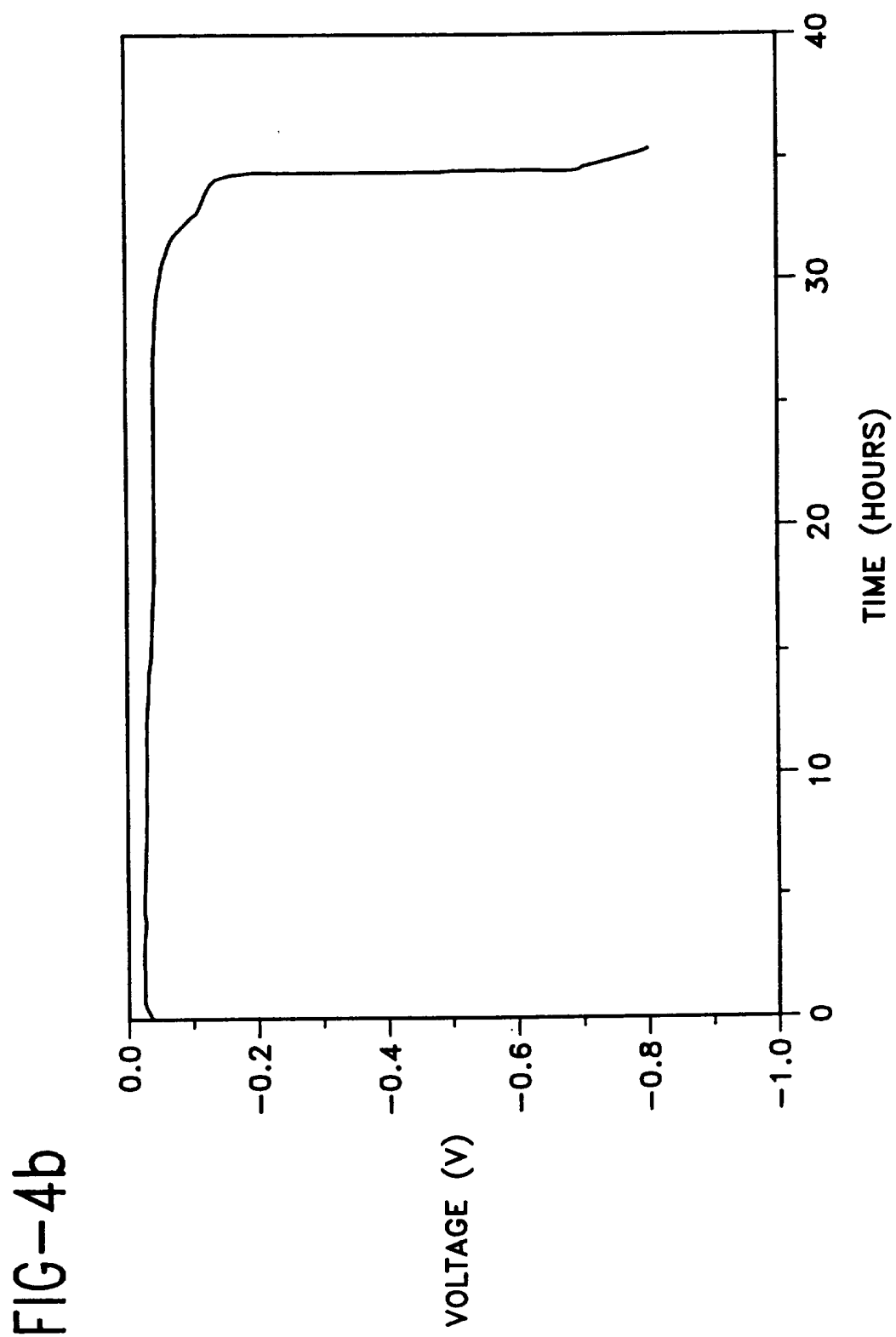
FIG-2e



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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 95/12398

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61N1/30

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 6 A61N

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 practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R.C.THOMAS 'Ion-sensitive intracellular microelectrodes' 1984, ACADEMIC PRESS, ENGLAND cited in the application Paragraph B. Chloriding silver wire see page 23	1,2,5, 12,13,16
A	--- JOURNAL OF APPLIED ELECTROCHEMISTRY, vol. 15, no. 5, September 1985 pages 727-735, A.AREVALO & ALL 'Preparation and reproductibility of a thermal silver-silver chloride electrode' cited in the application see page 728, left column, line 23 - page 729, left column, line 15 --- -/--	1,2, 10-13, 19-21

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

16 January 1996

Date of mailing of the international search report

26. 01. 96

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 95/12398

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 11216 (HILLMAN) 8 August 1991 see page 3, line 1 - line 23 ---	1-3, 12-14
A	WO,A,91 16944 (MYERS) 14 November 1991 see page 19, line 1 - line 23 -----	1-3, 12-15

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Information on patent family members

International Application No

PCT/US 95/12398

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		AU-B- 7894291	27-11-91
		AU-B- 647798	31-03-94
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		EP-A- 0528984	03-03-93
		ES-T- 2050541	16-05-94
		ES-T- 2069299	01-05-95
		WO-A- 9116946	14-11-91