A system and method is provided for treatment of end stage renal disease ("ESRD") using transdermal dialysis ("TDD"), such as to treat both acute and chronic ESRD. Generally, a patient's epidermal surface may be used as a dialysis membrane in the treatment of ESRD. A patient suffering from ESRD using TDD may be treated, where the patient's epidermal membrane ("EM") surface serves as the dialysis membrane. In such a system or method, the patient's EM may be contacted with a dialysate solution to thereby allow wastes and toxins to pass from beneath the patient's EM, through the patient's EM and into the dialysate solution. In a particular embodiment, the patient's EM is exposed to a prescribed electric field, to thereby increase the permeability of the patient's EM.
Published:

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SYSTEM AND METHOD FOR TRANSDERMAL DIALYSIS

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of priority to U.S. Provisional Patent Application Number 61/891,936, entitled "SYSTEM AND METHOD FOR TRANSDERMAL DIALYSIS," which is incorporated herein in its entirety.

FIELD

The invention relates generally to a system and method for the treatment of end-stage renal disease using transdermal dialysis. By utilizing the clinically proven technique of electroporation, an electric field is applied to the skin. The application of an electric field, temporarily increases the permeability of the skin, and allows the skin to become a dialysis membrane. Dialysis is then administered to the patient in a prescribed dialysate bath using the skin as a semi-permeable membrane.

BACKGROUND

Kidney failure, also known as renal failure, or end stage renal disease ("ESRD") is a condition wherein the kidneys are incapable of performing their normal functions. Certain metabolites that should be excreted through the kidneys, such as nitrogenous wastes, nutrients, ions and water, accumulate in the body. The levels of accumulated substances, if clinically abnormal, may cause symptoms including, but not limited to tiredness, weakness, loss of appetite and vomiting, arrhythmia, and ultimately cardiac or pulmonary arrest.
One accepted measurement of renal sufficiency is the glomerular filtration rate, (GFR). GFR is the amount of filtrate the kidneys produce each minute. Each kidney contains approximately 6 m$^2$ of filtration surface area. The result of this filtration surface area provides a healthy adult kidney a rate of 125 ml of filtrate per minute. The GFR is then a measurement of the effectiveness of the kidneys. The use of dialysis to treat a patient whose renal function is compromised is known. When renal filtration is impaired to a pathological level, dialysis is prescribed.

When dialysis is prescribed, two principal dialysis methods have typically been utilized: hemodialysis and peritoneal dialysis. In hemodialysis, the patient obtains a viable access to remove a volume of blood for filtration. The access site consists of two ports: one arterial port and one venous port. The blood from the patient is obtained from the arterial port at a prescribed rate by the physician, and returned at the same rate to the patient through the venous port. The rate of blood removal varies from 200ml/min to 600ml/min. This circulating blood is carried to an artificial membrane and is exposed to a dialysate solution for filtration. The artificial membrane is semi-permeable in design, which allows for the free diffusive and osmotic movement of particles across the artificial membrane. The dialysate solution which flows counter-currently around the artificial membrane contains solutes which will draw waste from the blood by diffusion and osmosis. Dialysate consists of purified water and various substances dissolved in it. With the exception of glucose, the substances dissolved in the dialysate are all electrolytes. Their concentration (besides potassium and the buffer solute) closely resembles the concentration of the electrolytes occurring naturally in the blood. Dialysate regulates the electrolytic and acid-base balance of the dialysis patient, while removing waste products.
Because it is an extracorporeal treatment, and requires special machinery and artificial filters, certain inherent disadvantages exist with hemodialysis. Some disadvantages of hemodialysis include, patient discomfort, blood loss, sepsis, and access failure.

To overcome some of the disadvantages associated with hemodialysis, peritoneal dialysis becomes a viable option. Peritoneal dialysis utilizes the patient’s own parietal and visceral peritoneum, *i.e.*, the membranous lining of the abdominal body cavity, as a semi-permeable membrane. Due to its perfusive characteristics, the peritoneum is capable of acting as a natural semi-permeable membrane. Dialysate solution is added to the space between and abdominal parietal and visceral membranes via a catheter placed in the abdominal cavity. Using the peritoneum as a semipermeable membrane, fluids and wastes can move into the dialysate solution then drained out via the catheter after a prescribed amount of time. Disadvantages of using peritoneal dialysis include sepsis, peritonitis and inadequate dialysis clearances.

The inherent dangers of hemodialysis and peritoneal dialysis suggest a safer and non-invasive dialysis procedure is needed.

**SUMMARY**

An aspect of the invention provides a system and method for the treatment of renal impairments using a process described herein and referred to generally as transdermal dialysis ("TDD") as well as providing a system and method for enhancing existing dialysis methods by using transdermal dialysis. As used herein, the term "renal impairments" is intended to include acute renal disease, chronic renal disease, *i.e.*, end stage renal disease ("ESRD") and other renal deficiencies.
A system according to an aspect of the invention includes at least one transdermal delivery assisting module and a dialysate solution contacting module. The system may further include a dialysate solution circulating module and/or a dialysate solution heating module, dialysate proportioning system, and a dialysate mixing module.

The transdermal delivery assisting module(s) operate to increase permeability of the patient's epidermal membrane ("EM") and enhance the ability of the EM to serve as a dialysis membrane. The transdermal delivery assisting module may include at least one treatment cuff through which be applied to the patient's epidermal membrane. An electric pulse of specific amplitude and length would be applied to the EM. Such application causes a dramatic decrease in skin resistance or impedance. The application of short-duration high-voltage pulse to the EM would be used to transiently permeabilize cells in the EM. Either exponentially decaying (ED) pulses or square wave (SW) pulses, a timed pulse, or a combination of both, at a magnitude of up to 1000V would be applied at a rate in micro-seconds.

In another aspect of the invention, a method of the invention includes the steps of using an assisted transdermal delivery mechanism to increase the permeability of a patient's epidermal membrane, and contacting the patient's EM to a dialysate solution to thereby allow wastes to pass through the patient's EM into the dialysate solution. As used herein, the term "waste" may be generally understood to include metabolites, nitrogenous compounds, ions, neutrally charged molecules, and fluids, but may also include other materials that are undesirable inside the human body. The dialysate solution, as known in the art, would vary in concentration, as prescribed by a physician.

In yet another aspect of the invention, a method for performing transdermal kidney dialysis is provided including the steps of using the EM of a patient to be treated as a dialysis
membrane, applying a prescribed voltage to the EM, and contacting the patient's EM with a dialysate solution to thereby allow wastes to pass from beneath the patient's EM, through the patient's EM and into the dialysate solution.

Another aspect of the invention involves use of transdermal dialysis in combination with hemo- or peritoneal dialysis. For example, a dialysis treatment program may involve interspersed treatments of transdermal dialysis and hemodialysis (e.g., two treatments of hemodialysis per week and one treatment of transdermal dialysis).

BRIEF DESCRIPTION OF THE DRAWINGS

These and other attributes of aspects of the invention will become more clear upon a thorough study of the following description of the best mode for carrying out the invention, particularly when reviewed in conjunction with the drawings, wherein:

Fig. 1 illustrates a system of a transdermal dialysis, according to some embodiments.

Fig. 2 illustrates a transdermal cuff of a transdermal dialysis, according to some embodiments.

Fig. 3 illustrates dialysate bath components, according to some embodiments.

DETAILED DESCRIPTION OF EMBODIMENTS

Aspects of the invention provide a system and method for the treatment of renal impairments using transdermal dialysis ("TDD") alone or in combination with other dialysis treatment modalities.

Generally, a system and method according to one aspect involves using a patient's epidermal surface as a dialysis membrane in the treatment of renal impairments. More
particularly, a system and method according to one embodiment involves treating a patient suffering from renal impairments using TDD, wherein the patient's epidermal membrane ("EM") surface serves as the dialysis membrane. In such a system or method, the patient's EM is contacted with a dialysate solution to thereby allow waste and fluid, to pass from beneath the patient's EM and pass through the patient's EM and into the dialysate solution.

A system and method of one aspect generally utilizes an assisted transdermal delivery mechanism to increase permeability of the EM and enhance the ability of the EM to serve as a dialysis membrane. Any assisted transdermal delivery mechanism, including those known in the art, may be used, including, but not limited to iontophoresis, and/or electroporation. Specifically, the electrodes will consist of electroporation anodes and cathodes. In a particular embodiment of the invention, a method for the treatment of renal impairments using TDD may include the steps of exposing a patient's EM to a pulsed electric field. The effect is to produce a pore inductive and flux-enhanced EM. The patient is then submerged in a dialysate solution to thereby allow wastes to pass through the patient's EM into the dialysate solution. Exposure to this environment allows for the free diffusive and osmotic passage of metabolites, electrolytes, and fluids, thereby providing the patient a safe and non-invasive dialysis treatment.

More particularly, when an electric field is applied across the human epidermal membrane (either direct or alternating current), the transport enhancement of ions across the EM is the result of (a) the direct interaction of electric field with the charge of the ion in question, and (b), convective solvent flow (electroosmosis). Further, in vitro studies indicate the stronger the voltage, the greater the EM flux. Dialysis treatment times may be calculated based on these models, or any other such models known in the art. In any event, treatment times may be determined based on factors such as, but not limited to, required clearances, GFR, urea reduction
rates, and other such values as known in the art. Treatment time may also be dependent upon
*inter-dialytic* fluid changes, the number of treatments per week, as well as other variables known
in the art.

A brief description of the drawings is provided below prior to detailed descriptions of
some embodiments.

Fig. 1 is a simplified version of the Transdermal Dialysis cuffs as worn by a prospective
patient. Each cuff, (200), is removable and secured with an apparatus such as Velcro or other
fastening system as known in the art, (202), to provide a secure fitting around an appendage or
torso. A patient will be fitted with a cuff, or cuffs, prior to receiving a pulsed electrical charge,
(201,204). Once the electroporative charge is administered at a prescribed rate and duration by
the physician, the patient will remove the cuff(s), and step into the dialysate bath, (300), for
treatment.

Fig. 2 is a simplified version of the transdermal cuff, (200). Each cuff may be designed
with its own AC or DC power source, (201). Each cuff consists of a fabric material in which is
housed a series of electrodes, (203). The electrodes are aligned in rows along the length of the
cuffs. Each electrode is housed in a protective basket to prevent direct contact with the skin,
(205). Each electrode, (204), will provide either: exponential decay, square wave or timed
electrical pulses. *Exponential Decay Pulse:* In this type of pulse, the set voltage is released from
the capacitor and decays rapidly and exponentially over time (milliseconds). The delivered pulse is
categorized by two parameters: the field strength (kV/cm) and the time constant. These
parameters can be adjusted by varying voltage and capacitance settings to achieve a wide pulse
gradient. *Square Wave Pulse:* This wave pulse is characterized by the voltage delivered, the
duration of the pulse, the number of pulses and the length of the interval between pulses. All of
these parameters can be set using many conventional electroporators. *Time Constant:* A constant pulse is applied for a set period of time at a set voltage. The electrophoretic cuff may also include a fastening mechanism for securing the cuff to the patient, (202).

*Fig. 3* is a simplified version of the dialysate bath components. The dialysate bath components consist of but are not limited to: bicarbonate, (303), acid, (302), deionized water, (301), and mixing tanks, (304). Bath components would also consist of, but not limited to a dialysate proportioner (304), a dialysate heater (308), a dialysate circulating pump, (309), and a tub drain, (307). Dialysate bath would consist of, but not limited to proportioned molar solutes such as sodium, potassium, calcium, magnesium, acetate, chloride, and dextrose, and -HC03 as known in the art. *Fig. 3* describes a permanent bath apparatus; however the dialysis bath components may also be more portable. Dialysate bath can be pre-mixed with deionized water, as known in the art, and provide the patient a more portable treatment option.

Figures 1-3 and the associated reference numbers are referenced below with regard to the following descriptions.

In a embodiment, the patient's EM may be exposed to a pulsed electric field using any assisted transdermal delivery mechanism known in the art using iontophoresis or electroporation, (200). Further, the patient's EM may be contacted with the dialysate solution by at least partially submerging the patient in a dialysate bath, (300). For instance, as described in more detail below, the patient is fitted with one or more electrophoretic cuffs on the patient's arms and legs and torso, *fig. 1,* through which an electric charge may be applied to a portion of the patient's EM (e.g., around one of the patient's limb, torso or a combination thereof), (200). The patient is exposed a pulsed electric charge in such a manner as to maximize pore inductance, EM surface area. The dialysate solution may be an aqueous solution that is similar in composition to the
normal, healthy fluids of the body except that it contains no wastes, such as urea, creatinine, uric acid, sulfates, phenols, or any such solution as known in the arts. Therefore, according to the invention, the EM contacted with the dialysate solution loses metabolites to the dialysate solution by diffusion or osmosis across the EM. By providing enough fresh dialysate to keep the concentrations of these wastes from building up in the dialysate solution, figs. 16, 17, 19, the body ultimately is cleansed of these wastes.

SoluteS, such as Na++ and K+, which should remain in the body in certain proper amounts, normally occur in excess in patients having ESRD. As such, to bring these solutes to the correct physiological levels, but no further, the dialysate solution should preferably be prepared with their concentrations set at the desired ultimate values, as is known in the art.

Water is also removed from the patient's body. This removal may be achieved using any method known in the art, such as but not limited to, applying a net hydrostatic pressure difference between the EM and the dialysate to thereby cause ultrafiltration of the water by adding hyperosmotic solutes to the dialysate as known in the art. In any event, the dialysate solution useful in conjunction with the invention may be formulated in any manner known in the art to thereby provide a dialysate solution specifically prescribed for a particular patient. For instance, the dialysate solution may include electrolytes, amino acids, and glucose in amounts correlated with a patient's pathology and/or specific needs.

As mentioned above, the dialysate solution may be determined by assessing the pathology of the patient to be treated. Changes in prescribed dialysate solutions may be mixed according to individual patient requirements directly in the dialysate bath. In general however, dialysate solutions may preferably be of similar proportioning and make-up as hemodialysis or peritoneal dialysate solutions known in the art. The temperature of the dialysate solution may
optionally be controlled, (305). While not being limited by theory, it is believed that EM flux may be enhanced through heating the dialysate solution. For instance, EM permeability is enhanced at a dialysate temperature of approximately 39 °C, fig. 18. The temperature of the dialysate bath may be regulated to maximize EM permeation, but minimize patient risk of hyperthermia.

The dialysate solution may also be circulated, (309), to ensure uniform mixing and to create flow along the EM if desired. It is believed that EM flux may also be enhanced by increased dialysate flows along the EM surface. Maximizing solvent flows would have an inverse affect upon dialysis treatment times.

In another aspect of the invention, a system for the treatment of renal impairments using TDD is provided which includes at least one transdermal delivery assisting module for increasing the permeability of a patient's EM, (200), and a dialysate solution contacting module, (300), for contacting the patient's EM with dialysate solution to thereby allow wastes to pass through the patient's EM into the dialysate solution. In one embodiment, the at least one transdermal delivery assisting module may increase the permeability of the patient's EM by exposing the EM to a pulsed electric field. As described above, the effect is to produce a pore inductive and flux-enhanced EM. Exposure to this environment, allows for the free diffusive and osmotic passage of metabolites, electrolytes, and fluids, thereby providing the patient a safe and non-invasive dialysis treatment.

The transdermal delivery assisting module, (200), is preferably capable of employing an assisted transdermal delivery mechanism such as iontophoresis, and electroporation. For instance, the patient may be fitted with one or more electroporetic cuffs, (100), which would
contact with at least a portion of the patient's EM. The dialysate solution contact module may be any apparatus for contacting a patient's EM with a dialysate solution.

In addition the dialysate solution contact module may include an appropriately sized dialysate bath or tub, (300). In the embodiment shown in Figure 3, a system for the treatment of renal impairments using TDD is provided which includes a treatment tub for holding a prescribed solution of dialysate bath and for at least partially submerging a patient to be treated, and at least one transdermal delivery assisting module, (200), for increasing the permeability of the patient's EM. The system may also optionally include a circulation module, (309) interfaced with the treatment tub for mixing and circulating the dialysate to insure uniform solution concentration and a heating module, (305), interfaced with the treatment tub for heating the dialysate to a prescribed temperature.

The treatment tub, circulation module, and heating module may be any apparatus known in the art for achieving the desired function. For instance, the treatment tub, (300), may be any type of vessel that is capable of holding the prescribed dialysate bath and appropriately sized for at least partially submerging the patient to be treated. Further, the treatment tub may be formed from any material known in the art that is substantially unreactive with the dialysate bath, such as, but not limited to, polymer materials used to store dialysate.

The circulating module, (309), may be any mixing/pumping apparatus known in the art. More particularly, in one embodiment of the invention as shown in Figure 3, the circulating module may include at least one dialysate supply, (302,303), at least one deionized water supply, (301), (e.g., Reverse Osmosis Deionized ("RODI") water), and at least one mixing vessel,(304). The mixing vessel may then interface with the treatment tub to provide the prescribed dialysate
solution. The dialysate solution may be mixed and circulated, (309), to the treatment tub using any mixer and pump known in the art.

Likewise, the prescribed dialysate solution may be heated, (305), using any heating apparatus known in the art. Further, the heating module may be a stand-alone heater that interfaces with either the treatment tub, (300), or the at least one mixing vessel of the circulation module to heat the dialysate solution to the prescribed temperature. Also and/or alternatively, the heating module may be incorporated into the at least one mixing vessel of the circulating module for heating the dialysate solution as it is mixed and circulated.

The at least one transdermal delivery assisting module of the invention may include at least one treatment cuff, (200), through which pulsed electric charge may be transmitted to the patient. In one embodiment of the invention, as shown in Figure 1, the at least one transdermal delivery assisting module may include at least one electrophoretic treatment cuff that may be used to deliver electric current to the skin of the patient to thereby enhance the permeability of the patient's EM.

The electrophoretic cuff may be formed from a mesh-like fabric or support structure,(203), which preferably allows for secured electrode adhesion. The electrophoretic cuff may further include positive and negative electrodes incorporated into the fabric or support structure for generating the low electric field. The electrophoretic cuff may also include an independent power source and a fastening mechanism for securing the cuff to the patient.

The electric current may be supplied as AC or DC, and may be delivered in a pulsed or non-pulsed manner. Further, the treatment cuff may optionally be constructed in a manner to deliver either or both of positive and negative electric fields to various, but regulated, points on the EM of the patient, (204). The electrodes may be formed from any suitable material known in
the art, such as, but not limited to, Pt, Au, Ag, or alloys thereof. The electrodes are surrounded by a support structure made of sturdy non-conducting material, (205), designed to maintain a buffer between electrode and the EM. The power source, (201), may be any suitable source known in the art. Likewise, the fastening mechanism may be any suitable mechanism known in the art that does not substantially interfere with the generation of the electric field, or substantially react with the dialysate solution or the patient's skin, including but not limited to, hook and loop, snaps, or zippers, (202).

In the embodiment of the invention shown in fig. 2, the electrodes may be uniformly spaced within the fabric or support structure. In the particular embodiment shown, the electrodes are spaced approximately 5 cm apart. However, one of skill in the art will recognize that various configurations and designs are possible depending on the desired electric field characteristics and the requirements of the patient to be treated.

Example

In a clinical setting, one embodiment of the invention may be practiced as follows. The patient enters the clinic and obtains a pre-dialysis weight. He is then fitted with electrophoretic treatment cuffs around his torso and/or limbs, fig. 1. He is exposed to a prescribed electric pulse, fig. 2. He then sits in a heated circulating dialysate tub for a prescribed treatment time, fig. 3. The patient then sits comfortably in the solution for a prescribed time while being monitored by qualified staff members. Upon completion of the dialysis treatment the patient obtains a post dialysis blood pressure and a post dialysis weight. The tub may then be drained, sanitized, and filled with the prescribed dialysate solution for the next patient.

The embodiments described herein-above are merely illustrative and are not intended to limit the scope of the invention. It is understood that various changes, alterations,
rearrangements and modification may be made by those skilled in the art without departing from the spirit and scope of the invention.
CLAIMS

What is claimed is:

1. A system for the treatment of end stage renal disease using transdermal dialysis comprising:
   at least one transdermal delivery assisting module for increasing the permeability of the epidermal membrane of a patient to be treated; and
   a dialysate solution contacting module for contacting the patient's epidermal membrane with a dialysate solution to thereby allow wastes to pass through the patient's epidermal membrane into the dialysate solution.

2. The system of claim 1 further comprising a dialysate solution circulating module for mixing the dialysate solution and circulating the dialysate solution along the surface of the patient's epidermal membrane.

3. The system of claim 1 further comprising a dialysate solution heating module for controlling the temperature of the dialysate solution.

4. The system of claim 1 wherein the at least one transdermal delivery assisting module includes at least one treatment cuff, or any number of un-cuffed electrodes which are capable of exposing the patient's epidermal membrane to an electric field.

5. A method for the treatment of end stage renal disease using transdermal dialysis comprising the steps of:
   using an assisted transdermal delivery mechanism to increase the permeability of a patient's epidermal membrane; and
   contacting the patient's epidermal membrane with a dialysate solution to thereby allow waste to pass through the patient's epidermal membrane into the dialysate solution.
6. The method of claim 5 further including the step of circulating the dialysate solution to thereby mix the dialysate solution and circulate the dialysate solution along the patient's epidermal membrane.

7. The method of claim 5 further including the step of controlling the temperature of the dialysate solution.

8. The method of claim 5 wherein the assisted transdermal delivery mechanism is selected from the group consisting of iontophoresis, and electroporation.

9. The method of claim 5 wherein the step of using an assisted transdermal delivery mechanism includes the step of exposing the patient's epidermal membrane to a prescribed electric field.

10. A method for performing kidney dialysis comprising the steps of:
    using the epidermal membrane of a patient to be treated as a dialysis membrane; and
    contacting the patient's epidermal membrane with a dialysate solution to thereby allow wastes to pass from beneath EM, through the patient's EM and into the dialysate solution.

11. The method of claim 10 further comprising the step of using an assisted transdermal delivery mechanism to increase the permeability of the patient's epidermal membrane.

12. The method of claim 10 further comprising the step of exposing the patient's epidermal membrane to an electric field to thereby increase the permeability of the patient's epidermal membrane.

13. The method of claim 10 further comprising the step of circulating the dialysate solution to thereby mix the dialysate solution and circulate the dialysate solution along the surface of the patient's epidermal membrane.
14. The method of claim 10 further comprising the step of controlling the temperature of the dialysate solution.

15. A transdermal delivery assisting module for increasing the permeability of the epidermal membrane of a patient to be treated by transdermal dialysis comprising:

- a support structure that secures the module to a portion of the patient's body and allows for free solvent flow of solution from donor to recipient solutions when portion of the patient's body is submerged in a dialysate solution; and
- one or more electrodes that apply an electrical current to the epidermal membrane of a patient to increase the permeability of the epidermal membrane.

16. The transdermal delivery module of claim 15 wherein the support structure comprises a fabric through which solution may pass.

17. The transdermal delivery module of claim 16 wherein the electrodes are incorporated into the fabric.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/61 130

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/05, A61M 1/16, B01D 63/00, C02F 1/44 (2014.01)
CPC - A61B 5/05, A61M 1/16, B01D 63/00, C02F 1/44

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8)- A61B 5/05, A61M 1/16, B01D 63/00, C02F 1/44 (2014.01);
CPC- A61B 5/05, A61M 1/16, B01D 63/00, C02F 1/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 210/321.75, 600/345, 604/4.01, 604/29, 604/65;
Patents and NPL (classification, keyword; search terms below)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages.</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>US 5,911,223 A (WEAVER et al.) 15 June 1999 (15.06.1999), Fig. 1; col 3, in 4-21; col 5, in 5-46; col 7, in 37-57; col 8, in 23-29; col 14, in 5-22; col 21, in 6.5 to col 22, in 6; col 22, in 64-67</td>
<td>1-15, 16, 17</td>
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<td>Y</td>
<td>WO 88/03821 A1 (POWERS et al.) 02 June 1988 (02.06.1988), pg 9, in 15-30; pg 11, in 20-35; pg 34, in 4-16</td>
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<td>Y</td>
<td>US 2011/0105871 A1 (ZIMMERMANN et al.) 05 May 2011 (05.05.2011), para [0121]-[0122]</td>
<td>1-17</td>
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Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search
15 December 2014 (15.12.2014)

Date of mailing of the international search report
06 Jan 2015

Name and mailing address of the ISA/US
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