A METHOD FOR DIALYSIS FLUID REGENERATION

Fig. 2

Abstract: The present invention provides a method to extract a substantial portion of the water content of the spent dialysis fluid by simple osmosis in which water is extracted down a concentration gradient to dilute a concentrated electrolyte solution then by reverse osmosis in which more water is extracted and used to further dilute the concentrate to obtain a regenerated dialysis fluid. A complementary method for urea removal is added to the osmosis treatment. By eliminating the need for a large supply of exogenous water, the present invention allows the construction of portable and wearable dialysis units.
A method for dialysis fluid regeneration

Technical Field

The present invention relates to the field of dialysis therapy and dialysis fluid regeneration methods.

Background Art

Renal failure is a condition in which advanced kidney disease causes the body to lose the ability to excrete harmful metabolites, maintain normal volume of body fluids, and control electrolyte and hydrogen ion concentrations within physiological ranges. In the absence of renal replacement therapy, death is inevitable.

Dialysis is used to replace kidney function. In hemodialysis the patient's blood passes through a dialyzer which is a semi-permeable membrane that intervenes between the patient's blood and a large volume of externally-supplied dialysate composed of an electrolyte solution whose osmolarity and composition are very similar to the physiological osmolality and composition of the extracellular fluid. Therapeutic dialysis is in essence a simple diffusion process that occurs across the membrane of the dialyzer whereby the uremic toxins dialyze out of the blood through the semi-permeable membrane into the dialyzate and meanwhile the electrolytes of the patient's blood is brought to a near physiological concentration through simple diffusion down their concentration gradients across the membrane of the dialyzer. A large volume of dialyzate must circulate through the dialyzer and then be discarded to maintain an effective concentration gradient to drive a useful rate of diffusion. Ultrafiltration is a process of mass transfer of water and solutes across the membrane of the dialyzer. The driving force of ultrafiltration is a pressure difference applied across the dialyzer. Ultrafiltration is usually done during the session of dialysis. Ultrafiltration is an important component of the clinical prescription of dialysis because it removes the excess fluid volume accumulated in the patient's body during the interdialytic interval which otherwise would result in hypertension, edema and ultimately heart failure.

Most patients on hemodialysis treatment are prescribed three dialysis sessions per week under medical supervision. The session usually lasts for 3 to 4 hours. A minority of patients receives home hemodialysis in which 5 to 7 sessions per week are performed at home. Special plumbing, a water treatment system, a dialysis machine, consumable and disposable supplies, patient training and a care giver at home are essential. Continuous and slow therapies for replacement of kidney function in which the patient undergoes dialysis for up to 24 hours per
day are rarely utilized. These therapies are reserved for critically ill patients under strict medical supervision usually in intensive care units.

Peritoneal dialysis is another form of dialysis therapy in which a sterile, hypertonic dialysis solution is introduced into the patient's peritoneal cavity. The peritoneal membrane acts as a natural dialyzer. Toxic uremic substances and various ions diffuse across the patient's peritoneum down their osmotic gradients. The dialysis solution is intermediately drained and replaced with fresh dialysis solution. Peritoneal dialysis requires draining, discarding and replacing large volumes of solution per day to achieve the needed clearance of uremic toxins. The need to prepare large volumes of dialysis fluid with tightly controlled composition and the strict patient safety requirements led to the use of costly, bulky, and difficult to maintain and operate water treatment systems and dialysis machines. The need for a considerable volume of specially treated water to reconstitute the dialysate is the major obstacle against developing implantable, wearable and portable dialysis devices.

To address this problem, devices have been developed to reconstitute the spent dialysis fluid to allow its reuse for dialysis. For example, the original Redy Sorbet system (Blumenkrantz et al., Artificial Organs 3(3):230-236, 1978) consists of a sorbet cartridge having five layers through which the spent dialysis solution containing uremic waste metabolites flows in order to be regenerated. In the Redy system, the first layer is a purification layer that removes heavy metals (i.e., copper and lead) and oxidants (i.e., chlorine and chloramines), an aluminum oxide layer bound to urease which degrades the urea in the dialysate into ammonium carbonate, a zirconium phosphate layer that adsorbs the ammonium ions produced from urea degradation along with other cations (i.e., potassium, magnesium and calcium), a hydrated zirconium oxide layer that exchanges phosphate and other anions (i.e., fluoride) for acetate and an activated carbon layer that absorbs other organic compounds (i.e., creatinine and uric acid). An alternative method to remove urea is to employ a bioreactor in which urea is degraded into ammonia by employing the urease enzyme and the generated ammonium ions are removed by electrodialysis. This process would necessarily require ammonium sensors to ensure that the highly toxic ammonia has been effectively removed prior to recirculation into the patient dialyzer.

In another approach to urea removal U.S. Pat. Nos. 3,933,753 and 4,012,317, disclose alkenylaromatic polymers containing phenylglyoxal that can bind urea. The phenylglyoxal polymeric material is made via acetylation performed in nitrobenzene followed by halogenation of the acetyl group and treatment with dimethylsulfoxide as disclosed in U.S. Pat. Nos. 3,933,753 and 4,012,317. Another example of a polymeric material that is capable
of selectively removing solutes, such as urea, from solution includes polymeric materials that contain a tricarbonyl functionality commonly known as ninhydrin as disclosed in U.S. Pat. No. 4,897,200. In another patent, U.S. patent No. 2000703213665, a wearable artificial kidney for use with a continuous flow peritoneal system was described. This device requires the intermittent exchange of a dialyzate cleaning cassette and the concurrent oral administration of a urea binder.

Intravenous urea infusion experiments in healthy subjects revealed that high blood urea levels are associated with minimal symptoms. In these experiments, blood urea levels similar to the usual levels found in patients with chronic renal failure were associated with minimal if any toxicity. In a vertebrate species, the sharks, the physiological blood urea level is around 10 times the human level without any untoward effects. Although urea is probably not a major uremic toxin, the current devices used for regeneration of dialysis fluid devote a great deal of their bulk and expense to ensure the safe removal of as much urea as possible. Urea clearance is a good measure of dialysis efficiency in the classic dialysis therapies in which the used dialysate is not regenerated because urea clearance is then directly proportional to the clearance of the other uremic toxins. If the dialysate is treated with a specific urea removing device before being recirculated, the clearance of urea will not be a good measure of the overall efficiency of the dialysis therapy. In dialysis systems using regenerated dialysis fluid, the ability to achieve separate control of urea clearance would have a clear advantage.

Although the fluid used for hemodialysis and peritoneal dialysis can be regenerated, no device has yet been created that has the required efficiency and the small bulk necessary to be comfortably worn by the patient for prolonged time. The expense of dialysis fluid regeneration entailed by the current methods is also a major consideration.

In the current practice of dialysis therapy, compromises must be made. In intermittent systems all the elements of the therapy must be accomplished during the several hour dialysis session. Small ions like sodium and chloride as well as small molecules like urea need shorter dialysis time to reach therapeutically acceptable levels, larger molecules like phosphate and β2-microglobulin are actually not removed to the desired levels. Similarly, intermittent ultrafiltration is definitely inferior to a continuous slow therapy in achieving physiological control of the body fluid volume. The session length cannot usually be much extended because of the patient's non-compliance or the time constraints on part of the dialysis unit schedule or the patient himself. The clinical outcome of intermittent therapy is so poor that the patient usually remains unemployed, dissatisfied, suffering from intradialytic and interdialytic symptoms and having significant complications, morbidity and mortality.
Compromise must also be made in the construction and choice of the dialyzer membrane. Ideal pore size, permeability, selectivity, efficiency, biocompatibility, safety and cost can never be optimized at the same time when choosing any membrane type in current use. A method to retrieve pure or nearly pure water from the spent dialysis fluid before using it to reconstitute a fresh dialysis solution would have a clear advantage when coupled with the use of a high efficiency dialyzer in a slow extended time dialysis prescription. There is a need for a more effective dialysis method that significantly improves the patient's quality of life over current methods. What is required is a dialysis device that effectively controls all the derangements of renal failure and better mimics the physiological function of the kidney. Extended-time treatment that allows ambulation during the therapy is necessary to achieve these goals. A dialysis method that does not require large volume of treated water will permit ambulatory therapy. Consequently, a more frequent and prolonged therapy that better mimics the physiological function of the natural kidney can be achieved. Osmosis is the movement of the solvent molecules across a solvent permeable but solute impermeable membrane. The following formula describes the osmosis phenomenon:

\[ J_w = A(\sigma \pi - P) \]

Where \( J_w \) is the water flux, \( A \) is the water permeability constant of the membrane, \( \sigma \) is the reflection coefficient, \( P \) is the applied hydraulic pressure across the membrane and \( \pi \) is the osmotic pressure. In simple osmosis, also known as forward osmosis, \( P \) is zero and consequently, water moves down the concentration gradient. In reverse osmosis, \( P > \pi \); and the water flow is in the reverse direction i.e. from the side with higher concentration to the side of lower concentration. Reverse osmosis is currently a widely used industrial process in the desalination and purification of water. It is also used in the industry for concentrating some solutions. Simple osmosis, also called forward osmosis, is a less commonly used process. Hydration bags used to prepare sugary beverages from unsafe water by immersing bags made of special simple osmosis membrane in water are a popular application of simple osmosis. Although using a concentrated physiologically balanced solution to draw its own dilution water from the spent dialysis fluid across an osmosis membrane forming a regenerated toxin free fluid that can be further treated to provide a recycled dialysis fluid seems attractive, no device or method that uses this principle has been described.

Disclosure of Invention

BRIEF DESCRIPTION OF THE INVENTION
The present invention provides a method to extract a substantial portion of the water content of the spent dialysis fluid and the fluid extracted from the patient by ultrafiltration. The extracted water directly dilutes a concentrate making its osmolarity more similar to the desired osmolarity of fresh dialysis solution.

In the present invention, the spent dialysis fluid is subjected to a simple osmosis treatment in which water is extracted down a concentration gradient across a water permeable but solute impermeable membrane to dilute a concentrated electrolyte solution that is circulated along the other side of the membrane. In addition, an additional fraction of water is extracted from the spent dialysis fluid by a reverse osmosis process wherein the spent fluid is subjected to hydraulic pressure while it is circulated alongside a reverse osmosis membrane to obtain a low solute permeate and a more concentrated spent fluid which is discarded while the permeate is used to further dilute the concentrate. Finally, exogenous water is added to obtain the desired osmolarity before using the obtained diluted concentrate as a fresh dialysis fluid.

The water extraction approach used in the present invention has definite advantages compared to the current methods for dialysis fluid regeneration which rely on adsorption and physio-chemical removal of the supposed uremic toxins. First, no consumable adsorption material is used and the need to use disposable, bulky and expensive cartridges is eliminated. Second, the inherent ability of the membranes to prevent the passage of microorganisms is very useful especially when compared to the susceptibility to microbial contamination of the systems currently used for dialysis fluid regeneration. Third, because uremic toxins are a diverse group of a large number of molecules with great heterogeneity in molecular weight and chemical structure, selective retrieval of water from the spent dialysis fluid if used in conjunction with a high efficacy dialyzer in an extended time dialysis treatment is able to achieve uniform clearance of the heterogeneous uremic toxins which are largely kept behind the osmosis membrane to the same degree regardless of their molecular weights and charge.

One feature of the present invention is the use of an independent method for complementary urea removal. The urea sieving ability of the currently used osmosis membrane filters is at most 40-50%. In the current invention, urea removal by binding to a urea binder or by an enzymatic method followed by ammonium adsorption is combined with the membrane treatment of the spent dialysis fluid. In the current invention, the degree of delivered urea clearance can be controlled separately. Because the reported clinical toxicity attributable to urea per se is small and consists of easily recognizable gastrointestinal symptoms, the ability to control the degree of urea removal in separation from the total delivered dialysis dose has the advantage of reducing the cost of the whole process and decreasing the burden of carrying
bulky equipment during the whole dialysis treatment time. This is particularly important when a wearable or portable dialysis system is used.

The current invention allows for the use of its different components in a variety of combinations that can be adapted to the patient's daily schedule so that the minimal bulk of equipment is carried on the patient when using the wearable unit of the system while, inside a portable unit, complementary spent dialysis fluid treatment is carried out separately. Exchange of the fluid between reservoirs mounted to the wearable unit and corresponding reservoirs in the portable unit is done upon brief connection of the two units.

Detailed Description of the Present Invention

Referring to the drawings in which each feature is referred to by a number made of three digits. The first digit is the number of the figure to which the described feature relates while the second 2 digits is the number given to the feature itself. The last 2 digits are the same if the particular feature are the same or are closely related in more than one figure.

The basic unit of the current invention is the osmosis unit. In reference to Fig. 1, the said osmosis unit consists of two fluid circuits separated by the simple osmosis membrane 101 and the reverse osmosis membrane 102. In the first circuit the said spent dialysis fluid passes through the unit's inlet 103 through a pump 104 to the spent dialysis fluid side of the simple osmosis membrane 105 then through the reverse osmosis pump 106 then through the high pressure side of the reverse osmosis membrane 109 and finally to the exhaust fluid reservoir 108. The permeate is re-directed from the permeate side of the reverse osmosis membrane 107 to the spent dialysis side of the simple osmosis unit 105. In the second circuit, the concentrate passes from its reservoir 110, to the concentrate side of the simple osmosis membrane 111, to a pump 112 which drives it through the outlet of the unit 113. Water passes from the fluid in the first circuit to the second circuit across the simple osmosis membrane 101 down the concentration gradient, and across the reverse osmosis membrane 102 down the hydraulic pressure gradient to dilute the concentrate that is circulated in the second circuit.

Water from the exogenous water reservoir 114 is pumped by a controlled pump 115 to the spent dialysis fluid side of the simple osmosis membrane 105 where it passes down the concentration gradient to the concentrate side of the simple osmosis membrane 111. Alternatively, the exogenous water from the water reservoir 114 is pumped to the high pressure side of the reverse osmosis membrane 109 (not shown in Fig. 1). At least one conductivity sensor that controls the said exogenous water pump via an electronic feedback control loop (not shown in Fig 1) is incorporated. The exogenous water need not be pre-treated with reverse osmosis as the osmosis membranes of the unit perform this form of
treatment. However, the water should be pretreated with de-chlorination, filtration and softening to preserve the osmosis membranes.

After treatment in the osmosis unit, two types of fluid are obtained. The first is the exhaust fluid (to be discarded) consisting from highly concentrated spent dialysis fluid that was concentrated by extracting out a considerable proportion of its water by simple osmosis then by reverse osmosis. The second fluid is the obtained diluted fluid obtained at the outlet of the unit which consists of the concentrate diluted with:

1. The water drawn down the concentration gradient across the simple osmosis membrane

2. The water fraction permeated down the hydraulic pressure gradient across the reverse osmosis membrane

3. The exogenous water added to the spent dialysis fluid side of the simple osmosis membrane or the high pressure side of the reverse osmosis membrane.

In the embodiment shown in Fig. 1, simple osmosis treatment preceded the reverse osmosis process. Alternatively, as shown in Fig. 2, the spent dialysis fluid treatment may start with the reverse osmosis process followed by the simple osmosis process and the permeate resulting from the reverse osmosis process is then directly mixed with the fluid obtained on the concentrate side of the simple osmosis membrane distal to the reverse osmosis device. An advantage of the said alternative arrangement is the decrease in the hydraulic pressure needed in the reverse osmosis unit because the concentration of the fresh spent dialysis fluid is substantially less than the feed fluid concentration if the spent dialysis fluid is treated first with simple osmosis. Another advantage of the alternative arrangement is a reduction in the back leak of salt across the simple osmosis membrane. In reference to Fig. 2, the alternative arrangement comprises two fluid circuits separated by the reverse osmosis membrane and the simple osmosis membrane.

The spent dialysis fluid passes through an inlet to the high pressure side of the reverse osmosis membrane then to the spent fluid side of the simple osmosis membrane and finally to the exhaust fluid reservoir while the concentrate passes from its reservoir to the concentrate side of the simple osmosis membrane, then it is mixed with the permeate obtained in the permeate side of the reverse osmosis unit after exiting the concentrate side of the simple osmosis unit. Finally a pump drives the obtained diluted solution to exit the osmosis unit through its outlet. A feed-back controlled pump pumps exogenous water from the water reservoir to the spent dialysis side of the simple osmosis membrane or, alternatively, to the high
pressure side of the reverse osmosis membrane 209 to achieve the desired osmolarity of the obtained diluted fluid

The composition of the concentrate
The concentrate should fulfill these requirements:

1. Its osmolarity should be high enough to effect meaningful water extraction from the spent dialysis fluid without the use of a big volume of the concentrate.
2. Some salt does leak back across the simple osmosis membrane into the spent dialysis fluid. Also, if a very highly concentrated concentrate is used, a very hyperosmolar diluted concentrate will be obtained. Consequently, too much salt in the concentrate is to be avoided.
3. Sodium chlofide must be the major salt in the concentrate, because sodium and chloride are the main blood ions. Other electrolytes e.g. calcium, magnesium and potassium are also essential for life. They must be added to the concentrate to obtain the prescribed dialysis fluid composition. Alternatively they may be directly added to the dialysis fluid.
4. A total osmolarity of the concentrate between 10 to 25 times the normal plasma osmolarity meets these requirements.
5. The concentrate must be sterile and fulfill the requirements of solutions used for intravenous injection if the regenerated fluid is used for re-infusion in an ultrafiltration/re-infusion slow process dialysis prescription.

It is noteworthy to mention that the obtained regenerated fluid may also be subjected to additional forms of treatment e.g. specific removal of phosphate, manipulation of pH and the addition of nutrients by adding additional devices. Similarly, pretreatment of the spent dialysis fluid to decrease fouling and improve the performance of the osmosis membranes may be used.

The simple osmosis membrane
The essential features of a successful simple osmosis membrane are high solute rejection and good water permeability. Current reverse osmosis membranes have the same basic features. Consequently, at least in principle, they are suitable for use in simple osmosis processes.

Theoretically, it is even possible to accomplish simple osmosis and reverse osmosis in one step across the same membrane by applying both a concentration gradient and a hydraulic pressure gradient working in the same direction. However, important differences between the conditions of the two processes do exist. Good membrane support on the permeate side is a
fundamental requirement of reverse osmosis membranes to withstand the big hydraulic pressure while reduced membrane thickness, high water permeability, big surface area, free fluid flow on both sides of the membrane and minimal internal concentration polarization are the main requirements of a membrane used in simple osmosis application. Consequently, the use of two types of membranes; one for simple osmosis and the second for reverse osmosis has definite advantages. Advantages of the simple osmosis process include its relatively low fouling potential, low energy consumption, simplicity, reliability and high rejection ratio of a wide range of contaminants because the trans-membrane pressure involved in the simple osmosis process is the very small pressure gradient due to flow resistance in the membrane module.

In the present invention, the role of the reverse osmosis process is to extract more water from the spent dialysis fluid by using more energy in the form of external hydraulic pressure. In the current invention, the osmotic treatment is done in two steps namely reverse osmosis and simple osmosis using two separate membranes each optimized for the particular process. A special membrane for simple osmosis was developed by Hydration Technologies Inc. (HTI)). This proprietary membrane is thought to be made of cellulose triacetate (CTA). Its thickness is less than 50 µm while its structure is quite different from standard reverse osmosis membranes which typically consist of a very thin active layer (less than 1 µm) and a thick porous support layer. The CTA (HTI) membrane lacks a thick support layer. Instead, the embedded polyester mesh provides mechanical support. In previous investigations, the CTA (HTI) was superior to the other reverse osmosis membranes in simple osmosis applications. Thinness of the CTA (HTI) membrane, its lack of a fabric support layer and its reduced internal concentration polarization are likely responsible for its superior performance.

In the present invention, The CTA (HTI) membrane is chosen for use in the simple osmosis process because it has outperformed the other membranes tested for simple osmosis applications. For a simple osmosis module serving a slow dialysis process producing 2-3 liters of spent dialysis fluid per hour a CTA membrane with a total surface area of approximately 0.3 m² is enough to reach a near maximal equilibrium between the concentrate and the spent dialysis fluid. While it is possible to build the direct osmosis module in a variety of designs e.g. hollow fiber, tubular or specially designed spiral wound designs that allows fluid circulation on both sides of the membrane, in the present invention a multi-layer (8-16 layers) flat sheet membrane in a frame and plate configuration was adopted. The said configuration was chosen because of the current popularity of flat sheet membranes in industry and their wide availability.
The reverse osmosis membrane
The said reverse osmosis membrane is chosen from the group of the commercially available reverse osmosis membranes. According to current practice, the chosen membrane must be able to withstand a hydraulic pressure of lpsi or more for each 100 ppm in the produced concentrate. Reverse osmosis may be accomplished in 1 to 4 membrane passes. Examples of suitable membranes include but are not limited to SW30-4040 and SW30-4021 membranes made by DOW-Filmtec, Minneapolis as well as Desal-SG2525TH membrane made by Osmonics.

For the proper function of the osmosis unit of the current invention and the protection of its integrity, unidirectional flow control valves, pressure sensors, valve controlled release recirculation loops, "controlled pumps with suitable specifications and a feed back control system are necessary. The current industry readily provides these accessories. The optimization of feed pressure to the reverse osmosis membrane, degassing of the solutions, operating temperature, membrane area, membrane support, membrane housing and the control of other similar parameters depend on the specification of the chosen membrane, its surface area, its maximal recommended pressure, osmolarity of the concentrate and the spent dialysis fluid flow rate. Current industry readily provides such knowledge. Complete systems comprising optimized combinations of the basic components of reverse osmosis systems are commercially available. The standard antifouling and safety measures for the proper function of the membrane are both applicable and desirable in the current invention.

The urea removing method
In the present invention, urea removal by the simple osmosis membrane and the reverse osmosis membrane is suboptimal because urea is a small uncharged molecule. The urea sieving ability of the currently used osmosis membrane filters is at most 40-50% of their sieving ability of most other uremic toxins. In the current invention, a complementary method for the specific removal of urea was added to the other components of the current invention.

Urea may be removed by employing an enzymatic process in which a urease enzyme converts urea into ammonia and carbon dioxide. The high toxicity of ammonia necessitates the use of a highly effective ammonium binder. Electrodialysis may be used for the same purpose. In both cases an ammonia sensing device is necessary to ensure that ammonia has been effectively removed prior to reusing the solution. Substances that bind the intact urea molecule may be used instead of the enzymatic method. For example, U.S. Pat. Nos. 3,933,753 and 4,012,317, disclosed that alkenylaromatic polymers containing phenylglyoxal can chemically bind urea
in solution. In general, the phenylglyoxal polymeric material is made via acetylation performed in, for example, nitrobenzene followed by halogenation of the acetyl group and treatment with dimethylsulfoxide as disclosed in U.S. Pat. Nos. 3,933,753 and 4,012,317. Another example of a polymeric material that is capable of selectively binding urea from solution includes polymeric materials that contain tricarbonyl commonly known as ninhydrin nucleus as disclosed in U.S. Pat. No.4,897,200.

The current invention includes a urea removing unit able to deliver the desired complementary degree of urea clearance. In reference to Fig. 3, the urea removing unit comprises 2 fluid circuits separated by the membrane of the dialyzer of the urea removing unit 321. In the first fluid circuit, the spent dialysis fluid that is to undergo the urea removing procedure is pumped by a pump 319 from the patient's dialyzer 318, to the first side of the urea removing unit dialyzer 322 then back to the patient's dialyzer. In the second circuit, a priming solution is circulated alongside the second side of the urea removing unit's dialyzer 320, by a pump 317 through the urea removing device 316, then back to the second side of the urea removing unit's dialyzer 320. The urea removing unit dialyzer is a simple diffusion membrane similar to the group of the commercially available dialyzers used in hemodialysis. The urea clearance of the chosen dialyzer and the flow rate in the 2 fluid circuits in the urea removal unit determine the rate of transfer of urea across the dialyzer and consequently the rate of urea delivery to the urea removing device. Dialyzer manufacturers provide the estimated clearance of their dialyzers at different blood flow rates as well as the KoA value which is the theoretical maximum urea clearance across the dialyzer in milliliter / minute at infinite flow rates of the blood and the dialysis fluid. In the present application, the urea clearance across the membrane will be slightly more than urea clearance in hemodialysis using the same membrane and the same fluid flow rates because of the slight decrease in urea clearance caused by the presence of red blood cells in the patient's blood in hemodialysis. The effective urea distribution volume in the red blood cells is 80% while the plasma distribution volume of urea is 90%. In the urea removing device urea is removed by either an enzymatic or a non enzymatic method as previously described. The advantage of this 2 fluid circuit design is twofold; first it allows for the independent setting of hydrostatic pressure and the fluid flow rate in each circuit. Second, it reduces the amount of lost blood and prevents contamination of the rest of the unit if a blood leak occurs across the patient's dialyzer. This two circuit urea removing unit is used in isolation from the rest of the osmosis unit wherein the said urea removing unit is temporary attached to the patient's dialyzer, a high blood flow dialysis prescription is conducted and the spent dialysis solution is circulated through the said
first fluid circuit of the urea removing unit wherein its urea is removed before pumping it back to the patient's dialyzer. During this treatment the pressure in the patient's blood compartment is kept higher than the pressure in the said second circuit to preserve the fluid volume in the urea removing unit. After achieving the prescribed urea clearance dose, the urea removing unit is detached from the patient's dialysis circuit. Further dialysis therapy is then conducted while the osmosis unit is attached to the patient's dialysis circuit in place of the urea removing unit and the patient's treatment is carried in 2 sequential steps. If this sequential therapy is used, the use of a high efficiency urea removing unit that is able to remove more than 60% of the daily produced urea within 1-2 hours is needed in order to keep the total treatment time within an acceptable limit. Alternatively, the urea removing device may also be used to treat the fluid obtained from the osmosis unit before its reuse in the patient's dialysis where the obtained diluted concentrate produced in the osmosis unit is circulated through the urea removing device before its reuse in the patient's dialysis. In this method, both urea removal and the main dialysis procedure are done simultaneously.

Methods for using the invention
The current invention allows for the use of its components in different combinations allowing the therapy provider to tailor the therapeutic process to the particular needs of the individual patients. In reference to Fig 4, the most obvious mode to use the current invention is to mount all its components: the osmosis unit 423, the urea removing device 416, together with their connecting tubing and fluid pump 417 to a portable frame and use it as a dialysis fluid regeneration unit to serve a simplified home dialysis machine. The main advantage of using this system over the current home dialysis systems is the elimination of the need for exchangeable cartridges or pre-constituted dialysis fluid bags, the elimination of the need for special plumbing, and suitability for indoor ambulation.

In contrast, all the components of the present invention together with an energy source e.g. a rechargeable battery may be assembled into a wearable unit. Miniaturization of the components of the unit is both possible and desirable when this method is used because ambulation makes extended time dialysis prescription easily acceptable to many patients. A small unit operated for 12 hours per day needs to have only one sixth of the efficiency of a much bigger unit operated for 2 hours per day to achieve the same daily dialysis dose. In reference to Fig (5), the said wearable unit comprises a dialysis unit 524 which is able to deliver an ultrafiltration rate up to 800 ml/hour and dialyzate flow rate up to 3 liters/hour. The spent dialysis fluid passes from the dialysis unit 524 to the osmosis unit 523 then through a pump 517 to the urea removing device 516 and finally back to the patient's dialysis unit 524.
to be re-used in the patient's dialysis. An example for the use of the said dialysis unit is given below:

- A 10 hour combined ambulatory dialysis and ultrafiltration session using the said wearable unit.
- Osmolarity of the concentrate is 12 times the physiological osmolality of human plasma and its flow rate = 200 ml/hour.
- Ultrafiltration rate of 600 ml/hour.
- The water extraction ratio in the reverse osmosis unit is 50% and 90% equilibrium is reached in the simple osmosis module.

- 3 liters of exogenous water is added.
- The calculated dialysis fluid osmolarity will be 1.2 times the normal plasma osmolarity.
- Dialysis fluid flow rate of approximately 2 liters / hour.
- Total clearance during the session will approximately be 25 liters.
- The drained exhaust fluid volume will be 0.75L / hour.

To maintain the physiological osmolarity the patient has to receive approximately 5.5 liters of water during the session. Stimulation of thirst by the resulting hyperosmolarity will result in excess drinking which will correct the hyperosmolar state. The resulting hypervolemia is corrected by ultrafiltration from the patient's blood. To decrease thirst and the consequent patient's inconvenience, partial correction of the dialyzate hyperosmolarity is carried out by adding exogenous water kept in a reservoir to the spent dialysis side of the simple osmosis membrane or to the high pressure side of the reverse osmosis membrane. The use of the oral root to provide water during the session is particularly attractive because no water treatment is needed and the weight of the fluid carried by the patient is reduced.

- If the capacity of the concentrate reservoir is 0.75L, refilling is to be done three times during the session.
- If the capacity of the water reservoir is 0.75 liters and refilling is done 4 times during the session, the remaining amount of water (3.5 liters) lost in the drained fluid is easy to compensate through oral intake during the dialysis session (10 hours). The robust physiological control mechanism against hyperosmolarity is so reliable in the awake ambulant patient that hyperosmolarity is not a concern.

For constructing a lighter weight wearable unit the components of the system are distributed into 2 units; a wearable unit and a portable unit. The function of the wearable unit is to
perform the patient's therapy with the minimal of equipment bulk and energy consumption while the portable unit is kept in the vicinity of the patient attached to a source of electric power. Inside the portable unit, the spent dialysis fluid undergoes treatment resulting in the production of regenerated fluid suitable for reuse in the patient's wearable unit. Fluid reservoirs in the wearable unit and the portable unit keep suitable volumes of the spent dialysis fluid and the regenerated fluid respectively. Exchange of the fluid between reservoirs mounted to the wearable unit and corresponding reservoirs in the portable unit is done upon brief connection between the two units. In reference to Fig (6), the wearable unit comprises only an ultrafiltration/re-infusion unit and 2 fluid reservoirs. The said wearable ultrafiltration unit comprises a wearable or implantable filter 625 which is chosen from the group of filters with high ultrafiltration coefficient currently used for continuous hemofiltration therapy e.g. the F 40 hemofilter produced by Fresenius or the CA 210 produced by Baxter, a blood pump 633, an ultrafiltrate pump 634 and an ultrafiltrate reservoir 629. The said ultrafiltrate reservoir is an approximately 1-3 liters reservoir attached with tubing to the ultrafiltrate side of the filter 626. If a veno-venous access is used, the patient's blood is pumped from a central vein or an arterio-venous fistula 628 to the blood side of the filter 627 then back to the venous access site 628. Alternatively, if an arterio-venous access is used, no blood pump is needed. A controlled hydraulic pressure difference is created across the filter by a pump 634 that creates negative pressure on the ultrafiltrate side of the filter 626. Re-infusion solution is pumped from the regenerated fluid reservoir 630 by a pump 635 to the patient's blood distal to the blood filter. Connection sites 631, 632 that fit with corresponding sites on the portable unit are fixed on the ultrafiltrate reservoir and the regenerated fluid reservoir. In reference to Fig.7, the portable unit to be used with the said wearable ultrafiltration/re-infusion unit comprises an ultrafiltrate reservoir 729 that receives the ultrafiltrate from the wearable unit, the osmosis unit 723 a fluid pump 717 a urea removing device 716 and a regenerated fluid reservoir 730 connected with tubing in a fluid circuit. Connection sites 731,732 that fit with corresponding sites on the patient's unit are fixed on the ultrafiltrate reservoir and the regenerated fluid reservoir. Inside the portable unit, the patient's ultrafiltrate is subjected to simple osmosis, and reverse osmosis followed by a urea removal procedure. Finally, it is diluted with water to the desired osmolarity. The regenerated solution is stored in the regenerated fluid reservoir 730 until exchanged for a new aliquot of the patient's ultrafiltrate upon the next attachment with the wearable unit.
The patient's treatment is carried out by combining high flow ultrafiltration with post filter re-infusion according to the well established methods currently used in the practice of continuous slow renal replacement therapies.

In this ultrafiltration method, the clearance of uremic toxins is achieved by conviction; a process in which the molecules dissolved in the patient's plasma is carried with the water of the ultrafiltrate. The concentration of uremic toxins in the ultrafiltrate is nearly equal to their concentration in the patient's plasma. Consequently, from a practical point of view, the hourly clearance of uremic toxins will be equal to the volume of fluid exchanged per hour. If the treatment time is 12 hours per day and the exchanged volume is 2 liters every 120 minutes, a clearance of nearly 12 liters per day will be accomplished. The patient will have to carry 2 kilograms of fluid on person and to do the exchange process 6 times during the day.

An important feature of the present invention is the feasibility of combining different modes of therapy into the patient's treatment plan. For example, a 1-2 hour separate urea removal can be combined with a 10 hour ambulatory dialysis therapy. Similarly, a short home dialysis prescription may be complemented with an ambulatory treatment using a wearable unit.

The present invention is also suitable for peritoneal dialysis fluid regeneration. When used for peritoneal dialysis regeneration, the use of a simple diffusion filter that prevents particulate matter and proteins from passage to the osmosis unit is necessary.

A simple diffusion filter very similar to the currently used hemodialysis filters can effectively prevent the passage of particulate matter and proteins. In reference to Fig.8, the peritoneal dialysis fluid is re-circulated in the first fluid circuit from the patient's peritoneal cavity 836 with the aid of a pump 837 through a catheter to the first side of the simple diffusion filter 838 then back to the patient's peritoneal cavity 836 through another catheter or the second lumen of the peritoneal catheter if a double lumen peritoneal catheter is used. In the meantime, a priming fluid is re-circulated in the second fluid circuit from the second side of the simple diffusion filter 839 with the aid of a pump 840, to the osmosis unit 823 then to the urea removing device 816 through a pump 817 then back to the second fluid path of the simple diffusion filter 839. Diffusion across the dialyzer membrane 841 occurs by simple diffusion down the concentration gradient that is created and maintained by the continuous treatment of the priming solution in the osmosis unit 823 and the urea removing device 816.

Brief description of the drawings

Fig. 1 represents the osmosis unit.

Fig. 2 represents an alternative arrangement of the osmosis unit.
Fig. 3 represents the urea removing unit.

Fig. 4 represents the portable unit for dialysis fluid regeneration.

Fig. 5 represents the wearable dialysis unit.

Fig. 6 represents the wearable ultrafiltration/re-infusion unit.

Fig. 7 represents the portable unit for use with the wearable ultrafiltration/re-infusion unit.

Fig. 8 represents a peritoneal dialysis fluid regeneration system.
What is claimed is:

Claim 1
A method for dialysis fluid regeneration wherein a substantial volume of the spent dialysis fluid water is extracted by simple osmosis down a concentration gradient and by reverse osmosis down a hydraulic pressure gradient to dilute a concentrated electrolyte solution which is used for the preparation of regenerated dialysis fluid.

Claim 2
An osmosis unit comprising a simple osmosis device and a reverse osmosis device arranged in series wherein the spent dialysis fluid water is extracted from the spent dialysis fluid by simple osmosis down a concentration gradient in the simple osmosis device then by reverse osmosis down a hydraulic pressure gradient in the reverse osmosis device.

Claim 3
The method of claim 2 wherein the spent dialysis fluid consists of the fluid used in the patient's dialysis process and/or the fluid extracted from the patient by ultrafiltration. The said dialysis process may be a conventional short dialysis session, a slow process, a nocturnal dialysis prescription, an ambulatory dialysis procedure or a combination of them.

Claim 4
The said simple osmosis unit according to claim 2 comprising a water permeable but highly solute impermeable simple osmosis membrane, its housing and its support. The said membrane is made of polyamide thin-film composite or cellulose acetate, however, any membrane with sufficiently high solute rejection and sufficient water flux may be used. The said membrane may have a modified spiral, hollow fiber, tubular, plate and frame configuration or any other technically feasible configuration.

Claim 5
The method in association with claim 4 wherein the said spent dialysis fluid is made to circulate along the said simple osmosis membrane while on the other side of the said membrane, a small volume of concentrate is made to circulate whereby water is drawn from the spent dialysis fluid down the concentration gradient by simple osmosis into the concentrate side. The extracted water directly dilutes the concentrate whose composition becomes more similar to the patient's extracellular fluid upon its passage through the said simple osmosis unit while during the passage of the said spent dialysis solution along the said simple osmosis membrane, water is extracted out of the said spent dialysis solution which therefore looses a substantial portion of its volume leading to the formation of a concentrated
spent solution with a substantially smaller volume and higher concentration of the uremic toxins which are mostly kept on the spent dialysis side of the said membrane.

Claim 6
The method according to claim 5 wherein the osmolarity of the said concentrate is substantially higher than the osmolarity of the patient's extracellular fluid, preferably, but not limited to, between 10 to 25 times the normal plasma osmolarity. The said concentrate is composed mainly of sodium chloride. Other solutes are added to make the concentrate more physiological and to further increase its total osmolarity and consequently its efficiency in extracting water from the spent dialysis fluid. The concentrate is to be sterile and fulfills the requirements of solutions prepared for intravenous injection if used for re-infusion in an ultrafiltration/re-infusion therapy.

Claim 7
After passing through the simple osmosis unit the said concentrated spent dialysis fluid is subjected to a hydraulic pressure while it is circulated alongside a reverse osmosis membrane to accomplish a reverse osmosis process and extract a permeate containing a low solute concentration. The extracted permeate is then redirected to the spent dialysis side of the said simple osmosis membrane of claim 4 where its low osmolarity enhances the transfer of an additional amount of water into the concentrate side. Consequently, the composition of the obtained solution formed on the concentrate side of the simple osmosis membrane becomes more similar to the composition of the fresh dialysis solution without using a large volume of exogenous specially purified water for its dilution.

Claim 8
After being subjected to simple osmosis and subsequently to reverse osmosis procedures the spent dialysis fluid volume decreases substantially while the concentration of its uremic toxins increases proportionately to form a smaller volume of exhaust fluid to be discarded.

Claim 9
A method wherein the osmolarity of the said obtained solution formed on the concentrate side of the said simple osmosis membrane is brought to the desired therapeutic level by controlled dilution with exogenous water before reusing it in the patient's dialysis procedure. The said exogenous water may be introduced into the spent dialysate side of the said simple osmosis membrane, to the high pressure side of the said reverse osmosis membrane or directly mixed with the said obtained solution using a feed back controlled pump.
An alternative arrangement of the said osmosis unit of claim 2 wherein the spent dialysis fluid passes through the reverse osmosis device before passing through the simple osmosis device and the resulting low solute permeate obtained by the reverse osmosis process is mixed with the obtained diluted concentrate distal to the said simple osmosis device.

Claim 11
A device and method for hypertonic low flow prolonged hemodialysis and ultrafiltration treatment wherein the said obtained solution formed on the concentrate side of the simple osmosis membrane is not diluted down to the physiological level of the patient's plasma before its reuse and consequently the volume of the water used in diluting the said obtained solution is substantially reduced. In the said hypertonic low flow dialysis, the stimulation of thirst and increased water intake correct the resulting hyperosmolarity and the resulting increase in the body fluid volume is corrected by ultrafiltration across the patient's dialyzer. In the said hypertonic low flow hemodialysis, the dialysis fluid flow through the dialyzer is set at a very low rate, preferably but not limited to between 1-3 liters/hour while the dialysis time is set at 7-12 hours/day to allow enough time for physiological correction of the resulting hyperosmolarity.

Claim 12
The method according to claim 9 wherein in conventional high flow short treatment time dialysis e.g. a prescription of 2-3 hours/session, 5-7 times/week, blood flow rate = 200-400 ml/minute, dilution of the said obtained solution down to the physiological plasma osmolarity is done by the controlled addition of the appropriate amount of water.

Claim 13
A complementary process to remove urea from the said obtained solution of claim 7 or directly from the patient's dialysis fluid circuit. The prescription and measurement of urea clearance are done independently while the prescription and measurement of the overall dialysis dose are done using the clearance of another marker e.g. creatinine.

Claim 14
A urea removing unit comprising a highly urea permeable dialyzer whose design and membrane material are generally similar to the currently used hemodialysis dialyzers which defines two fluid paths separated by the dialyzer membrane. In one fluid path, a priming fluid is re-circulated with the aid of a pump along one side of the dialyzer membrane to pass through a urea removing device and then back to the same side of the said dialyzer while the second fluid path on the other side of the dialyzer is provided with tubing with two
attachment sites that are connected to the inlet and outlet of the dialyzate side of the patient's dialysis circuit.

Claim 15

The method of claim 14 wherein, after priming, the said urea removing unit is temporary attached to the patient's dialysis unit in place of the osmosis unit where a high flow dialysis prescription is conducted and the spent dialysis solution is circulated along the said highly urea permeable dialysis membrane. Along the other side of the said highly urea permeable dialysis membrane a priming fluid is circulated. Urea is removed from the said priming fluid resulting in its continuous removal down the created concentration gradient. Separate urea removal is carried out for the duration of time necessary to achieve the desired urea clearance.

Claim 16

An ambulatory ultrafiltration and re-infusion system comprising: a wearable unit and a portable unit. The said wearable unit comprises: a wearable or implantable hemofilter, a blood pump and a 0.5-3 liters ultrafiltrate reservoir attached to the ultrafiltrate side of the filter. The said wearable unit comprising also a re-infusion set that comprises a regenerated fluid reservoir connected to a fluid pump that re-infuses the regenerated fluid into the patient's blood distal to the hemofilter. The said portable unit comprises an ultrafiltrate reservoir that receives and stores the ultrafiltrate from the corresponding ultrafiltrate reservoir of the wearable unit, the said osmosis unit, a pump, a urea removing device and a regenerated fluid reservoir connected in a fluid circuit. The said portable unit regenerated fluid reservoir further having a connection site that fits with a corresponding site on the regenerated fluid reservoir of the wearable unit.

Claim 17

The method in association with claim 16 wherein the treatment is carried out by combining high flow ultrafiltration with re-infusion of the regenerated fluid and the removal of uremic toxins is achieved by conviction.