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(71) Applicant (for all designated States except US): **DOW GLOBAL TECHNOLOGIES INC.** [US/US]; Washington Street, 1790 Building, Midland, MI 48674 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **STRICKLAND, Alan, D.** [US/US]; 101 Waterlilly, Lake Jackson, TX 77566 (US). **SIMON, Jaime** [US/US]; 316 C. R. 605, Angleton, TX 77515 (US).

(74) Agent: **JOZWIAK, Elisabeth, T.**; THE DOW CHEMICAL CO., 2030 Dow Center, Midland, MI 48674 (US).

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(54) Title: DIALYSIS SOLUTION INCLUDING WATER-SOLUBLE POLYELECTROLYTE OSMOTIC AGENT

(57) Abstract: Dialysis solutions comprising aqueous solutions including physiologically acceptable salts and a polyelectrolyte osmotic agent are disclosed. The subject solutions provide an improved osmotic gradient resulting in reduced dialysis times and/or reduced volumes of required dialysis solution. Moreover, the subject osmotic agents do not significantly migrate into the patient's blood over the time period of dialysis nor are the subject osmotic agents as susceptible to forming detrimental degradation products during gamma sterilization. The subject osmotic agents are much less susceptible to microbial contamination than currently available osmotic agents used in dialysis. The use of free radical scavengers is also described along with the use of a filter to reduce the introduction of bacteria into the peritoneal cavity.



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DIALYSIS SOLUTION INCLUDING WATER-SOLUBLE
POLYELECTROLYTE OSMOTIC AGENT

5 Cross-reference to related application

 This application claims the benefit of U.S. Provisional Application No. 60/703,486, filed July 28, 2005.

Background of the Invention

10 Renal dialysis involves the diffusion of water and waste products, (e.g., urea, excess salts, toxins, impurities, etc.) from a patient's blood, through a semipermeable membrane, and into a dialysis solution. Dialysis most commonly takes one of two forms: hemodialysis involves contacting a portion of the patient's blood with a synthetic semipermeable membrane wherein water and waste products diffuse from the blood through the membrane
15 and into a dialysis solution. The "cleansed" blood is then returned to the patient. Peritoneal dialysis involves infusing a dialysis solution into the patient's peritoneum. The peritoneum comprises a cavity surrounded by blood vessels and capillary beds allowing it to act as a natural semipermeable membrane. Water and waste products diffuse from the blood, through the peritoneum and into the dialysis solution, which is subsequently removed from
20 the patient.

 Dialysis solutions are typically aqueous solutions including electrolytes, bicarbonate buffer, and an osmotic agent, i.e., a constituent utilized to create an osmotic gradient between a patient's blood and the dialysis solution. The most commonly used osmotic agents include a carbohydrate containing osmotic agent such as glucose and dextrose.

25 There are several problems associated with peritoneal dialysis. One problem is the high volume of liquid required to conduct treatment. Patients typically keep a month's supply of dialysate solution on hand. This requires a large storage room and moving large amounts of liquid from the storage place to the treatment place. In addition, there is significant risk for infection. These procedures are done in the home by the patient or a
30 helper to the patient that may not necessarily be well trained in aseptic techniques. As a result, introduction of bacteria due to the procedures causing an infection frequently occur.

There are several problems associated with the use of carbohydrate containing osmotic agents. For example, dextrose and glucose migrate through the peritoneum and into the blood stream resulting in elevated blood levels of these constituents. As a consequence, only relatively low concentrations of these osmotic agents can be used; thus, leading to the use of relatively large volumes of solutions and long dialysis times.

Another disadvantage associated with carbohydrate osmotic agents results from the common practice of using gamma radiation to sterilize the dialysis solution. Gamma radiation tends to degrade the osmotic agents yielding degradation products that lower the pH of the solution.

U.S. Patent 4,886,789 (incorporated herein in its entirety) describes mixtures containing at least 15 weight percent of glucose polymers having a degree of polymerization greater than 12. Glucose polymers of this type can be relatively expensive to synthesize and are susceptible to degradation when subjected to gamma sterilization.

U.S. Patent 4,339,433 (incorporated herein in its entirety) discloses a variety of dialysis solutions including non-carbohydrate osmotic agents. Unfortunately, these agents can be susceptible to degradation when subjected to gamma sterilization. Moreover, these agents are relatively expensive to produce.

Low cost, non-carbohydrate osmotic agents are sought which address the shortcomings associated with known osmotic agents. Moreover, a means for reducing the detrimental effects associated with radiation induced degradation products is sought.

Summary of the Invention

In one aspect, the present invention is a dialysis solution including an osmotic agent comprising a physiologically acceptable, water soluble polyelectrolyte. Preferably, the osmotic agent comprises a complete or partial salt of one or more alkali metals and polyacrylic acid. The dialysis solution optionally includes a free radical scavenger.

In a second aspect, the present invention is a method for performing dialysis utilizing the dialysis solution described above. The dialysis solutions of the present invention may be infused into the peritoneum for peritoneal dialysis, or they may be used for hemodialysis by

contacting a patient's blood with a semipermeable membrane wherein water and waste products flow from the blood, through the membrane and into the dialysis solution.

Species of the subject polyelectrolytes are well known for their biocompatibility and safety in medical uses, e.g., cosmetics, oral pharmaceuticals, pharmaceutical excipients, hygiene products, etc.

Detailed Description of the Invention

The dialysis solution of the present invention includes a physiologically acceptable aqueous solution including a water-soluble polyelectrolyte. The solution has a physiologically acceptable pH and preferably includes physiologically acceptable salts, buffers and other constituents, as is well known in the art. For example, U.S. Patent 4,308,255 to Raj et al. (incorporated herein by reference) describes dialysis solutions including physiologically acceptable quantities of sodium, chloride, potassium, bicarbonate, calcium, and magnesium.

Selection of a specific polyelectrolyte species may be at least partially based upon the pore size of the semipermeable membrane used in the dialysis treatment. The pore size of such membranes tends to be distribution of sizes rather than a uniform size. Nonetheless, such membranes are commonly characterized in terms of a "molecular weight cut-off" value. Materials having a molecular weight greater than the specified molecular weight cut-off of a membrane are substantially blocked, or incapable of passing through the membrane. The molecular weight of the subject polyelectrolyte must be sufficiently high to prevent significant quantities of polyelectrolyte from passing through the semipermeable membrane during dialysis treatment. However, the molecular weight must be low enough that the polyelectrolytes easily dissolve in the dialysis solution.

Although dependant upon the specific composition and structure (e.g., linear, branched, etc.), the subject polyelectrolytes have a molecular weight of greater than 500 daltons, preferably greater than about 1,000 daltons, and more preferably greater than about 3,000 daltons, and even greater than about 50,000 daltons in some applications, depending at least partially upon the molecular weight cut-off of the membrane being utilized for

dialysis. The subject polyelectrolytes have a molecular weight of less than about 2,000,000 daltons, preferably less than about 1,000,000 daltons, depending at least partially upon the molecular weight cut-off of the membrane being utilized for dialysis. For most applications, molecular weights from about 3,000 to 1,000,000 daltons are particularly preferred. It
5 should be understood that higher molecular weight polyelectrolytes may be used in combination with those falling within the specified range.

For purposes of this invention, the term "water-soluble polyelectrolytes" is intended to include physiologically compatible water soluble polymers including in their chains groups with ionic character which become hydrated or solvated when placed in water.
10 Physiologically compatible is intended to mean that contact of the materials with living mammalian tissues in osmotically neutral situations does not cause damage to the tissues or the mammal. Examples of such polyelectrolytes include polyacrylate materials such as carbomer, polycarbophil, and the like. Water soluble polyvinylacetic acid and polyglutamate salts are other examples. Counterexamples include polyethyleneimine which,
15 though water soluble and containing groups which can have ionic character and hydrate in water, cause severe morbidity and mortality when administered to mammals.

Preferred species of polyelectrolytes include alkali metal salts of acrylic acid polymers whether branched or straight chain. The alkali metal can be sodium, potassium, or a combination thereof. Such polymers can be produced by polymerizing, grafting,
20 crosslinking or otherwise reacting individual acrylic acid molecules, individual acrylate salts, individual acrylate esters, previously prepared polymers or pre-polymers, or combinations of these. By way of further example, other compounds falling within the subject definition of polyelectrolytes can be formed through use of polymers based on polysulfonates or polyphosphonates. In light of the preceding description those skilled in
25 the art will readily appreciate alternative routes for making applicable polyelectrolytes within the scope of the present invention. As compared to linear polymers, relatively smaller molecular weights of such branched polymers may be utilized, depending upon the specific configuration of the polymer and the pore size of the semipermeable membrane used therewith. That is, branched polymers may offer added steric hinderance such that
30 relatively smaller molecular weight species will not pass through the pores of the semipermeable membrane used during dialysis.

The subject polyelectrolytes may be used in combination with other known osmotic agents such as glucose, dextrose, and other carbohydrate containing osmotic agents. Moreover, the subject polyelectrolytes may be used in combination with the osmotic agents described in U.S. Patents 5,869,444; 4,761,237; 4,976,683; 4,604,379; 4,959,175; 5 4,339,433; and 4,886,789, all of which are incorporated herein by reference. However, the subject polyelectrolytes preferably are not combined with significant amounts of other osmotic agents.

The subject osmotic agents are substantially impermeable through the peritoneum and the semipermeable membranes typically used in hemodialysis. Consequently, relatively 10 high concentrations of the subject osmotic agent can be safely used, resulting in a significant reduction in the total volume of dialysis solution required and the time required for dialysis treatment. Moreover, many polyelectrolytes suitable for use in the present invention are produced on a large commercial scale and are relatively inexpensive. For example, pharmaceutical grade sodium polyacrylate having a range of suitable molecular weights are 15 available.

Peritoneal dialysis solutions of the present invention typically include a quantity of the polyelectrolyte sufficient to provide osmotic pressure to remove 500 to 1500 milliliters of fluid from the body during a two to four hour period through the peritoneum into the peritoneal cavity for drainage from the body. As a non-limiting example, a polyelectrolyte 20 capable of hydration of 1 gram of polyelectrolyte with 50 grams of physiologic saline would typically be placed into the dialysate in quantities between 10 and 30 grams per volume of dialysate used in one typical infusion/dwell/drain cycle. Typically, the volume of fluid infused at the start of a cycle is 1 to 3 liter, making the range of concentration of the polyelectrolyte typically 3 gram per liter to 30 gram per liter dialysate. Most typically, such 25 a polyelectrolyte based dialysate would contain 10 gram of polyelectrolyte in 1.5 liter (6.7 g/l) for a single dialysis cycle. Amounts of polyelectrolyte would vary depending on whether other osmotic agents were contained in the dialysate.

The osmotic agent used in the present invention requires more than 10 gram of physiologic saline per gram of polyelectrolyte to completely hydrate the polyelectrolyte, but 30 preferably more than 20 gram of physiologic saline per gram of polyelectrolyte, more preferably more than 30 gram of physiologic saline per gram of polyelectrolyte, even more

preferably more than 40 gram of physiologic saline per gram of polyelectrolyte, and most preferably more than 50 gram of physiologic saline per gram of polyelectrolyte to completely hydrate the polyelectrolyte.

5 Hemodialysis solutions of the present solution typically would be prepared to contain from about 5 percent to about 20 percent of the concentration of polyelectrolyte as a peritoneal dialysate would contain. For instance, a polyelectrolyte capable of hydration of 1 gram of polyelectrolyte with 50 grams of physiologic saline would typically be used in a concentration of 0.15 to 6 gram polyelectrolyte per liter hemodialysis solution. Most typically, a hemodialysis solution based on such a polyelectrolyte would have a
10 concentration of between 0.3 and 0.6 gram of polyelectrolyte per liter of dialysate.

The subject dialysis solution preferably includes a free radical scavenger to reduce complications caused by the production of degradation products from gamma sterilization. In this manner, sterilization of the solution using gamma radiation can be accomplished with minimal damage to solution components while maintaining a physiological pH. Examples
15 of preferred free radical scavengers include: salicylic acid, dihydroxybenzoic acid (gentisic acid), human serum albumin, glutathione, ascorbic acid, benzyl alcohol, BHT, citric acid, and glycerol. It will be appreciated that the use of such free radical scavenger is independent of the specific osmotic agent and may be used with traditional, prior art, or non-polyelectrolyte containing dialysis solutions.

20 In performing dialysis according to the present invention, risk of infection is minimized by including an in-line filter when introducing the present solution into the peritoneal cavity. Filters rejecting materials larger than 0.2 microns are well known to prevent the passage of bacteria.

The subject polyelectrolytes are less susceptible to forming detrimental degradation
25 products when exposed to sterilization conditions than conventional glucose solutions. By way of illustration, comparable dialysis solutions were prepared utilizing different osmotic agents: glucose and sodium polyacrylate. The solutions were subjected to common sterilization conditions, i.e., autoclave and gamma radiation. After sterilization, the pH of each solution was measured. The pH of the glucose containing solutions had dropped

significantly; whereas the pH of sodium polyacrylate containing solutions had remained stable.

Specific Embodiments of the Invention

The following example illustrates the invention and should not be construed as
5 limiting the scope of the appended claims.

Example 1:

The following quantities of solutes were dissolved in one liter of water:

10 Calcium Chloride 0.194 g
Magnesium Chloride 0.071 g
Sodium Chloride 5.668 g
Sodium Lactate 3.922 g
Sodium polyacrylate 100g as osmotic agent

15 Five milliliters of this solution were injected into the peritoneum of a 185 g male Sprague Dawley rat. The rat was given free access to water and food. The rat began showing signs of dehydration after 90 minutes and was euthanized. The peritoneal cavity contained approximately 17 milliliters of fluid. Estimated blood volume of a 185 gram rat is 12
20 milliliters, so this represents approximately the entire blood volume being added to the injected dialysate.

Example 2:

25 The following quantities of solutes were dissolved in one liter of water:

Calcium Chloride 0.194 g
Magnesium Chloride 0.071 g
Sodium Chloride 5.668 g
30 Sodium Lactate 3.922 g
Sodium polyacrylate 10g as osmotic agent

Four male Sprague Dawley rats (150-175 g body weight) were intraperitoneally injected
35 with 5 milliliters of this solution. After 2 hours, a needle was placed into the peritoneal space and the fluid was drained by gravity. An average of 8 milliliters of fluid was obtained.

Example 3:

40 The following quantities of solutes were dissolved in one liter of water:

Calcium Chloride 0.194 g
Magnesium Chloride 0.071 g
Sodium Chloride 5.668 g
Sodium Lactate 3.922 g
Sodium polyacrylate 10g as osmotic agent

5

Six male Sprague Dawley rats were anesthetized and underwent bilateral ligation of the renal pedicle and nephrectomy. Three of these rats also had placement of peritoneal dialysis catheters. Following recovery, the rats were housed individually and given free access to food and water. The three rats with peritoneal dialysis catheters were begun on dialysis with the above dialysis solution with four cycles per day. Control rats died at 41 +/- 2 hours after the nephrectomy. Dialyzed rats were maintained with the peritoneal dialysis regimen for one week and then euthanized. Post-mortem examination revealed no peritoneal damage.

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What Is Claimed Is:

1. A dialysis solution including an osmotic agent comprising a physiologically acceptable, water soluble polyelectrolyte.
2. The dialysis solution of Claim 1 wherein the osmotic agent requires more than 10
5 gram of physiologic saline per gram of polyelectrolyte to completely hydrate the polyelectrolyte.
3. The dialysis solution of Claim 1 wherein the osmotic agent comprises a complete or partial salt of one or more alkali metals and polyacrylic acid.
4. The dialysis solution of Claim 3 wherein the alkali metal is sodium, potassium, or
10 a combination thereof.
5. The dialysis solution of Claim 1 further comprising a free radical scavenger.
6. The dialysis solution of Claim 5 wherein the free radical scavenger is selected from at least one of: salicylic acid, dihydroxybenzoic acid, human serum albumin, glutathione, ascorbic acid, BHT, and citric acid.
7. The dialysis solution of Claim 1 comprising from about 0.15 g to about 30 g of
15 osmotic agent per liter of dialysate.
8. The dialysis solution of Claim 7 comprising from about 0.3 to about 0.6 gram of osmotic agent per liter of dialysate.
9. The dialysis solution of Claim 7 comprising from about 3 to about 10 gram of
20 osmotic agent per liter of dialysate.
10. A method for performing dialysis utilizing the dialysis solution of Claim 1.
11. The method of Claim 10 wherein the dialysis solution is infused into the peritoneum.
12. The treatment of Claim 10 wherein the dialysis solution is used for hemodialysis
25 by contacting a patient's blood with a semipermeable membrane wherein water and waste products flow from the blood, through the membrane and into the dialysis solution.