

## DESCRIPTION

TITLE OF THE INVENTION: THREE-PACK TYPE DIALYSIS AGENT  
CONTAINING ACETIC ACID AND ACETIC ACID SALT

### TECHNICAL FIELD

[0001]

The present invention relates to a three-pack type dialysis agent containing acetic acid and an acetate salt. More particularly, the present invention relates to a three-pack type dialysis agent with which it is possible to set the total acetate ion content in a dialysis fluid at a low value of less than 6 mEq/L and which is excellent in terms of the storage stability and can be reduced in the odor of acetic acid. Therewith, it is possible to prepare a dialysis fluid so that the bicarbonate ion concentration can be changed at will according to need.

### BACKGROUND ART

[0002]

Dialysis therapy has been established as a treatment for patients with renal insufficiency, and performed for the purpose of controlling the concentration of blood electrolyte components, removal of uremic substances, correction of acid-base balance, or the like. The dialysis fluid used in the dialysis treatment includes a plurality of components, which should be combined at appropriate concentrations so as to satisfy objectives of treatment with less strain on the living body.

[0003]

In recent years, bicarbonate dialysis fluids formed with use of sodium hydrogen carbonate for the correction of acid-base balance are popular, and it is also essential to combine an acid to make the dialysis fluid neutral. If these are distributed

in the same container in which they coexist, such components generate carbon dioxide gas in the container and become very unstable, because of which, in general, two agents of agent A and agent B are produced as a dialysis agent to be mixed at the time of use for the preparation of the dialysis fluid.

[0004]

Usually, the agent A contains sodium chloride, potassium chloride, calcium chloride, magnesium chloride, pH adjusting agent (acid and buffer components as optional components), and glucose, and the agent B contains sodium hydrogen carbonate. Moreover, in order to prevent the precipitation of insoluble salts, the formulation of calcium chloride and magnesium chloride into the agent B is contraindicated.

[0005]

Conventionally, these agents A and B have been used as a liquid filled in a polyethylene container, but problems have arisen concerning transportation costs and poor operability in hospitals (weight, storage space, and disposal method of polyethylene container). As a result, today, a dialysis agent in powder form to be mixed with water before use has been put into practical use.

[0006]

Although original dialysis agents in powder form are comprised of three agents including an agent A-1 containing a pH adjusting agent and an electrolyte, an A-2 agent consisting of only glucose, and an agent B consisting of sodium hydrogen carbonate, currently the two-pack type dialysis agents consisting of the agent A and the agent B are popular where the agent A-1 and the agent A-2 are combined.

[0007]

Today, the bicarbonate dialysis agent is formulated so as to have the following

composition and concentration when clinically used as a dialysis fluid.

[0008]

[Table 1]

|                               |                 |
|-------------------------------|-----------------|
| Na <sup>+</sup>               | : 130~150 mEq/L |
| K <sup>+</sup>                | : 0~3.0 mEq/L   |
| Ca <sup>2+</sup>              | : 2.0~4.0 mEq/L |
| Mg <sup>2+</sup>              | : 0~2.0 mEq/L   |
| Cl <sup>-</sup>               | : 90~120 mEq/L  |
| HCO <sub>3</sub> <sup>-</sup> | : 20~40 mEq/L   |
| Acetic acid                   | : 0~12 mEq/L    |
| Citric acid                   | : 0~3 mEq/L     |
| Glucose                       | : 0~250 mg/dL   |

[0009]

At the time of dialysis treatment, a liquid type agent A, or the agent A obtained by dissolving a powder type agent A, or the agent A obtained by dissolving powder type agents A-1 and A-2, and a liquid type agent B or the agent B obtained by dissolving a powder type agent B are diluted and mixed to be used as the dialysis fluid. However, as mentioned above, the bicarbonate dialysis fluid generates carbon dioxide gas as a result of coexistence of an acid and sodium hydrogen carbonate over time and the pH rises at the same time, so that an insoluble calcium carbonate and the like may be generated. This phenomenon raises such a problem that calcium concentration effective in the treatment is reduced and crystals are adhered to the tube or hose of the dialysis machine.

[0010]

On the other hand, acetic acid has been used for a long time as a pH adjusting

agent, but, in recent years, peripheral vasodilator action and cardiac inhibitory effect, induction of inflammatory cytokines, and strain on the patient with acetate intolerance, due to acetic acid have been questioned. That is, although acetic acid is metabolized in a short time and is not accumulated in the living body, it has a cardiac inhibitory effect, a peripheral vasodilator action, and, as a result, an action of reducing blood pressure. Since dialysis treatment is also a treatment for the removal of moisture in the body, a reduction in blood pressure due to moisture removal during and after dialysis would inevitably occur. The symptomatic treatment such as control of moisture removal and administration of vasopressors is often used in combination to prevent the reduction in blood pressure. The presence or absence of symptoms caused by these effects are different for each patient, and thus it is thought that such symptoms may also be attributed to the concentration of acetic acid contained in the dialysis fluid. In recent years, a dialysis method without acetic acid (an acetate free dialysis method) as one approach to overcome such a situation has been proposed.

[0011]

Therefore, nowadays, those obtained by formulating citric acid in place of acetic acid as a pH adjusting agent are commercially available and have been clinically used (for example, see Patent Documents 1 to 4). However, there has been raised such a problem that because citric acid has a strong chelating action, a portion of the calcium in the dialysis fluid is chelated, thereby to decrease the ionized calcium concentration, and because citric acid is a stronger acid than acetic acid, the pH of the concentrated solution A lowers to cause a risk of corrosion of parts of a dissolution apparatus or a dialysis machine. If a large amount of organic acid salts are formulated in order to increase the pH of the solution A, crystals of calcium citrate are precipitated to affect the composition, which is also a problem. In other words, since citric acid is easy to

form a chelate with an alkaline earth metal, it forms a chelate with calcium and magnesium in the dialysis fluid ingredient. This action has a great effect on calcium in particular, and since control of the amount of calcium is very important in dialysis treatment, there is a drawback such that decrease of ionized calcium concentration due to such a chelate significantly affects the calcium balance in patients. For example, if the calcium and citric acid were included at almost the same concentration (ion equivalent ratio) in the dialysis fluid, about 35% of calcium is chelated to reduce the ionized calcium concentration in the dialysis fluid by a corresponding amount, resulting in a difficulty to control the blood calcium level. In addition, since citric acid also enters the body by dialysis, there is a risk such that citric acid binds to calcium in the blood to generate a poorly soluble calcium citrate, which is then deposited in the blood vessel. In addition, there is a concern such that it becomes difficult to control the calcium in the body, which is important for dialysis patients, because there is no explicit dynamics of the ingredients such as citric acid and calcium after they enter the blood at the same time. Furthermore, there is a problem in the following points in that the decrease in ionized calcium concentration due to citric acid promotes the relaxation of cardiac muscle and vascular smooth muscle, leading to low blood pressure, and that citric acid is difficult to use in patients with bleeding tendency because it has an anticoagulant effect.

[0012]

Further, citric acid is easy to handle in the normal handling because it is a solid, but since its concentrate is strongly acidic, hydrogen chloride gas is easily generated upon partial moisture absorption even if it is stored in powder form, which may cause a partial metal corrosion of the dissolution apparatus, resin deterioration, and the like. For example, Patent Document 1 describes a powder-type dialysis agent free from

acetic acid, said dialysis agent being able to prevent the formation of insoluble compounds, suppress the precipitation of calcium carbonate, and inhibit the degradation of glucose by using a citric acid. These effects can be achieved by using citric acid within a limited range of pH 2.2 to 2.9. With such a pH range, there is a risk of corrosion of the dissolution apparatus and the dialysis machine, and the decrease in the ionized calcium concentration due to the strong chelation effect of citric acid may also affect the therapeutic effect as described above.

[0013]

Therefore, it is not optimal to use citric acid as an acid other than acetic acid. Although organic acids other than citric acid which are safe for the living body, such as malic acid, lactic acid, fumaric acid, gluconic acid, etc. could be used, it is not clear about their behavior in the body after dialysis in chronic use and thus the amount of these acids should be reduced as much as possible, and it is also important to take into account the influence of these acid ingredients on the dialysis fluid preparation apparatus and the dialysis machine.

[0014]

On the other hand, as described above, it is concerned that citric acid etc. would decrease the ionized calcium concentration due to its strong chelating action, but, strictly speaking, acetic acid also reduces the ionized calcium concentration. The clinical problem of acetic acid has been neglected probably because acetic acid is metabolized fast, but, in practice, a dialysis fluid formed with use of acetic acid has a lower ionized calcium concentration than a dialysis fluid formed with use of hydrochloric acid as the pH adjusting agent, and the ionized calcium concentration is further reduced as the content of acetic acid is increased. Although not known in general, it is certain that a large content of acetic acid is a factor in lowering the ionized

calcium concentration, but not as much as citric acid. From this point, it is clear that a less content of acetic acid is desirable.

[0015]

All the dialysis agents A containing acetic acid which have been sold in Japan in the past have a total acetic acid content of 8 mEq/L or higher and a ratio of sodium acetate to acetic acid of 2.2 or more, regardless of whether the dialysis agent A is a liquid or a solid. Since the pH of the liquid A is 4.7 or more under this condition, there is such an advantage that the dialysis fluid preparation apparatus is less likely to be corroded and the dialysis fluid is easy to handle, in view of production of the liquid formulation.

[0016]

The reason of the formulation of 8 mEq/L or higher of the total acetate content in Japan is because the past acetate dialysis fluid (in which sodium acetate is formulated in 30 mEq/L or higher without using sodium bicarbonate) is changed to the bicarbonate dialysis agent so that benefits of bicarbonate and benefits of acetate can be brought about in combination, i.e., blood bicarbonate ions can be directly corrected whereas bicarbonate ions can be slowly corrected through the acetate metabolism.

[0017]

On the other hand, liquid preparations (liquid A) are sold primarily outside of Japan. Sodium acetate is used as a part of the alkalizing agent in Japan, whereas only sodium hydrogen carbonate of the agent B is used as the alkalizing agent outside of Japan and sodium acetate is not used. Therefore, as an acetate ingredient, only acetic acid in an amount of 4 mEq/L or less has been used mainly as a pH adjusting agent.

[0018]

However, when sodium acetate is not included as described above, the pH of

liquid A is 3 or less, resulting in adverse effects such as corrosion of the metal member of the dialysis fluid preparation apparatus and the dialysis machine, and strong irritation to the skin. In late years, a liquid A (including those prepared by dissolving an agent A powder) having a pH of 3 or less has been commercially available and the dialysis fluid preparation equipment manufacturers also deal with such a liquid A by employing parts made of acid resistant materials strongly resistant to corrosion. However, these materials are economically unfavorable because they are expensive.

[0019]

In addition, the dialysis fluid containing acetic acid has a very strong and uncomfortable odor of acetic acid and thus, in the dialysis facilities where large quantities of dialysis fluid are handled, it is necessary to care the dialysis agent not to be placed in an open system as much as possible during its manufacturing or handling even though it is a liquid.

[0020]

Next, in Japan, powder formulations of dialysis agents are popular as a result of a trend toward powdering of dialysis agents, and a large number of patents relating to bicarbonate dialysis agents that can be used in powder form have been disclosed. For example, Patent Document 5 describes that the manufacturing of the powder preparation becomes easier, when sodium acetate is combined to acetic acid in a ratio (molar ratio) of 1.56 to 3.29, preferably 2.49 to 3.29, in a powdery dialysis agent A because sodium acetate easily adsorbs acetic acid and is difficult to volatilize. However, even in the technique disclosed in Patent Document 5, the total acetate ion content of the finally prepared dialysis fluid is assumed to be 8 mEq/L or higher.

[0021]

In addition, it is typical that sodium acetate is combined in an amount of from

more than two times to five times, relative to acetic acid, and, for example, combination ratio of sodium acetate is 2.2 times (acetic acid 2.5 mEq/L : sodium acetate 5.5 mEq/L) for commercially available LYMPACK TA-1 in Japan, three times (acetic acid 2 mEq/L : sodium acetate 6 mEq/L) for KINDALY 2E, 4.5 times (acetic acid 2 mEq/L : sodium acetate 9 mEq/L) for HI-SOLV F, and 5 times (acetic acid 2 mEq/L : sodium acetate 10 mEq/L) for HI-SOLV D. Even apart from the transition of formulation in the past, the reason why the ratio of two times or less of sodium acetate to acetic acid has not yet been disclosed is because of a problem with acetic acid odor. In other words, as the ratio of sodium acetate is increased to three times, four times and so on, the acetic acid odor in powder preparation is reduced. In contrast, as the ratio of sodium acetate relative to acetic acid becomes close to double or becomes double or less, an excruciating odor of acetic acid occurs, because of which its practical use is not possible.

[0022]

As seen from the above, even in Japan and abroad, there are only dialysis fluids containing acetic acid and having a total acetate ion content of 4 mEq/L or less, or 8 mEq/L or higher, and there has been no dialysis agent put to practical use, wherein the pH of the liquid A (concentrate) obtained by dissolving a solid agent A in water is set to about 4 and the total acetate ion content in the dialysis fluid is set to 4 to 8 mEq/L.

[0023]

Only Patent Document 6 discloses that a preferable total acetate ion content is up to 5 mEq/L in the dialysis fluid containing acetic acid and sodium acetate. However, Patent Document 6 discloses a primary concentrate (sodium hydrogen carbonate, sodium chloride, and sodium acetate) and an individual concentrate (sodium, potassium, calcium, magnesium, hydrochloric acid/or acetic acid, glucose), and

describes that the molar ratio of acetate/sodium in the final dialysis fluid obtained by combining the primary concentrate with the individual concentrate is 0.03 or less. That is, if the sodium content in the dialysis fluid is set to 140 mEq/L as typical cases, the total content of acetate ions in the dialysis fluid corresponds to 4.2 mEq/L or less. Further, Patent Document 6 describes that the sodium acetate to be combined with the primary concentrate is in an acetate/sodium ratio of less than 0.03, which indicates that the acetate ion content in the dialysis fluid is less than about 4 mEq/L. That is, Patent Document 6 discloses the embodiment of only a dialysis agent useful in the production of a dialysis fluid having a total acetate ion content of less than about 4 mEq/L.

[0024]

In addition, according to Patent Document 6, the dialysis agent of Patent Document 6 enables individual patients to select various individual concentrates that can be provided, and the object of combining sodium acetate is to improve the stability and preserving property of the primary concentrate at low temperatures. In other words, a small amount of sodium acetate in the primary concentrate increases the solubility of sodium hydrogen carbonate and suppresses the formation of precipitates.

[0025]

That is, since the dialysis agent of Patent Document 6 enables to perform the dialysis with various formulations according to the individual patients (calcium, magnesium, potassium, etc.) and requires a fairly complex system so that acetic acid and acetate salt are designed to be combined into different preparations, it differs from a two-pack type dialysis agent generally comprising agent A and agent B or a three-pack type dialysis agent comprising agent A-1, agent A-2, and agent B in its dosage form and preparation method of the dialysis fluid. In addition, the technical means for reducing the acetic acid odor in the dialysis agent has not been studied at all in Patent Document

6. Further, in the dialysis agent of Patent Document 6, since the individual concentrate includes hydrochloric acid or acetic acid and does not include a basic ingredient, so that it will be exposed to a strong acidic condition of pH 3 or less, the dialysis agent of Patent Document 6 is not necessarily a good preparation in regard to corrosion problems of the dialysis fluid manufacturing apparatus, stability of glucose, and the like.

[0026]

As described above, among general two-pack type dialysis agents that are widely used and contain the agent A (electrolytes, acids, glucose, etc.) and the agent B (sodium hydrogen carbonate) in combination, a dialysis agent having a total acetate ion content of 4 to 8 mEq/L does not exist, let alone any practical dialysis agent in powder form due to its strong acetic acid odor. The above-mentioned problems are also exactly the same for conventional three-pack type dialysis agents that are widely used and contain agent A-1 (electrolyte/acid), agent A-2 (glucose), and agent B (sodium hydrogen carbonate) in combination.

[0027]

In fact, domestically and abroad, there is no successful example of any actual commercialization of dialysis agents in powder form, wherein the total acetate ion content has been set to less than 8 mEq/L in the dialysis fluid. This is probably because dialysis agents in powder form are difficult to commercialize as such dialysis agents poorly withstand clinical use in terms of fluidity and stability, and acetic acid odor. For example, acetic acid has a big influence on environment due to its pungent odor. Clinical dialysis fluid preparation is generally performed by a clinical engineer, but there is a problem of discomfort associated with pungent odor. Therefore, it is necessary to find the optimal formulation while sufficiently considering such problems.

[0028]

In recent years, it has been reported at conferences and the like that a lower content of total acetate ion in a dialysis fluid is physiologically desirable and the total acetate ion are preferably less than 6 mEq/L or less than 4 mEq/L. Thus, there is an increasing demand for development of a dialysis agent that can be set to a lower total acetate ion content. It is believed that, by suppressing the total acetate ion content within a low range as described above, the onset of symptoms such as decrease in blood pressure can be suppressed almost without raising blood acetic acid concentration of the patient during dialysis, thereby to significantly improve safety, because the metabolic rate of acetic acid is faster than that of other organic acids and the content of acetic acid is less than that of conventional products. However, since a dialysis fluid having a low level of total acetate ion content, reported in the academic conferences, etc., is prepared by simply halving the amount of each of acetic acid and sodium acetate of the dialysis agent A that is set to the total acetate ion content of 8 mEq/L, there is a disadvantage that the pH of the dialysis fluid is inevitably high. In such a dialysis fluid with a high pH, its continuous use potentially causes vascular calcification of the patient, and there is also a problem of calcium deposition in the dialysis fluid preparation apparatus and the dialysis machine.

[0029]

Meanwhile, the applicant of the present application has developed a three-pack type dialysis agent for the preparation of a dialysis fluid and an apparatus for preparing the dialysis fluid, in which bicarbonate ion concentration can be freely changed according to the disease state of a patient while maintaining the concentrations of trace metal ions at constant levels (see Patent Document 7). If a technique for formulating a three-pack type dialysis agent in which the bicarbonate ion concentration can be freely changed and the total acetate ion content in the dialysis fluid can be set to a low value as

described above, the three-pack type dialysis agent being excellent in storage stability of the agent A and capable of reducing the acetic acid odor is developed, it will result in a good news to not only dialysis patients but also workers in dialysis therapy.

#### PRIOR ART DOCUMENTS

#### PATENT DOCUMENTS

[0030]

Patent Document 1: Japanese Patent Laid-open Publication No. 2003-104869

Patent Document 2: International Patent Application Publication No. WO  
2005/094918

Patent Document 3: Japanese Patent Laid-open Publication No. 10-087478

Patent Document 4: International Patent Application Publication No. WO  
2010/112570

Patent Document 5: Japanese Patent Laid-open Publication No. 7-24061

Patent Document 6: Japanese Patent Laid-open Publication No. 6-245995

Patent Document 7: Japanese Patent No. 5099464

#### SUMMARY OF THE INVENTION

#### PROBLEMS TO BE SOLVED BY THE INVENTION

[0031]

The purpose of the present invention is to provide a three-pack type dialysis agent with which it is possible to set the total acetate ion content in a dialysis fluid at a low value and which is excellent in terms of the storage stability of glucose, etc. and can be reduced in the odor of acetic acid. Therewith, it is possible to prepare a dialysis fluid so that the bicarbonate ion concentration can be changed at will according to need, while the concentrations of trace metal ions such as potassium ions, calcium ions, and

magnesium ions are maintained constant.

## MEANS FOR SOLVING THE PROBLEM

[0032]

As a result of intensive studies to solve the above problems, the present inventors have found that in the three-pack type dialysis agent including an agent S containing sodium chloride, an agent B containing sodium bicarbonate, and an agent A containing glucose and an electrolyte component which is neither sodium chloride nor sodium bicarbonate, by including acetic acid and acetate salt in the agent A and allowing the molar ratio of acetic acid: acetate salt to satisfy 1:0.5 to 2, it becomes possible to prepare a bicarbonate dialysis fluid having a total acetate ion concentration of 2 mEq/L or higher but less than 6 mEq/L so that in addition to the excellent stability of the components such as glucose and the like in the dialysis agent A, the acetic acid odor can be reduced. Further, according to the three-pack type dialysis agent, it is needless to say that the agent S and the agent A can be dissolved at the same time, and the resulting solution can be used as a general two-pack type dialysis agent. In addition, as in Patent Document 7, it also becomes possible to change the bicarbonate ion concentration and/or the sodium concentration in the dialysis fluid by adjusting the amount of each of the agent S, agent B, and agent A during the preparation of the dialysis fluid. The present invention has been completed by further studies on the basis of these findings.

[0033]

That is, the present invention provides the invention with the following embodiments.

Item 1. A three-pack type dialysis agent used in the preparation of a bicarbonate

dialysis fluid, comprising an agent S containing sodium chloride, an agent B containing sodium bicarbonate, and an agent A containing an electrolyte component other than sodium chloride and sodium bicarbonate and containing glucose, wherein

the agent A contains acetic acid and acetate salt, and the molar ratio of acetic acid:acetate salt is 1:0.5 to 2, and

the three-pack type dialysis agent is used for preparing a dialysis fluid having a total acetate ion concentration of 2 mEq/L or higher but less than 6 mEq/L.

Item 2. The three-pack type dialysis agent according to Item 1, wherein the molar ratio of acetic acid:acetate salt in the agent A is 1:1 to 1.5.

Item 3. The three-pack type dialysis agent according to Item 1 or 2, which is used in the preparation of a dialysis fluid having a total acetate ion concentration of 2 mEq/L or higher but less than 5 mEq/L.

Item 4. The three-pack type dialysis agent according to any one of Items 1 to 3, wherein when the agent A is converted into a state of an aqueous solution that is concentrated to 175 times the concentration of each component in the finally prepared dialysis fluid, the aqueous solution has a pH of 3.9 to 4.7.

Item 5. The three-pack type dialysis agent according to any one of Items 1 to 4, wherein the acetate salt is an alkali metal salt of acetic acid.

Item 6. The three-pack type dialysis agent according to any one of Items 1 to 5, wherein the agent A further contains a physiologically available electrolyte component other than acetic acid, acetate salt, sodium chloride, and sodium bicarbonate.

Item 7. The three-pack type dialysis agent according to Item 6, wherein the electrolyte includes potassium chloride, magnesium chloride, and calcium chloride.

Item 8. The three-pack type dialysis agent according to Item 6 or 7, wherein the agent A further contains an organic acid salt other than acetate salt as the electrolyte and/or

contains an organic acid other than acetic acid as a pH adjusting agent.

Item 9. The three-pack type dialysis agent according to any one of Items 1 to 8, wherein the agent A is in the form of a solid.

Item 10. The three-pack type dialysis agent according to Item 6, wherein the agent A is in the form of a solid and the magnesium chloride and/or calcium chloride is a dry material or an anhydride.

Item 11. The three-pack type dialysis agent according to Item 9 or 10, wherein the acetic acid and acetate salt are contained as a mixture thereof.

Item 12. The three-pack type dialysis agent according to any one of Items 9 to 11, wherein at least some of the acetic acid and acetate salt are contained in the form of an alkali metal diacetate.

Item 13. The three-pack type dialysis agent according to Item 12, wherein the alkali metal diacetate is sodium diacetate and/or potassium diacetate.

Item 14. The three-pack type dialysis agent according to Item 8, wherein the organic acid salt is at least one kind selected from the group consisting of sodium lactate, sodium gluconate, sodium citrate, sodium malate, and sodium succinate.

Item 15. The three-pack type dialysis agent according to Item 8, wherein the organic acid is at least one kind selected from the group consisting of lactic acid, gluconic acid, glucono- $\delta$ -lactone, citric acid, malic acid, and succinic acid.

Item 16. The three-pack type dialysis agent according to any one of Items 9 to 15, wherein:

the agent A comprises a first material containing a mixture of acetic acid and acetate salt, and a second material containing a composition including a physiologically available electrolyte other than acetic acid and acetate salt,

all of the acetate salt in the dialysis agent A are contained in the first material,

or some of the acetate salt in the dialysis agent A are also contained in the second material, and

glucose is contained in the composition of the second material, and/or a third material containing glucose separately from the first material and the second material is contained.

Item 17. The three-pack type dialysis agent according to Item 16, wherein the second material contains potassium chloride, magnesium chloride, and calcium chloride as an electrolyte.

Item 18. The three-pack type dialysis agent according to Item 16 or 17, wherein the second material further contains as an electrolyte an organic acid salt other than acetate salt.

Item 19. The three-pack type dialysis agent according to any one of Items 9 to 18, wherein the agent S, agent B, and agent A are accommodated in a packaging container having a water vapor transmission of  $0.5 \text{ g/m}^2 \cdot 24\text{h}$  or less.

Item 20. The three-pack type dialysis agent according to any one of Items 9 to 19, wherein the agent S, agent B, and agent A are accommodated in the packaging container together with a desiccant.

Item 21. The three-pack type dialysis agent according to any one of Items 1 to 20, which is used by adjusting the addition amount of the agent S, agent B, and agent A so that the bicarbonate ion concentration and/or the sodium concentration in the dialysis fluid is changed.

Item 22. A method for preparing a dialysis fluid, comprising the step of mixing an agent S containing sodium chloride, an agent B containing sodium bicarbonate, and an agent A with water in such an amount that the dialysis fluid has total acetate ion of 2 mEq/L or higher but less than 6 mEq/L, wherein

the agent A contains an electrolyte component other than sodium chloride and sodium bicarbonate and contains glucose, acetic acid and acetate salt, wherein the molar ratio of acetic acid:acetate salt is 1:0.5 to 2.

Item 23. The method for preparing a dialysis fluid according to Item 22, wherein the dialysis fluid is prepared so as to change the bicarbonate ion concentration and maintain the sodium ion concentration at a constant level during dialysis according to a disease state of a patient, in the mixing step.

Item 24. The method for preparing a dialysis fluid according to Item 22, wherein the dialysis fluid is prepared so as to change the bicarbonate ion concentration and at the same time change the sodium ion concentration during dialysis according to a disease state of a patient, in the mixing step.

## EFFECTS OF THE INVENTION

[0034]

According to the three-pack type dialysis agent of the present invention, a bicarbonate dialysis fluid can be prepared so as to have a total acetate ion concentration of less than 6 mEq/L, and it is possible to suppress the onset of symptoms such as hypotension and the like and significantly improve safety during dialysis, as well as to effectively suppress the reduction of ionized calcium concentration in the dialysis fluid. In addition, the dialysis agent A of the present invention is improved in stability of components such as glucose and the like and reduction of the acetic acid odor, and is less likely to corrode the dialysis fluid preparation apparatus and the dialysis machine so that the quality is improved and the improvement in a usage environment is achieved in the medical practice, resulting in a marked improvement of handling in the medical practice.

[0035]

Especially, as for the agent A in the three-pack type dialysis agent of the present invention, the pH of the liquid A (concentrate) obtained by dissolving a solid agent A in water or the pH of a liquid agent A can be adjusted to about 4.4 by setting the total acetate ion concentration in the dialysis fluid to 2 to 5 mEq/L and by setting the molar ratio of acetic acid:acetate salt to 1:1 to 1.5, so that a three-pack type dialysis agent that is clinically safer and more excellent in the stability during production and in qualitative quality can be provided.

[0036]

Thus, according to the present invention, a bicarbonate dialysis fluid can be prepared so as to have a total acetate ion concentration of less than 6 mEq/L, and there can be provided a three-pack dialysis agent that is clinically more useful and more excellent in the storage property and handling property than the conventional dialysis agents.

[0037]

In addition, according to the present invention, it is also possible to freely change the bicarbonate ion concentration and/or the sodium concentration in the dialysis fluid by optionally controlling the amount of the agent S, agent B, and agent A in the preparation of the dialysis fluid as in Patent Document 7. For example, according to the present invention, since it is possible to freely change the bicarbonate ion concentration while maintaining the ion concentrations of trace metals, such as potassium ions, calcium ions, and magnesium ions, in the dialysis fluid at a constant level, as well as control the pH within an optimal range, it becomes possible to correct the metabolic acidosis according to the patient's disease state. Therefore, the present invention is able to reduce the mortality and hospitalization risk in dialysis patients, and

is extremely useful in the future of dialysis treatment.

#### MODE FOR CARRYING OUT THE INVENTION

[0038]

As used herein, the indication “to” showing the numerical range means that it is equal to or more than the number at the left side and equal to or less than the number at the right side, and, for example, the numerical range of “X to Y” means “equal to or more than X and equal to or less than Y”.

[0039]

The present invention relates to a three-pack type dialysis agent used in the preparation of a bicarbonate dialysis fluid, which is characterized by comprising an agent S containing sodium chloride, an agent B containing sodium bicarbonate, and an agent A containing acetic acid, acetate salt, and an electrolyte component which is neither sodium chloride nor sodium bicarbonate, wherein the molar ratio of acetic acid:acetate salt is 1:0.5 to 2, and the three-pack type dialysis agent is used for the preparation of a dialysis fluid having a total acetate ion of 2 mEq/L or higher but less than 6 mEq/L. The three-pack type dialysis agent of the present invention will be described in detail below.

[0040]

#### Agent S

The agent S contains sodium chloride. It is desirable that the agent S does not contain any electrolyte component other than sodium chloride, and it is preferable that the agent S is substantially composed solely of sodium chloride. The agent S may be provided in a solid or aqueous solution form, and is desirably in a solid form from the viewpoint of easy transportation and storage. Specific examples of the solid form of the agent S include powder, granule, and the like. Herein, the agent S in a solid form

may be referred to as a "solid agent S", and the agent S in an aqueous solution form may be referred to as a "liquid agent S".

[0041]

Where the liquid agent S is used, the sodium chloride content in the liquid agent S is, for example, 8 to 32 g/100 ml, preferably 26 to 32 g/100 ml, and more preferably 30 to 31 g/100 ml.

[0042]

The packaging container for accommodating the agent S during distribution is not particularly limited, and examples thereof include those similar to the packaging container for accommodating the agent A.

[0043]

Agent B

The agent B contains sodium bicarbonate. It is desirable that the agent B does not contain any electrolyte component other than sodium bicarbonate, and it is preferable that the components of the agent B are substantially composed solely of sodium bicarbonate. As with the agent S, the agent B also may be provided in a solid or aqueous solution form, and is desirably in a solid form from the viewpoint of easy transportation and storage. Specific examples of the solid form of the agent B include powder, granule, and the like. Herein, the agent B in a solid form may be referred to as a "solid agent B", and the agent B in an aqueous solution form may be referred to as a "liquid agent B".

[0044]

Where the liquid agent B is used, the sodium bicarbonate content in the liquid agent B may be such that the desired bicarbonate ion concentration is satisfied in the eventually obtained dialysis fluid, and for example, 7 to 12 g/100 ml, preferably 8 to 12

g/100 ml, and more preferably 9 to 11 g/100 ml.

[0045]

The packaging container for accommodating the agent B during distribution is not particularly limited, and examples thereof include those similar to the packaging container for accommodating the agent A.

[0046]

Agent A

The agent A contains an electrolyte component which is neither sodium chloride nor sodium bicarbonate. In addition, the agent A contains at least acetic acid and acetate salt as an electrolyte component, and the molar ratio of acetic acid:acetate salt is 1:0.5 to 2.

[0047]

The acetic acid contained in the agent A may be glacial acetic acid. Further, the acetate salt contained in the agent A is not particularly limited as long as it is acceptable for dialysis fluid, but examples thereof include an alkali metal acetate, such as sodium acetate, potassium acetate, and the like, and an alkaline earth metal acetate, such as calcium acetate, magnesium acetate, and the like. Among these acetate salts, an alkali metal acetate is preferable and sodium acetate is more preferable, from the viewpoint of safety and cost as a result of use for many years. Moreover, such acetate salts may be used alone or in combination of two or more kinds thereof.

[0048]

Also, when the agent A is in the form of a solid, at least a portion of acetic acid and acetate salt contained may be in the form of an alkali metal diacetate. The alkali metal diacetate is a complex  $(MH(C_2H_3O_2)_2)$ ; M represents an alkali metal atom) formed from 1 mol of alkali metal acetate and 1 mol of acetic acid. From 1 mol of

alkali metal diacetate are supplied 1 mol of acetate salt (alkali metal acetate) and 1 mol of acetic acid. Specific examples of the alkali metal diacetate include sodium diacetate, potassium diacetate, etc. These alkali metal diacetates may be used alone or in combination of two or more kinds thereof. Among the alkali metal diacetates, sodium diacetate is preferable.

[0049]

The agent A contains acetic acid and acetate salt so as to satisfy a molar ratio of acetic acid:acetate salt of 1:0.5 to 2. By satisfying such molar ratio, it is possible to adjust the pH of a liquid A (concentrate) obtained by dissolving a solid agent A in water or the pH of a liquid agent A to about 3.9 to 4.7, even if the total acetate ion concentration in the dialysis fluid is set to less than 6 mEq/L, so that it becomes possible to suppress the corrosion of the dialysis fluid preparation apparatus and the dialysis machine. Furthermore, by satisfying such molar ratio, it becomes possible to increase the storage stability of the agent A and further possible to reduce the acetic acid odor.

[0050]

As the ratio of acetic acid to acetate salt in the agent A of the present invention, the molar ratio of acetic acid:acetate salt is preferably 1:0.75 to 1.75, more preferably 1:0.75 to 1.5, even more preferably 1:1 to 1.5, and especially preferably 1:1 to 1.25, from the viewpoint of exerting actions more effectively, including improvement of storage stability of the dialysis agent A, reduction of acetic acid odor, suppression of the corrosion of the dialysis fluid preparation apparatus and the dialysis machine, and the like. Here, as described above, since the alkali metal diacetate is a complex of 1 mol of acetic acid and 1 mol of alkali metal acetate, each of the acetic acid and acetate salt derived from 1 mol of alkali metal diacetate is calculated as 1 mol when such an alkali metal diacetate is used as at least a portion of the acetic acid and acetate salt. That is,

for example, in the case of acetic acid and acetate salt that are derived only from alkali metal diacetate, the molar ratio of acetic acid:acetate salt is 1:1. Also, for example, in the case of acetic acid and acetate salt that are derived from X mol of alkali metal diacetate, Y mol of acetic acid, and Z mol of acetate salt, the molar ratio of acetic acid:acetate salt is  $1:(X + Z)/(X + Y)$ .

[0051]

For the content of acetic acid and acetate salt contained in the agent A, it may be appropriately set depending on whether the agent A is solid or liquid, but is usually set so as to satisfy a total acetate ion content in the finally prepared dialysis fluid, of 2 mEq/L or higher but less than 6 mEq/L, preferably 2 mEq/L or higher but 5.5 mEq/L or less, and more preferably 2 mEq/L or higher but 5 mEq/L or less. Thus, according to the dialysis agent A of the present invention, since it is possible to set the total acetate ion content in the dialysis fluid to a lower level that has not been realized in the conventional dialysis agent, onset of symptoms such as hypotension induced by acetate ions during dialysis can be suppressed, thereby making it possible to improve the safety markedly.

[0052]

Also, the agent A may contain, in addition to acetic acid and acetate salt, one or two or more electrolyte components that can be sources for magnesium ions, calcium ions, sodium ions, potassium ions, chloride ions, citrate ions, lactate ions, gluconate ions, succinate ions, malate ions, etc. It is desirable to include sources for at least chloride ions, magnesium ions, and calcium ions as the electrolyte components (neither acetic acid nor acetate salt) contained in the agent A, and it is more desirable to further include a source for potassium ions in addition to such sources mentioned above.

[0053]

Examples of a source for magnesium ions include magnesium salts.

Examples of the magnesium salt used in the agent A include, but not particularly limited to, magnesium chloride, magnesium lactate, magnesium citrate, magnesium gluconate, magnesium succinate, magnesium malate, etc., as long as it is acceptable for the dialysis fluid. Among these magnesium salts, magnesium chloride is preferably used as a source for magnesium because its water solubility is high. These magnesium salts may be in the form of hydrates or dehydrated products obtained by drying the hydrates. Further, such magnesium salts may be used alone or in combination of two or more kinds thereof.

[0054]

Examples of a source for calcium ions include calcium salts. Examples of the calcium salt used in the agent A include, but not particularly limited to, calcium chloride, calcium lactate, calcium citrate, calcium gluconate, calcium succinate, calcium malate, etc., as long as it is acceptable for the dialysis fluid. Among these calcium salts, calcium chloride is preferably used as a source for calcium because its water solubility is high. These calcium salts may be in the form of hydrates or dehydrated products obtained by drying the hydrates. Further, such calcium salts may be used alone or in combination of two or more kinds thereof.

[0055]

Examples of a source for sodium ions include sodium salts. When sodium acetate is used as an acetate salt, the sodium acetate serves as a source for sodium ions. In addition, sodium ions can be supplemented by using also sodium salts other than sodium acetate so that a desired sodium ion concentration can be provided in the dialysis fluid. Examples of the sodium salt include, but not particularly limited to, sodium lactate, sodium citrate, sodium gluconate, sodium succinate, sodium malate, etc.,

as long as it is acceptable for the dialysis fluid. These sodium salts may be in the form of hydrates. Further, such sodium salts may be used alone or in combination of two or more kinds thereof.

[0056]

Examples of a source for potassium ions include potassium salts. Examples of the potassium salt formulated in the agent A include, but not particularly limited to, potassium chloride, potassium lactate, potassium citrate, potassium gluconate, potassium succinate, potassium malate, etc., as long as it is acceptable for the dialysis fluid. Among these potassium salts, potassium chloride is preferably used as a source for potassium because the chloride ion is the most physiological substance. These potassium salts may be in the form of hydrates. Further, such potassium salts may be used alone or in combination of two or more kinds thereof.

[0057]

Examples of a source for chloride ions include chloride salts. Examples of the chloride salt formulated in the agent A include, but not particularly limited to, calcium chloride, magnesium chloride, potassium chloride, etc., as long as it is acceptable for the dialysis fluid. These chloride salts are preferably used because their water-solubility is high and they can achieve the role as the source for potassium, magnesium or potassium. These chloride salts may be in the form of hydrates. Further, such chloride salts may be used alone or in combination of two or more kinds thereof. In addition, hydrochloric acid that also serves as a pH adjusting agent can also be used as a source for chloride ions.

[0058]

As described above, the electrolyte component to be incorporated into the agent A may be in the form of a hydrate, but preferably in the form of an anhydride from the

viewpoint of more effectively reducing the acetic acid odor and improving the storage stability.

[0059]

The kind and the combination of the electrolyte components to be formulated in the agent A are appropriately set according to the composition of ions to be contained in the finally prepared dialysis fluid, but preferred examples of the electrolyte component contained in the agent A (neither acetic acid nor acetate salt) include the combination of magnesium chloride, calcium chloride, and potassium chloride. Further, when a combination of magnesium chloride, calcium chloride, and potassium chloride is used as an electrolyte component, it may further contain an organic acid salt (other than acetate salt). Examples of such organic acid salt include, for example, sodium lactate, sodium gluconate, sodium citrate, sodium malate, sodium succinate, and the like. These organic acid salts may be used alone or in combination of two or more kinds thereof.

[0060]

The content of each electrolyte component contained in the agent A is appropriately set depending on each ion concentration provided in the finally prepared dialysis fluid. Specifically, in view of the kind and content of acetate salts and the amount of the electrolyte components contained in the agent S and the agent B, the content of the electrolyte components (neither acetic acid nor acetate salt) contained in the agent A may be appropriately set in such a manner that the finally prepared dialysis fluid will satisfy each ion concentration as shown below in Table 2.

[0061]

[Table 2]

|                                 | Concentration in dialysis fluid         |
|---------------------------------|-----------------------------------------|
| In the case of sodium ions      | 120~150 mEq/L, preferably 135~145 mEq/L |
| In the case of potassium ions   | 0.5~3 mEq/L, preferably 1.5~2.5 mEq/L   |
| In the case of calcium ions     | 1.5~4.5 mEq/L, preferably 2.5~3.5 mEq/L |
| In the case of magnesium ions   | 0~2.0 mEq/L, preferably 0.5~1.5 mEq/L   |
| In the case of citrate ions     | 0~18 mEq/L, preferably 0~3 mEq/L        |
| In the case of chloride ions    | 90~135 mEq/L, preferably 100~120 mEq/L  |
| In the case of lactate ions     | 0~10 mEq/L                              |
| In the case of malate ions      | 0~10 mEq/L                              |
| In the case of gluconate ions   | 0~10 mEq/L                              |
| In the case of succinate ions   | 0~10 mEq/L                              |
| In the case of bicarbonate ions | 20~40 mEq/L, preferably 25~35 mEq/L     |

[0062]

In addition, the above Table 2 shows each concentration of ions that include ions derived from acetate salts, and the amount of the electrolyte component contained in the agent A is also determined by taking into consideration the amount of ions supplied from the acetate salts. Further, the amount of the electrolyte component (other than sodium acetate) serving as a source for sodium contained in the agent A is determined so as to satisfy the sodium ion concentration shown in the above Table 2 described above, after taking into consideration the amount of sodium supplied from sodium hydrogen carbonate in the dialysis agent B and the amount of sodium supplied from sodium acetate when sodium acetate is used as the acetate salt.

[0063]

For example, when the agent A contains acetic acid and sodium acetate, as well as potassium chloride, magnesium chloride, and calcium chloride as other electrolyte

components, the proportion of potassium chloride is set to 0.08 to 1.5 mol, preferably to 0.3 to 1.25 mol; magnesium chloride to 0 to 0.5 mol, preferably 0.05 to 0.38 mol; and calcium chloride to 0.13 to 1.13 mol, preferably 0.25 to 0.88 mol, per 1 mol based on the total moles of acetic acid and sodium acetate, so that each ion concentration contained in the dialysis fluid satisfies the range shown in the above Table 1.

[0064]

In addition, for the purpose of maintaining the blood sugar level of the patient, glucose in addition to the electrolyte components described above is included in the agent A. The glucose content in the agent A is appropriately set depending on glucose concentration to be provided in the finally prepared dialysis fluid. Specifically, the content of glucose in the agent A is appropriately set depending on the glucose concentration provided in the finally prepared dialysis fluid. Specifically, the content of glucose in the dialysis agent A may be appropriately set so that the glucose concentration in the finally prepared dialysis fluid is 0 to 2.5 g/L, preferably 1.0 to 2.0 g/L.

[0065]

The agent A is prepared in such a manner that the finally prepared dialysis fluid has a reasonable pH range by containing acetic acid and acetate salt at a predetermined ratio, but it may separately contain a pH adjusting agent, if necessary. Examples of the pH adjusting agent that can be used in the dialysis agent A include, but not particularly limited to, liquid acids (e.g. hydrochloric acid, lactic acid, gluconic acid, etc.), solid acids (e.g. citric acid, succinic acid, fumaric acid, malic acid, glucono-delta-lactone, etc.), and their sodium, potassium, calcium, magnesium salts and the like, as long as it is acceptable for the dialysis fluid. Among these pH adjusting agents, an organic acid is preferably used. The pH adjusting agent may be used alone

or in combination of two or more kinds thereof. Further, when such a pH adjusting agent is allowed to be included in the dialysis agent A, the content thereof may be appropriately set so that the pH adjusting agent is able to satisfy the pH of the liquid A that will be described later and is obtained by dissolving the solid agent A in water, or of the liquid agent A, and the pH of the dialysis fluid that is finally obtained.

[0066]

The dosage form of the agent A is not particularly limited, and may be either solid or liquid form. As used herein, the solid dialysis agent A may also be referred to as “solid agent A”, and the liquid dialysis agent A may also be referred to as “liquid agent A”. The solid agent A is preferred as the dosage form of the agent A, from the viewpoint of space saving, and alleviation of a burden of the workers.

[0067]

The shape of the solid agent A is not particularly limited, but includes, for example, powders, granules, and the like. Each component content in the solid agent A can be appropriately set so as to satisfy each ion concentration in the dialysis fluid described above.

[0068]

In addition, as for each component content in the liquid agent A, it is not particularly limited, but may be concentrated to, for example, 150 to 200 times, preferably 170 to 180 times the concentration of each component in the finally prepared dialysis fluid.

[0069]

The dialysis agent A does not cause corrosion of the dialysis fluid preparation apparatus and the dialysis machine and ensures the safety in case of contact with the skin of workers in the clinical or manufacturing settings or in patients with dialysis at

home, because acetic acid and acetate salt satisfy the above-mentioned ratio so that the pH of the liquid A obtained by dissolving the solid agent A in water or the pH of the liquid agent A is about 4.

[0070]

As for the pH of the liquid A obtained by dissolving the solid agent A in water or of the liquid agent A, more concretely, examples of the dialysis agent A include those that exhibit a pH of typically 3.9 to 4.7, preferably 4.1 to 4.4, and more preferably about 4.3 after made into an aqueous solution concentrated to 175 times the concentration of each component in the finally prepared dialysis fluid (hereinafter referred to as “175-fold concentrated agent A solution”). Here, the pH of the 175-fold concentrated agent A solution is a value measured at 25°C.

[0071]

By satisfying the above-mentioned pH range with the agent A, it is possible to further enhance the stability of glucose. It is said that glucose is generally most stable around pH 3 (Shokuhin Seibun no Sougosayo (The Interaction between Food components), publisher: Shoichi NOMA, pages 5-15, editor: Mitsuo NAMIKI, Setsuro MATSUSHITA, issued May 1, 1980), the reason of which has been confirmed that glucose is very stable in the agent A because glucose in the agent A satisfies the ratio of acetic acid:acetate salt of 1:0.5 to 2, and the total acetate ion concentration of the finally prepared dialysis fluid is set to be 6 mEq/L or less.

[0072]

Further, by satisfying the above-mentioned pH range with the agent A, it is also possible to effectively reduce the acetic acid odor. If the amount of the acetate salt in the liquid agent A is more than 2 mol per 1 mol of acetic acid, the acetic acid odor tends to increase. Also, if the amount of the acetate salt in the solid agent A is smaller than

0.5 mol per 1 mol of acetic acid, and the pH is lower than the above-mentioned pH range, the acetic acid odor tends to increase.

[0073]

From the viewpoint of exerting more improved effects, such as reduction in acetic acid odor, and storage stability of glucose, the agent A is preferably one wherein the molar ratio of acetic acid:acetate salt is 1:0.5 to 2, the total acetate ions in the formation of the dialysis fluid are set to 2 mEq/L or higher but less than 6 mEq/L, and the pH of the 175-fold concentrated agent A solution is 3.9 to 4.7; more preferably one wherein the molar ratio of acetic acid:acetate salt is 1:0.75 to 1.5 (more preferably 1:1 to 1.5), the total acetate ion in the formation of the dialysis fluid are set to 2 mEq/L or higher but 5.5 mEq/L or less, and the pH of the 175-fold concentrated agent A solution is 4.1 to 4.4; and especially preferably one wherein the molar ratio of acetic acid:acetate salt is 1:1 to 1.25, the total acetate ion in the formation of a dialysis fluid are set to 2 mEq/L or higher but 5 mEq/L or less, and the pH of the 175-fold concentrated agent A solution is about 4.3.

[0074]

If the agent A is a solid agent A, it is possible to reduce the acetic acid odor more effectively and further improve the storage stability more effectively by reducing the moisture content.

[0075]

The production method of the agent A is not particularly limited, but is appropriately set according to the dosage form, and a suitable production method will be described below, separately for the solid agent A and the liquid agent A.

[0076]

Examples of a suitable production method of the solid agent A include a

production method comprising a first step of mixing acetic acid and acetate salt and a second step of mixing the mixture obtained in the first step, with other formulation components.

[0077]

By preparing in advance a mixture of acetic acid and acetate salt (hereinafter, referred to as a first material in some cases) in the first step, it becomes possible to significantly reduce the acetic acid odor of the solid agent A that is finally obtained. Especially, in the case of using anhydrous sodium acetate, a more effective suppression of the acetic acid odor becomes possible, and thus it is preferred to use glacial acetic acid as the acetic acid and anhydrous sodium acetate as the acetate salt in the production of the solid agent A.

[0078]

Further, the total amount of the acetate salt contained in the solid agent A may be supplied to the preparation of the mixture in the first step, or a portion of the acetate salts contained in the solid agent A may be supplied to the preparation of the mixture in the first step and the remainder of the acetate salt may be mixed in the second step. Of the acetate salts contained in the solid agent A, the amount of the acetate salt to be supplied to the first step is not particularly limited, but, for example, it is usually 20 to 100 parts by weight, preferably 50 to 100 parts by weight, per 100 parts by weight of the total amount of acetate salts contained in the solid agent A.

[0079]

Furthermore, the total amount of the acetic acid contained in the solid agent A may be supplied to the preparation of the mixture in the first step, or a portion of the acetic acid contained in the solid agent A may be supplied to the preparation of the mixture in the first step and the remainder of the acetic acid may be mixed in the second

step. The acetic acid odor can be more effectively reduced as the amount of acetic acid contained in the solid agent A is increasingly supplied to the first step, and it is preferable to supply the total amount of acetic acid contained in the solid agent A to the first step. Of the acetic acid contained in the solid agent A, specifically, the amount of acetic acid to be supplied to the first step is usually 50 to 100 parts by weight, preferably 75 to 100 parts by weight, and more preferably 100 parts by weight, per 100 parts by weight of the total amount of acetic acid contained in the solid agent A.

[0080]

The method of mixing acetic acid and acetate salt in the first step is not particularly limited, but a mixing method performed under low moisture conditions, such as mixing under heating, drying, and blowing, and treatment under reduced pressure, etc., is preferred from the viewpoint of reducing the acetic acid odor more effectively.

[0081]

The mixture obtained in the first step, which has a low moisture content, emits the acetic acid odor only slightly in a low humidity environment, but tends to emit a strong acetic acid odor when the moisture content is large or in high humidity environments. In this regard, it is possible to more suppress the acetic acid odor by lowering the moisture content of the mixture in the manufacturing process or the humidity during storage. For example, it is possible to remove the moisture content by heating sodium acetate to 50 to 150°C so that the moisture content is sufficiently reduced or by adding a moisture adsorbent such as molecular sieves to glacial acetic acid. It becomes possible to obtain a mixture with low acetic acid odor by mixing these under conditions of 60% RH or less, preferably 50% RH or less, and more preferably 40% RH or less (at 25°C for all cases). Further, the effect of suppressing

the acetic acid odor can be further improved by using a means for removing such excess moisture, such as heating to 30 to 90°C when mixed, blowing a dry air with low absolute humidity of, for example, 1.5 g/m<sup>3</sup> or less, or reducing the pressure, or by temporal storage in a sealed container after mixing or optional warming after mixing.

[0082]

In the second step, the solid agent A is prepared by mixing the first material obtained in the first step with other components. In the second step, the mixing of the mixture obtained in the first step with other components may also be a simple mixing, or may be performed using wet granulation and dry granulation, such as agitating granulation, fluidized bed granulation, tumbling fluidized bed granulation, and pressure granulation.

[0083]

In the second step, each of other components to be mixed may be mixed individually with the first material, or a composition comprising some or all of the other components to be mixed may be previously prepared and then the composition may be mixed with the first material. Preferably, there is exemplified a method wherein a composition containing an electrolyte component (neither acetic acid nor acetate salt) and an acetate salt as needed (hereinafter also referred to as the second material) is previously prepared and then mixed with the first material. In the case of allowing an organic acid salt to be contained in the dialysis agent A of the present invention, the organic acid salt is preferably contained in the second material. Further, the glucose may be contained in the second material, or may be mixed as a third material, with being separated from the first material and the second material, with the first material and the second material. In addition, some of glucose may be contained in the second material and the remainder may be mixed as a third material. Furthermore, in the case

of mixing a portion of the acetic acid in the second step, the acetic acid may be mixed with the second material, but may be mixed as a fourth material, with being separated from the first material, the second material and the optional third material. In addition, the organic acid other than acetic acid may be contained in at least one of the second material, the third material, and the fourth material, or may be mixed as a fifth material, with being separated from these materials.

[0084]

Further, the composition subjected to the second step as the second material needs to be in the state of a mixture containing each electrolyte components, and is preferably in the state of granules. The method for producing a second material in the state of granules is not particularly limited, but examples include the following method. In the case of producing granules (second material) containing potassium chloride, calcium chloride, and magnesium chloride as the electrolyte components, an aqueous solution of at least a portion of calcium chloride and magnesium chloride, and the remainder as a powder are added to potassium chloride; the mixture is mixed under heating at 50 to 90°C; optional other components (organic acid salts, glucose etc.) are added thereto; and further mixing is performed under heating to form granules. Further, in the formation of the granules, calcium chloride and magnesium chloride in the form of powder may be added instead of adding an aqueous solution of calcium chloride and magnesium chloride, and a suitable amount of water may be added before or after the addition of such powdery calcium chloride and magnesium chloride. Note that the granules should be preferably dried thoroughly, regardless of which granulation operation is employed. In addition, magnesium chloride and calcium chloride in the form of anhydride may be used, or dehydrated products obtained by drying their hydrates may also be used.

[0085]

As a preferred embodiment of the second step, there is exemplified a method wherein a first material (a mixture of acetic acid and acetate salt, a second material (a composition containing an electrolyte which is neither acetic acid nor acetate salt), a third material (glucose), an optional fourth material (acetic acid), and an optional fifth material (an organic acid other than acetic acid) are mixed under a low humidity condition (60% RH or less, preferably 50% RH or less, and more preferably 40% RH or less (at 25°C in all cases)). At the time of mixing in the second step, similarly to the first step, a suppression effect on the reduction of the acetic acid odor can be more enhanced by using the means for removing the excess moisture, such as heating to 30 to 90°C, blowing of a dry air having a low absolute humidity, or reducing the pressure. From the viewpoint of more reducing the acetic acid odor of the solid agent A to be manufactured, it is preferred that the first material, the second material, and the third material are in the state of low moisture content. Examples of such a method of reducing the moisture content in this way include a method comprising drying in advance each raw material to be supplied to the second step, at 90 to 140°C and cooling the dried material by a cold air having an absolute humidity of 1.5 g/m<sup>3</sup> or less.

[0086]

Also, as mentioned above, since the alkali metal diacetate is a complex of acetic acid and acetate salt, it is possible to use the alkali metal diacetate as a mixture of acetic acid and acetate salt of the first material. In addition, the alkali metal diacetate may be a commercially available product, or those obtained by a known method (for example, a reaction product of acetic acid and an alkali metal hydroxide, a reaction product of acetic acid and an alkali metal carbonate, and an impregnated product of an alkali metal acetate with acetic acid).

[0087]

The solid agent A thus produced is optionally subjected to a drying treatment and is then provided as being accommodated in a packaging container. The packaging container used for packaging the solid agent A includes, for example, a flexible bag and a hard bottle. As the packaging container, it specifically includes silica vapor deposition laminated bag, aluminum vapor deposition laminated bag, aluminum oxide vapor deposition laminated bag, aluminum laminate bag, polyethylene hard bottle, and the like. Especially, a packaging bag formed with use of a metal foil such as an aluminum foil (aluminum laminated bag, etc.) can keep water vapor transmission at a low level and suppress more effectively acetic acid from being volatilized and moisture absorption from the environment. In addition, the water vapor transmission of these packaging containers is preferably  $0.5 \text{ g/m}^2 \cdot 24 \text{ h}$  ( $40^\circ\text{C}$ , 90% RH) or less, and more preferably  $0.2 \text{ g/m}^2 \cdot 24 \text{ h}$  ( $40^\circ\text{C}$ , 90% RH) or less from the viewpoint of reducing the acetic acid odor more effectively. The water vapor transmission is a value measured according to the measurement method specified in JIS Z0208 “Testing Methods for Determination of the Water Vapor Transmission Rate of Moisture-Proof Packaging Materials (Dish Method)”.

[0088]

Furthermore, in order to more effectively reduce moisture content of the solid agent A to be accommodated in the packaging container, a desiccant may be accommodated in the packaging container together with the solid agent A. The desiccant is not particularly limited, but includes, for example, zeolite, magnesium sulfate, sodium sulfate, silica gel, alumina, and the like. When the desiccant is accommodated in a packaging container, the desiccant may be combined into a part of the plastic (for example, polyethylene layers) constituting the container and such a

container may be used, or a space (a separate room) to accommodate the desiccant in the packaging container may be provided. Further, the desiccant being in a state where it is placed in a nonwoven fabric so as not to mix with the solid agent A may be accommodated in a packaging container.

[0089]

The liquid agent A is prepared by weighing out a predetermined amount of acetic acid, an acetate salt, other electrolytes, and glucose, and dissolving them in water while mixing. In addition, the liquid agent A can also be prepared by dissolving in water a predetermined amount of the solid agent A described above. Further, after dissolving each component in water, they may be subjected, if necessary, to a treatment such as filtration and the like.

[0090]

The liquid agent A thus prepared is accommodated in a packaging container and then provided. The packaging container used for packaging the liquid agent A includes, for example, plastic containers, such as polyethylene bottles and the like.

[0091]

#### Preparation of Dialysis Fluid

A dialysis fluid is prepared through the step of adding/mixing the desired amounts of the above-described agent S, agent B and agent A, as well as water, if necessary.

[0092]

In the preparation of a dialysis fluid using the dialysis agent of the present invention, water is added as necessary in order to adjust the concentrations of the components of the eventually obtained dialysis fluid. Water used when preparing a dialysis fluid from the three-pack type dialysis agent of the present invention may be

purified to such an extent that it is pharmacologically acceptable. Specifically, water needs to satisfy the quality of purified water defined by The Japanese Pharmacopoeia. For example, water for use in the preparation of a dialysis fluid is prepared by subjecting tap water or ground water to activated carbon treatment, softening treatment, or the like for pretreatment, and then subjecting the pretreated water to purification treatment by reverse osmosis membrane filtration, distillation, ultrafiltration, or the like. Also, water used when preparing a dialysis fluid may be commercially available purified water or distilled water.

[0093]

Further, the pH of the dialysis fluid prepared by the three-pack type dialysis agent of the present invention is not particularly limited as long as it satisfies the range that is acceptable as a dialysis fluid, but it is preferably 7.2 to 7.6, more preferably 7.3 to 7.5, especially preferably 7.3 to 7.4, in view of avoiding the risk of excessive correction of acidosis of dialysis patients. The agent A used in the present invention is set to be able to prepare a dialysis fluid within the above pH range by the buffering action of acetic acid- acetate salt as a result of satisfying a specific composition with a source of acetic acid and acetate salt in addition to the buffering action of bicarbonate.

[0094]

The bicarbonate ion concentration in the dialysis fluid that is prepared with the three-pack type dialysis agent of the present invention may be set so as to be within the range of 20 to 40 mEq/L, preferably 25 to 35 mEq/L, more preferably 27 to 33 mEq/L, during dialysis. Also, the total acetate ion concentration and other ion concentration of the dialysis fluid prepared by the three-pack type dialysis agent of the present invention are as described above.

[0095]

With the three-pack type dialysis agent of the present invention, a dialysis fluid wherein the concentration of bicarbonate ions and each concentration of other ions are maintained at a constant level (constant ion concentration type) can also be prepared. Also, a dialysis fluid in which bicarbonate ion concentration and/or sodium ion has been freely changed while maintaining the ion concentrations of potassium, calcium, magnesium, etc. at a constant level can be prepared (variable ion concentration type). [0096]

#### Preparation of Constant Ion Concentration Type of Dialysis Fluid

Preparation of a constant ion concentration type of dialysis fluid is carried out by mixing the agents S, B, and A, and optionally water collectively or intermittently or continuously while maintaining each addition amount at a constant level based on the total amount of the finally obtained dialysis fluid. Also, when preparing the constant ion concentration type of dialysis fluid, the agents A, B, and S may be mixed in any order. For example, by previously preparing a concentrated solution A by dissolving the agents S and A at the same time, the resulting general two-pack type dialysis agent comprising the concentrated solution A and the agent B can also be used for the preparation of a constant ion concentration type of dialysis fluid.

[0097]

#### Preparation of Variable Ion Concentration Type of Dialysis Fluid

Preparation of a variable ion concentration type of dialysis fluid is carried out by appropriately controlling the amounts of the agents S, B, and A to be added. For example, by controlling the addition amount of the agent B while maintaining the proportion of the addition amount of the agent A at a constant level based on the total amount of the finally obtained dialysis fluid, it is also possible to freely change the bicarbonate ion concentration while maintaining the ion concentrations of trace metals

such as potassium, calcium, magnesium, etc. in the dialysis fluid at a constant level. Further, by controlling the addition amount of the agent S while maintaining the proportion of addition amount of the agent A at a constant level based on the total amount of the finally obtained dialysis fluid, the concentration of sodium ions can also be freely changed while maintaining the ion concentration of trace metals in the dialysis fluid at a constant level. Furthermore, by controlling the addition amounts of the agents S and B while maintaining the proportion of addition amount of the agent A at a constant level based on the total amount of the finally obtained dialysis fluid, both the bicarbonate ion concentration and sodium ion concentration can be varied while maintaining the ion concentration of trace metals in the dialysis fluid at a constant level, or it is also possible to change one while maintaining the other at a constant level.

[0098]

Specifically, the bicarbonate ion concentration in the dialysis fluid can be set within the aforementioned range individually according to the disease state of a patient and, for example, may be set so as to be at a constant level or may be set so as to change within the aforementioned range during dialysis treatment. The disease state of a patient as referred to herein includes, for example, the degree of metabolic acidosis, the nutritional status, and the condition during dialysis of a patient.

[0099]

The bicarbonate ion concentration in the dialysis fluid is changed, for example, in the following manners (1) to (8):

- (1) Lower the bicarbonate ion concentration from the beginning to the end of dialysis treatment;
- (2) Raise the bicarbonate ion concentration from the beginning to the end of dialysis treatment;

- (3) Lower the bicarbonate ion concentration from the beginning to halfway through dialysis treatment, and then maintain the bicarbonate ion concentration at a constant level to the end;
- (4) Raise the bicarbonate ion concentration from the beginning to halfway through dialysis treatment, and then maintain the bicarbonate ion concentration at a constant level to the end;
- (5) Maintain the bicarbonate ion concentration at a constant level from the beginning to halfway through dialysis treatment, and then raise the bicarbonate ion concentration level to the end;
- (6) Maintain the bicarbonate ion concentration at a constant level from the beginning to halfway through dialysis treatment, and then lower the bicarbonate ion concentration to the end;
- (7) Lower the bicarbonate ion concentration from the beginning to halfway through dialysis treatment, and then raise the bicarbonate ion concentration to the end; and
- (8) Raise the bicarbonate ion concentration from the beginning to halfway through dialysis treatment, and then lower the bicarbonate ion concentration to the end.

These manners of changing the bicarbonate ion concentration are merely illustrative, and needless to say, the bicarbonate ion concentration may be continuously, stepwise, intermittently, or repetitively changed during dialysis in a manner different from (1) to (8) above according to the disease state or physiological condition of a patient.

[0100]

In addition, the sodium ion concentration in the dialysis fluid may be set to a constant value within the above range according to the disease state of individual patients or the patient's conditions during dialysis, or may be set so as to change within

the above range during dialysis.

[0101]

For example, it is in some cases difficult to sufficiently drain water from patients who are likely to be overhydrated, such as hypotensive patients and patients suffering diabetes, with the sodium ion concentration (140 mEq/L) of a dialysis fluid that is now widely used. For such patients, a high-sodium dialysis fluid having a sodium concentration of about 145 to 160 mEq/L is sometimes used. High-sodium dialysis raises plasma osmolarity, efficiently draws intracellular water into the blood, and increases the circulating plasma volume, and is thus thought to be useful to prevent a blood-pressure decrease during dialysis, but high-sodium dialysis is problematic in that it increases the body weight due to thirst during an interdialysis period, and therefore, a method that sets the sodium ion concentration at a high level at the beginning of dialysis and lowers the sodium ion concentration in a stepwise manner thereafter, a method that alternately switch between a high sodium concentration and a proper or low sodium concentration at a specific interval, and the like are more preferable for patients because such a method makes it possible to change the sodium ion concentration according to the patient and at the same time change the bicarbonate ion concentration.

[0102]

The conditions for preparing a variable ion concentration type of dialysis fluid using the three-pack type dialysis agent is disclosed in detail in Patent Document 7, and detailed conditions for preparing a variable ion concentration type of dialysis fluid using the three-pack type dialysis agent of the present invention may be appropriately set by referring to the disclosure of Patent Document 7. Moreover, in the preparation of a variable ion concentration type of dialysis fluid, it is desirable to set in advance the kind

of ions to be changed and the concentration change according to the patient's conditions before the dialysis treatment.

[0103]

Preparation of a dialysis fluid using the three-pack type dialysis agent of the present invention can be carried out using a dialysis fluid preparation apparatus in which the agents B, S, and A, and optionally added water can be mixed together at a predetermined ratio. Also, when the bicarbonate ion concentration in the dialysis fluid is allowed to change over time, a dialysis fluid preparation apparatus with means for controlling the addition amount of the agent B or with means for controlling the ratio between the addition amounts of the agent S and the agent B may be used. Such a dialysis fluid preparation apparatus is shown in Patent Document 7 and is publicly known.

## EXAMPLES

[0104]

Hereinafter, the present invention is specifically described by way of Examples. However, the present invention is not to be construed as being limited to the following.

[0105]

### Test Example 1

#### (1) Preparation of Liquid Agent A

Potassium chloride 2.61 g, calcium chloride hydrate 3.86 g, magnesium chloride hydrate 1.78 g, glucose 17.50 g, glacial acetic acid (a predetermined amount shown in Table 3), and anhydrous sodium acetate (a predetermined amount shown in Table 3) were dissolved in water to prepare a total volume of 100 mL of a liquid dialysis agent A. The liquid dialysis agent A is one in a state of an aqueous solution

(potassium ion concentration of 350 mEq/L) that was concentrated to 175 times the concentration of each component in the finally prepared dialysis fluid.

[0106]

[Table 3]

|                       | Glacial acetic acid (g) | Sodium acetate (g) | Molar ratio of acetic acid : sodium acetate |
|-----------------------|-------------------------|--------------------|---------------------------------------------|
| Comparative Example 1 | 2.10                    | 0                  | 1:0                                         |
| Example 1             | 2.10                    | 1.44               | 1:0.5                                       |
| Example 2             | 2.10                    | 2.87               | 1:1                                         |
| Example 3             | 2.10                    | 4.31               | 1:1.5                                       |
| Example 4             | 2.10                    | 5.74               | 1:2                                         |
| Comparative Example 2 | 2.10                    | 8.61               | 1:3                                         |

[0107]

(2) Evaluation of pH, Volatilized Acetic Acid Concentration, Amount of 5-HMF, and Corrosiveness of Liquid Agent A

The pH of each liquid agent A was measured. The pH was measured at a liquid temperature of 25°C by using a pH meter (manufacturer: Horiba, Ltd.; model number: F-73).

[0108]

The concentration of volatilized acetic acid of each liquid agent A obtained above was measured in the following manner. Specifically, each liquid agent A was accommodated in an Erlenmeyer flask, allowed to stand for 15 minutes to set a gas detector tube for the acetic acid measurement over the liquid surface, and a fixed amount of a gaseous sample was passed through the gas detector tube so that the concentration of volatilized acetic acid was measured by a gas detector tube type gas measuring instrument (manufacturer: GASTEC CORPORATION, model number:

GV-100S).

[0109]

In addition, for each liquid agent A immediately after the preparation, the amount of 5-hydroxymethylfurfural (hereinafter referred to as 5-HMF) which is a degradation product of glucose was measured. Furthermore, the each liquid agent A was accommodated in a polyethylene bottle and stored at 40°C and 75% RH for one month, after which time the amount of 5-HMF was measured. With respect to the amount of 5-HMF, the absorbance of 5-HMF at the absorption wavelength (wavelength 284 nm) on the filtrate that was obtained by filtration with a 0.2 µm filter was measured using a spectrophotometer.

[0110]

In addition, corrosive properties of each liquid agent A obtained above to stainless steel were evaluated by the following method. Each liquid dialysis agent A 100 mL was placed in a 200 ml-transparent polystyrene container, and an almost half area of 40 mm × 100 mm of a stainless steel (SUS304) plate was allowed to stand to soak in the each liquid agent A, after which a lid was put on the transparent polystyrene container and the plate was left at room temperature for two months. Two months after the storage, the concentration of iron in the liquid agent A was measured. The measurement of iron concentration was performed according to the Method A that is defined in "General Tests 1. Chemical Methods 1.10 Iron Limit Test" of The Japanese Pharmacopoeia, Sixteenth Edition. Specific measurement conditions are as follows. An acetic acid-sodium acetate buffer 5 mL for iron limit test and an L-ascorbic acid solution 2 mL (1 g → 100 mL) were added to the liquid agent A 5 mL, then mixed, and allowed to stand for 30 minutes. Next, a solution 1 mL (0.25 g → 50 mL) of 2,2'-bipyridyl in ethanol (95) was added thereto, water was added thereto to accurately

make up a volume of 50 mL, and the mixture was allowed to stand for 30 minutes, thereby to obtain a sample solution. An iron standard solution 2 mL of the Japanese Pharmacopoeia (Japanese Pharmacopoeia 0.01 mg/mL) was used as the reference standard solution. For the sample solution and the standard solution, after a blank correction of the sample solution, the absorbance at an absorption wavelength (wavelength 522 nm) was measured using a spectrophotometer to calculate the iron concentration. The evaluation of corrosive properties was performed in  $n = 2$ , thereby to calculate the average value of iron concentration in the liquid agent A.

[0111]

The results obtained are shown in Table 4. As is clear from Table 4, the liquid agent A (Examples 1 to 4) having an acetic acid : sodium acetate molar ratio in the range of 1:0.5-2 shows a pH of 3.9 or more, and can be handled safely in clinical practice. Such liquid agent A has no fear of corrosion of the dialysis fluid preparation apparatus and the dialysis machine. On the other hand, in the liquid agent A having an acetic acid:sodium acetate molar ratio of 1:0 (Comparative Example 1), it showed a strong acidity of a pH less than 3, which is not sufficiently safe for handling.

[0112]

In the liquid agent A having an acetic acid : sodium acetate molar ratio of 1:0.5 to 2 (Examples 1 to 4), the volatilized acetic acid concentration was lower than that in Comparative Example 2, revealing that such liquid agent A has a dramatically reduced volatilized acetic acid concentration.

[0113]

In addition, the amount of 5-HMF that is the degradation product of glucose, in the liquid agent A (Examples 1 to 4) having an acetic acid:sodium acetate molar ratio of 1:0.5 to 2, was little. In particular, in the case of the molar ratio of 1:0.5 to 1.5

(Examples 1 to 3), the amount of 5-HMF was much less and thus the degradation of glucose was effectively suppressed. Although the conventional dialysis agent A (total acetic acid concentration of 8 mEq/L or higher in the dialysis fluid) can be improved in transportation costs and operability in hospitals if such dialysis agent A is concentrated to 175 times the concentration of each component in the finally prepared dialysis fluid, such concentrated conventional dialysis agent A is susceptible to each electrolyte component because of the electrolyte component which is neither sodium chloride nor sodium bicarbonate as well as glucose concentrated to a high level. In addition, when the total amount of acetic acid and acetate salt is increased, such effects increase and degradation of glucose is likely to be accelerated (see, for example, the results of Comparative Example 2). However, in the liquid agent A of Examples 1 to 4, it is considered that, since the acetate ion concentration in the finally prepared dialysis fluid is being set to be less than 6 mEq/L and thus the total amount of acetic acid and acetate salt is small, even 175-fold concentrated liquid agent A was able to effectively suppress the degradation of glucose.

[0114]

Furthermore, in the liquid agents A having an acetic acid:sodium acetate molar ratio of 1:0 (Comparative Examples 1), the iron concentration after storage was high, and corrosion of the stainless steel plate was in progress. In contrast, in the liquid agents A having a molar ratio of 1:0.5 to 2 (Examples 1 to 4), the iron concentration after storage was maintained at a low value, with which the corrosion of the dialysis fluid preparation apparatus and the dialysis machine can be suppressed.

[0115]

[Table 4]

|                       | Molar ratio of acetic acid:sodium acetate | pH of liquid dialysis agent A | Volatilized acetic acid concentration (ppm) | Amount of 5-HMF (absorbance of liquid agent A (284 nm)) |                                            | Corrosiveness (iron concentration in liquid agent A (mg/L)) |
|-----------------------|-------------------------------------------|-------------------------------|---------------------------------------------|---------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------|
|                       |                                           |                               |                                             | Before storage                                          | After one month storage at 40°C and 75% RH | After two months storage at room temperature                |
| Comparative Example 1 | 1:0                                       | 2.19                          | 76                                          | 0.0118                                                  | 0.1556                                     | 0.89                                                        |
| Example 1             | 1:0.5                                     | 3.94                          | 78                                          | 0.0102                                                  | 0.1627                                     | 0.28                                                        |
| Example 2             | 1:1                                       | 4.27                          | 81                                          | 0.0093                                                  | 0.1905                                     | 0.29                                                        |
| Example 3             | 1:1.5                                     | 4.49                          | 84                                          | 0.0088                                                  | 0.2337                                     | 0.24                                                        |
| Example 4             | 1:2                                       | 4.64                          | 82                                          | 0.0087                                                  | 0.3064                                     | 0.26                                                        |
| Comparative Example 2 | 1:3                                       | 4.90                          | 100                                         | 0.0087                                                  | 0.6878                                     | 0.18                                                        |

[0116]

### (3) Preparation and Evaluation of Bicarbonate Dialysis Fluid

A bicarbonate dialysis fluid was prepared by weighing each liquid dialysis agent A (2 mL) accurately, adding purified water thereto to a volume of 300 mL, adding a dialysis agent S (sodium chloride) (in a predetermined amount shown in Table 5) and 0.882 g of a dialysis agent B (sodium hydrogen carbonate) to the mixture (the bicarbonate ion concentration in the dialysis fluid was 30 mEq/L), and adding purified water thereto to accurately make a volume of 350 mL. All of the obtained bicarbonate dialysis fluids (the liquid dialysis agents A in Examples 1 to 4 and Comparative Examples 1 to 2 were used.) contain sodium ions of 140 mEq/L, potassium ions of 2 mEq/L, calcium ions of 3 mEq/L, and magnesium ions of 1 mEq/L. The pH and the ionized calcium concentration of the bicarbonate dialysis fluid obtained were measured. The pH was measured by using a pH meter (manufacturer: Horiba, Ltd.; model number: F-73) at a liquid temperature of 25°C and the ionized calcium concentration was

measured by using a blood gas analyzer cobas b121 (manufacturer: Roche Diagnostics).

[0117]

The total acetate ion concentration, pH, and ionized calcium concentration in the resulting bicarbonate dialysis fluid are shown in Table 6. The bicarbonate dialysis fluids prepared by using the liquid dialysis agents A of Examples 1 to 4 had a total acetate ion concentration of 2 mEq/L or higher but less than 6 mEq/L and maintained a suitable pH as dialysis fluid, and moreover maintained the ionized calcium concentration at a high level in comparison with Comparative Example 2.

[0118]

[Table 5]

|                       | Sodium chloride (g) |
|-----------------------|---------------------|
| Comparative Example 1 | 2.25                |
| Example 1             | 2.23                |
| Example 2             | 2.21                |
| Example 3             | 2.19                |
| Example 4             | 2.17                |
| Comparative Example 2 | 2.13                |

[0119]

[Table 6]

| Dialysis agent A used | Bicarbonate dialysis fluid              |      |                                        |
|-----------------------|-----------------------------------------|------|----------------------------------------|
|                       | Total acetate ion concentration (mEq/L) | pH   | Ionized calcium concentration (mmol/L) |
| Comparative Example 1 | 2                                       | 7.39 | 1.503                                  |
| Example 1             | 3                                       | 7.40 | 1.484                                  |
| Example 2             | 4                                       | 7.40 | 1.478                                  |
| Example 3             | 5                                       | 7.40 | 1.466                                  |
| Example 4             | 5.997                                   | 7.40 | 1.452                                  |
| Comparative Example 2 | 8                                       | 7.40 | 1.419                                  |

[0120]

## Test Example 2

### (1) Preparation of Solid Agent A

Potassium chloride 2.61 g, calcium chloride hydrate 3.86 g, magnesium chloride hydrate 1.78 g, and further water 0.53 g were added, mixed, and dried at 150°C to obtain an electrolyte composition. The electrolyte composition was mixed with glucose 17.50 g, acetic acid (a predetermined amount shown in Table 7), sodium diacetate (a predetermined amount shown in Table 7), and sodium acetate (a predetermined amount shown in Table 7) under stirring to obtain a solid dialysis agent A.

[0121]

[Table 7]

|                       | Kind and amount of components added as acetic acid and/or acetate salt |                                       |                                  | Molar ratio of acetic acid:sodium acetate |
|-----------------------|------------------------------------------------------------------------|---------------------------------------|----------------------------------|-------------------------------------------|
|                       | Sodium diacetate <sup>#1</sup> (g)                                     | Glacial acetic acid <sup>#2</sup> (g) | Sodium acetate <sup>#3</sup> (g) |                                           |
| Comparative Example 3 | 0                                                                      | 2.10                                  | 0                                | 1:0                                       |
| Example 5             | 2.49                                                                   | 1.05                                  | 0                                | 1:0.5                                     |
| Example 6             | 4.97                                                                   | 0                                     | 0                                | 1:1                                       |
| Example 7             | 4.97                                                                   | 0                                     | 1.44                             | 1:1.5                                     |
| Example 8             | 4.97                                                                   | 0                                     | 2.87                             | 1:2                                       |
| Comparative Example 4 | 0                                                                      | 2.10                                  | 8.61                             | 1:3                                       |

# 1 "Sodium diacetate" is a commercially available product (distributor: Wako Pure Chemical Industries, Ltd.).

# 2 "Glacial acetic acid" is a commercially available glacial acetic acid that is not in the form of sodium diacetate (distributor: Wako Pure Chemical Industries, Ltd.).

# 3 "Sodium acetate" is a commercially available powdered anhydrous sodium acetate that is not in the form of sodium diacetate (distributor: Wako Pure Chemical Industries, Ltd.).

[0122]

### (2) Evaluation of Solid Agent A

(pH of 175-fold Concentrated Agent A Solution)

A 175-fold concentrated agent A solution was prepared by dissolving in purified water each solid agent A obtained above, and concentrating the resulting solution to 175 times the concentration of each component in the finally prepared dialysis fluid. Specifically, the 175-fold concentrated agent A solution was prepared by dissolving the total amount of each solid agent A in purified water to make a volume of 100mL. The pH of the obtained 175-fold concentrated agent A solution was measured at a liquid temperature of 25°C by using a pH meter (manufacturer: Horiba, Ltd.; model number: F-73).

[0123]

(Volatilized Acetic Acid Concentration and 5-HMF Amount)

For each solid agent A, the total amount of each solid agent A obtained was accommodated in a polyethylene bag. Furthermore, this was accommodated in a packaging bag shown in Table 8, and the bag was sealed. Then, the solid agent A was stored for 2 months at 25°C and 60% RH, and 40°C and 75% RH.

[0124]

[Table 8]

| Notation of packaging bag    | Composition of packaging bag                                                                                                                                                                               |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PET/AL/PE bag                | A laminated bag (water vapor transmission is substantially 0 g/m <sup>2</sup> ·24h) made of a laminate wherein a polyethylene terephthalate film, an aluminum foil, and a polyethylene film are laminated. |
| PET/AL/PE bag + Zeolite (5%) | The PET/AL/PE bag in which 5 parts by weight of zeolite is added as a desiccant, per 100 parts by weight of a solid dialysis agent A to be accommodated therein.                                           |

[0125]

Before storage, after two weeks storage, and after one month storage, a detector tube was set in a polyethylene bag in which each solid agent A is accommodated, so that a fixed amount of a sample gas was passed through the detector tube for the

measurement of acetic acid, and the volatilized acetic acid concentration was measured by using a gas detector tube type gas measuring instrument (manufacturer: GASTEC CORPORATION, model number: GV-100S).

[0126]

Also, a 175-fold concentrated agent A solution was prepared by dissolving the total amount of each solid dialysis agent A obtained above before storage, after two weeks storage, and after one month storage, in purified water to 100 mL wherein such an agent A was concentrated to 175 times the concentration of each component in the finally prepared dialysis fluid. The amount of 5-HMF in the resulting 175-fold concentrated agent A solution was measured in the same manner as described above.

[0127]

The measurement results of pH of the 175-fold concentrated agent A solution are shown in Table 9, the measurement results of volatilized acetic acid concentration are shown in Tables 10 and 11, and the measurement results of the amount of 5-HMF are shown in Tables 12 and 13.

[0128]

In the 175-fold concentrated agent A solution prepared from the solid dialysis agent A (Comparative Example 3) having the molar ratio of acetic acid:acetate salt of 1:0, it had a low pH of about 2.2, was strongly acidic, failed to exhibit a sufficient safety for handling, and was such a formulation that raises concern for corrosion of the dialysis fluid preparation apparatus and the dialysis machine. Further, in the solid dialysis agent A of Comparative Example 3, the volatilized acetic acid concentration exceeded 1000 ppm that was an unacceptable level in the clinical practice. In addition, the absorbance at 284 nm of the absorption wavelength of 5-HMF was higher than that in other Examples during storage, and glucose was not able to be stably maintained.

Moreover, in spite of the molar ratio of 1:3 of acetic acid:acetate salt in the solid dialysis agent A of Comparative Example 4, the volatilized acetic acid concentration showed a high value of 900 ppm.

[0129]

In contrast, the 175-fold concentrated agent A solution prepared from the solid dialysis agent A (Examples 5 to 8) having the molar ratio of acetic acid:acetate salt within a range of 1:0.5 to 2 showed a pH of 3.9 or more, which can be handled safely in the clinical practice and will not cause the corrosion of the dialysis fluid preparation apparatus and the dialysis machine. Also, in the solid dialysis agent A of each of Examples 5 to 8, the volatilized acetic acid concentration was lower than that of each of Comparative Examples 3 and 4. Further, the 175-fold concentrated agent A solution prepared from the solid dialysis agent A (Examples 5 to 8) showed a sufficiently low value of the absorbance at a wavelength of 284 nm, which is the absorption wavelength of 5-HMF after preparation, as compared to Comparative Example 3, and thus glucose degradation was sufficiently suppressed. In particular, Examples 6 to 8 (acetic acid:acetate salt = 1:1 to 2) showed significantly lower values of the volatilized acetic acid concentration, and the absorbance at a wavelength of 284 nm.

[0130]

[Table 9]

| Solid dialysis agent A used | Molar ratio of acetic acid: sodium acetate | pH of 175-fold concentrated agent A solution |
|-----------------------------|--------------------------------------------|----------------------------------------------|
| Comparative Example 3       | 1:0                                        | 2.21                                         |
| Example 5                   | 1:0.5                                      | 3.96                                         |
| Example 6                   | 1:1                                        | 4.30                                         |
| Example 7                   | 1:1.5                                      | 4.52                                         |
| Example 8                   | 1:2                                        | 4.66                                         |
| Comparative Example 4       | 1:3                                        | 4.88                                         |

[0131]

[Table 10]

Measurement results of volatilized acetic acid concentration (ppm)

25°C, 60% RH

|                       | Before storage | After two weeks |                              | After one month |                              | After two months |                              |
|-----------------------|----------------|-----------------|------------------------------|-----------------|------------------------------|------------------|------------------------------|
|                       |                | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag    | PET/AL/PE bag + zeolite (5%) |
| Comparative Example 3 | >1000          | >1000           | >1000                        | >1000           | >1000                        | >1000            | >1000                        |
| Example 5             | 550            | 430             | 180                          | 900             | 300                          | Not measured     | 250                          |
| Example 6             | 5              | 50              | 45                           | 15              | 10                           | 20               | 20                           |
| Example 7             | 15             | 40              | 40                           | 5               | 30                           | 25               | 50                           |
| Example 8             | 5              | 45              | 20                           | 60              | 50                           | 30               | 10                           |
| Comparative Example 4 | 900            | 700             | 300                          | 400             | 250                          | 350              | 180                          |

[0132]

[Table 11]

Measurement results of volatilized acetic acid concentration (ppm)

40°C, 75% RH

|                       | Before storage | After two weeks |                              | After one month |                              | After two months |                              |
|-----------------------|----------------|-----------------|------------------------------|-----------------|------------------------------|------------------|------------------------------|
|                       |                | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag    | PET/AL/PE bag + zeolite (5%) |
| Comparative Example 3 | >1000          | >1000           | >1000                        | >1000           | >1000                        | >1000            | >1000                        |
| Example 6             | 5              | 80              | 50                           | 10              | 10                           | 10               | 20                           |
| Example 7             | 15             | 40              | 30                           | 20              | 50                           | 35               | 30                           |
| Example 8             | 5              | 60              | 45                           | 30              | 15                           | 10               | 20                           |
| Comparative Example 4 | 900            | 800             | 800                          | 400             | 150                          | 150              | 60                           |

[0133]

[Table 12]

Measurement results of 5-HMF (absorbance: 284 nm)

25°C, 60% RH

|                       | Before storage | After two weeks |                              | After one month |                              | After two months |                              |
|-----------------------|----------------|-----------------|------------------------------|-----------------|------------------------------|------------------|------------------------------|
|                       |                | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag    | PET/AL/PE bag + zeolite (5%) |
| Comparative Example 3 | 0.0218         | 0.1493          | 0.0895                       | 0.2152          | 0.5588                       | 0.5648           | 2.3978                       |
| Example 5             | 0.0192         | 0.0780          | 0.0695                       | 0.0418          | 0.0211                       | Not measured     | 0.0402                       |
| Example 6             | 0.0194         | 0.0209          | 0.0201                       | 0.0191          | 0.0211                       | 0.0333           | 0.0225                       |
| Example 7             | 0.0201         | 0.0220          | 0.0214                       | 0.0226          | 0.0181                       | 0.0228           | 0.0180                       |
| Example 8             | 0.0216         | 0.0240          | 0.0198                       | 0.0194          | 0.0207                       | 0.0231           | 0.0212                       |
| Comparative Example 4 | 0.0225         | 0.0269          | 0.0216                       | 0.0194          | 0.0203                       | 0.0220           | 0.0176                       |

[0134]

[Table 13]

Measurement results of 5-HMF (absorbance: 284 nm)

40°C, 75% RH

|                       | Before storage | After two weeks |                              | After one month |                              | After two months |                              |
|-----------------------|----------------|-----------------|------------------------------|-----------------|------------------------------|------------------|------------------------------|
|                       |                | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag   | PET/AL/PE bag + zeolite (5%) | PET/AL/PE bag    | PET/AL/PE bag + zeolite (5%) |
| Comparative Example 3 | 0.0218         | 3.9277          | 3.9139                       | 3.9233          | 3.9261                       | 3.9177           | 3.9229                       |
| Example 6             | 0.0194         | 0.0232          | 0.0233                       | 0.0332          | 0.0227                       | 0.0275           | 0.0273                       |
| Example 7             | 0.0201         | 0.0229          | 0.0207                       | 0.0219          | 0.0213                       | 0.0225           | 0.0229                       |
| Example 8             | 0.0216         | 0.0248          | 0.0242                       | 0.0226          | 0.0219                       | 0.0236           | 0.0244                       |
| Comparative Example 4 | 0.0225         | 0.0272          | 0.0270                       | 0.0306          | 0.0535                       | 0.1038           | 0.0398                       |

[0135]

### (3) Preparation of Dialysis Fluid

Two milliliters of 175-fold concentrated agent A solution prepared above was accurately weighed and purified water was added thereto to make a volume of about 300 mL. To the solution were added a dialysis agent S (sodium chloride) (in a predetermined amount shown in Table 14), a dialysis agent B (sodium hydrogen carbonate) 0.882 g (the bicarbonate ion concentration of the dialysis fluid was 30 mEq/L), and purified water to accurately make a volume of 350 mL, thereby to prepare a bicarbonate dialysis fluid. Any of the obtained bicarbonate dialysis fluids (solid agents A of Examples 5 to 8 and Comparative Examples 3 to 4 were used) contains sodium ions of 140 mEq/L, potassium ions of 2 mEq/L, calcium ions of 3 mEq/L, and magnesium ions of 1 mEq/L.

[0136]

[Table 14]

|                       | Sodium chloride (g) |
|-----------------------|---------------------|
| Comparative Example 3 | 2.25                |
| Example 5             | 2.23                |
| Example 6             | 2.21                |
| Example 7             | 2.19                |
| Example 8             | 2.17                |
| Comparative Example 4 | 2.13                |

[0137]

Also, the total acetate ion concentrations in the resulting bicarbonate dialysis fluids (using the solid agents A of Examples 5 to 8 and Comparative Examples 3 to 4) are shown in Table 15, and it was confirmed that the bicarbonate dialysis fluid prepared by using the solid agent A having a molar ratio of acetic acid:sodium acetate of 1:0.5 to 2 was able to satisfy the total acetate ion concentration within a range of 2 mEq/L or higher but less than 6 mEq/L.

[0138]

[Table 15]

| Solid agent A used    | Molar ratio of acetic acid:sodium acetate | Total acetate ion concentration in bicarbonate dialysis fluid (mEq/L) |
|-----------------------|-------------------------------------------|-----------------------------------------------------------------------|
| Comparative Example 3 | 1:0                                       | 2                                                                     |
| Example 5             | 1:0.5                                     | 3                                                                     |
| Example 6             | 1:1                                       | 4                                                                     |
| Example 7             | 1:1.5                                     | 5                                                                     |
| Example 8             | 1:2                                       | 5.997                                                                 |
| Comparative Example 4 | 1:3                                       | 8                                                                     |

[0139]

Test Example 3

### (1) Preparation of Solid Agent A

#### (Example 9)

Potassium chloride 2.61 g, calcium chloride hydrate 3.86 g, magnesium chloride hydrate 1.78 g, and further water 0.53 g were added, mixed, and dried at 150°C to obtain an electrolyte composition. Further, separately, glacial acetic acid 0.105 kg and anhydrous sodium acetate 0.144 kg were mixed to give an acetic acid/sodium acetate mixture. The electrolyte composition was mixed with glucose 17.50 g, sodium diacetate 3.48 g, and a mixture 1.49 g of acetic acid and sodium acetate under stirring to obtain a solid dialysis agent A. The molar ratio of acetic acid:sodium acetate in the obtained solid dialysis agent A is 1:1.

[0140]

#### (Example 10)

Potassium chloride 2.61 g, calcium chloride hydrate 3.86 g, magnesium chloride hydrate 1.78 g, and further water 0.53 g were added, mixed, and dried at 150°C to obtain an electrolyte composition. Further, separately, glacial acetic acid 0.105 kg and anhydrous sodium acetate 0.144 kg were mixed to give an acetic acid/sodium acetate mixture. The electrolyte composition was mixed with glucose 17.50 g, sodium diacetate 2.49 g, and a mixture 2.49 g of acetic acid and sodium acetate under stirring to obtain a solid dialysis agent A. The molar ratio of acetic acid:sodium acetate in the obtained solid dialysis agent A is 1:1.

[0141]

#### (Example 11)

Potassium chloride 2.61 g, calcium chloride hydrate 3.86 g, magnesium chloride hydrate 1.78 g, and further water 0.53 g were added, mixed, and dried at 150°C to obtain an electrolyte composition. Further, separately, glacial acetic acid 0.105 kg

and anhydrous sodium acetate 0.144 kg were mixed to give an acetic acid/sodium acetate mixture. The electrolyte composition was mixed with glucose 17.50 g, sodium diacetate 0.99 g, and a mixture 3.98 g of acetic acid and sodium acetate under stirring to obtain a solid dialysis agent A. The molar ratio of acetic acid:sodium acetate in the obtained solid dialysis agent A is 1:1.

[0142]

(Example 12)

Potassium chloride 2.61 g, calcium chloride hydrate 3.86 g, magnesium chloride hydrate 1.78 g, and further water 0.53 g were added, mixed, and dried at 150°C to obtain an electrolyte composition. Further, separately, glacial acetic acid 0.105 kg and anhydrous sodium acetate 0.144 kg were mixed to give an acetic acid/sodium acetate mixture. The electrolyte composition was mixed with glucose 17.50 g and a mixture 4.97 g of acetic acid and sodium acetate under stirring to obtain a solid dialysis agent A. The molar ratio of acetic acid:sodium acetate in the obtained solid dialysis agent A is 1:1.

[0143]

For each solid dialysis agent A (Examples 9 to 12), the kind and amount of the components added as acetic acid and/or acetate salt, and the molar ratio of acetic acid:sodium acetate are shown in Table 16.

[0144]

[Table 16]

|            | Kind and amount of components added as acetic acid and/<br>or acetate salt |                               |                                  | Molar ratio of acetic<br>acid:sodium acetate |
|------------|----------------------------------------------------------------------------|-------------------------------|----------------------------------|----------------------------------------------|
|            | Sodium diacetate <sup>#1</sup> (g)                                         | Acetic acid <sup>#2</sup> (g) | Sodium acetate <sup>#3</sup> (g) |                                              |
| Example 9  | 3.48                                                                       | 0.63                          | 0.86                             | 1:1                                          |
| Example 10 | 2.49                                                                       | 1.05                          | 1.44                             | 1:1                                          |
| Example 11 | 0.99                                                                       | 1.68                          | 2.30                             | 1:1                                          |
| Example 12 | 0                                                                          | 2.10                          | 2.87                             | 1:1                                          |

# 1 "Sodium diacetate" is a commercially available sodium diacetate (distributor: Wako Pure Chemical Industries, Ltd.).

# 2 "Acetic acid" is a commercially available glacial acetic acid that is not in the form of sodium diacetate (distributor: Wako Pure Chemical Industries, Ltd.).

# 3 "Sodium acetate" is a commercially available powdered sodium acetate that is not in the form of sodium diacetate (distributor: Wako Pure Chemical Industries, Ltd.).

[0145]

## (2) Evaluation of Long-Term Stability and Accelerated Stability of Solid Dialysis Agent

### A

For each dialysis agent A (Examples 9 to 12), the total amount of each of the obtained solid agents A was accommodated in a polyethylene bag. Furthermore, this was accommodated in a PET/AL/PE bag shown in Table 8, sealed, and stored at 25°C and 60% RH, and 40°C and 75% RH for two months.

[0146]

The volatilized acetic acid concentration of each dialysis agent A before storage, after two weeks storage, and after one month storage was measured in the same manner as in Test Example 2. Further, a 175-fold concentrated agent A solution was prepared by dissolving in purified water a total amount of each solid dialysis agent A before storage, after two weeks storage, and after one month storage to a volume of 100 mL wherein such an agent A was concentrated to 175 times the concentration of each component in the finally prepared dialysis fluid. The pH and the amount of 5-HMF of

the 175-fold concentrated agent A solution obtained were measured in the same manner as in Test Example 2.

[0147]

The results obtained are shown in Tables 17 and 18. From these results, the solid dialysis agents A of Examples 9 to 12 sufficiently suppressed the volatilization of acetic acid and the degradation of glucose after long-term and accelerated testing. This demonstrated that such agents A had excellent storage stability.

[0148]

[Table 17]

25°C, 60% RH

|            | pH of 175-fold concentrated agent A solution | Volatilized acetic acid concentration (ppm) |                         |                         |                          | 5-HMF (absorbance: 284 nm) |                         |                         |                          |
|------------|----------------------------------------------|---------------------------------------------|-------------------------|-------------------------|--------------------------|----------------------------|-------------------------|-------------------------|--------------------------|
|            | Before storage                               | Before storage                              | After two weeks storage | After one month storage | After two months storage | Before storage             | After two weeks storage | After one month storage | After two months storage |
| Example 9  | 4.31                                         | 10                                          | 40                      | 10                      | 60                       | 0.0193                     | 0.0188                  | 0.0178                  | 0.0190                   |
| Example 10 | 4.32                                         | 5                                           | 30                      | 35                      | 40                       | 0.0176                     | 0.0196                  | 0.0180                  | 0.0189                   |
| Example 11 | 4.31                                         | 10                                          | 20                      | 10                      | 40                       | 0.0176                     | 0.0182                  | 0.0151                  | 0.0158                   |
| Example 12 | 4.31                                         | 5                                           | 20                      | 5                       | 10                       | 0.0156                     | 0.0175                  | 0.0138                  | 0.0142                   |

[0149]

[Table 18]

40°C, 75% RH

|            | pH of 175-fold concentrated agent A solution | Volatilized acetic acid concentration (ppm) |                         |                         |                          | 5-HMF (absorbance: 284 nm) |                         |                         |                          |
|------------|----------------------------------------------|---------------------------------------------|-------------------------|-------------------------|--------------------------|----------------------------|-------------------------|-------------------------|--------------------------|
|            | Before storage                               | Before storage                              | After two weeks storage | After one month storage | After two months storage | Before storage             | After two weeks storage | After one month storage | After two months storage |
| Example 9  | 4.31                                         | 10                                          | 55                      | 15                      | 20                       | 0.0193                     | 0.0225                  | 0.0212                  | 0.0214                   |
| Example 10 | 4.32                                         | 5                                           | 20                      | 20                      | 20                       | 0.0176                     | 0.0196                  | 0.0197                  | 0.0205                   |
| Example 11 | 4.31                                         | 10                                          | 60                      | 20                      | 5                        | 0.0176                     | 0.0197                  | 0.0187                  | 0.0192                   |
| Example 12 | 4.31                                         | 5                                           | 20                      | 5                       | 15                       | 0.0156                     | 0.0193                  | 0.0172                  | 0.0176                   |

[0150]

#### Test Example 4

##### (1) Preparation of Solid Agent A (Examples 13 to 15)

Potassium chloride 2.61 g, calcium chloride hydrate 3.86 g, and magnesium chloride hydrate 1.78 g were added and mixed to obtain an electrolyte composition. Further, separately, glacial acetic acid 0.105 kg and anhydrous sodium acetate 0.144 kg were mixed to give an acetic acid/sodium acetate mixture. The electrolyte composition 8.25 g was mixed with glucose 17.50 g, a mixture (a predetermined amount shown in Table 19) of acetic acid and acetate salt, and sodium diacetate (a predetermined amount shown in Table 19) under stirring to obtain a solid dialysis agent A.

[0151]

##### (2) Preparation of Solid Agent A (Examples 16 to 18)

Potassium chloride 2.61 g, anhydrous calcium chloride 2.91 g, and anhydrous magnesium chloride 0.83 g were added and mixed to obtain an electrolyte composition. Further, separately, glacial acetic acid 0.105 kg and anhydrous sodium acetate 0.144 kg were mixed to give an acetic acid/sodium acetate mixture. The electrolyte composition 6.35 g was mixed with glucose 17.50 g, a mixture (a predetermined amount shown in Table 19) of acetic acid and acetate salt, and sodium acetate (a predetermined amount shown in Table 19) under stirring to obtain a solid dialysis agent A.

[0152]

[Table 19]

|            | Addition amount of<br>acetic acid:acetate salt<br>mixture (g) | Addition amount of<br>sodium acetate (g) | Molar ratio of acetic<br>acid:sodium acetate |
|------------|---------------------------------------------------------------|------------------------------------------|----------------------------------------------|
| Example 13 | 4.97                                                          | 0                                        | 1:1                                          |
| Example 14 | 4.97                                                          | 0.72                                     | 1:1.25                                       |
| Example 15 | 4.97                                                          | 1.44                                     | 1:1.5                                        |
| Example 16 | 4.97                                                          | 0                                        | 1:1                                          |
| Example 17 | 4.97                                                          | 0.72                                     | 1:1.25                                       |
| Example 18 | 4.97                                                          | 1.44                                     | 1:1.5                                        |

[0153]

### (3) Evaluation of Solid Agent A

(pH of 175-Fold Concentrated Agent A Solution)

Using each solid agent A obtained above, the pH, the volatilized acetic acid concentration, and the amount of 5-HMF of the 175-fold concentrated agent A solution were measured in the same manner as in Test Example 2.

[0154]

The measurement results of the pH of the 175-fold concentrated agent A solution are shown in Table 20, the measurement results of the volatilized acetic acid concentration are shown in Table 21, and the measurement results of the amount of 5-HMF are shown in Table 22.

[0155]

All of the 175-fold concentrated agent A solutions obtained by using the solid dialysis agents A (Examples 13 to 18) having a molar ratio of acetic acid:sodium acetate of 1:1 to 1.5 showed a pH of 4 or more, which can be handled safely in the clinical practice and will not cause the corrosion of the dialysis fluid preparation apparatus and the dialysis machine. In Examples 13 to 15 in which calcium chloride hydrate and

magnesium chloride hydrate were used and no drying process was included, the volatilized acetic acid concentration before storage was low in comparison with Comparative Examples 3 and 4 of Test Example 2 in which the drying process is included. In Examples 16 to 18 in which anhydrous calcium chloride and anhydrous magnesium chloride were used, such 175-fold concentrated agent A solutions showed low values of the volatilized acetic acid concentration and the absorbance at a wavelength of 284 nm, which is the absorption wavelength of 5-HMF, before storage and also during storage at 40°C and 75% RH as compared with Examples 13 to 15 in which calcium chloride hydrate and magnesium chloride hydrate were used and a drying process was not included. It was revealed that improvement in stability of dialysis agents as well as reduction of acetic acid odor can be achieved more effectively by using the anhydride for the electrolyte components to be incorporated.

[0156]

[Table 20]

| Solid dialysis agent A used | Molar ratio of acetic acid: sodium acetate | pH of liquid dialysis agent A |
|-----------------------------|--------------------------------------------|-------------------------------|
| Example 13                  | 1:1                                        | 4.28                          |
| Example 14                  | 1:1.25                                     | 4.39                          |
| Example 15                  | 1:1.5                                      | 4.49                          |
| Example 16                  | 1:1                                        | 4.29                          |
| Example 17                  | 1:1.25                                     | 4.40                          |
| Example 18                  | 1:1.5                                      | 4.50                          |

[0157]

[Table 21]

Measurement results of volatilized acetic acid concentration (ppm)

40°C, 75% RH

|            | Before storage | After two weeks | After one month | After two months |
|------------|----------------|-----------------|-----------------|------------------|
|            |                | PET/AL/PE bag   | PET/AL/PE bag   | PET/AL/PE bag    |
| Example 13 | 700            | >1000           | >1000           | >1000            |
| Example 14 | 800            | >1000           | >1000           | >1000            |
| Example 15 | 400            | >1000           | >1000           | >1000            |
| Example 16 | 40             | 30              | 140             | 150              |
| Example 17 | 30             | 400             | 110             | 100              |
| Example 18 | 60             | 150             | 160             | 140              |

[0158]

[Table 22]

Measurement results of 5-HMF (absorbance: 284 nm)

40°C, 75% RH

|            | Before storage | After two weeks | After one month | After two months |
|------------|----------------|-----------------|-----------------|------------------|
|            |                | PET/AL/PE bag   | PET/AL/PE bag   | PET/AL/PE bag    |
| Example 13 | 0.0103         | 0.3745          | 1.9619          | 3.4302           |
| Example 14 | 0.0106         | 0.3415          | 1.1608          | 2.7101           |
| Example 15 | 0.0090         | 0.2567          | 0.8680          | 2.9590           |
| Example 16 | 0.0114         | 0.0110          | 0.0129          | 0.0126           |
| Example 17 | 0.0108         | 0.0147          | 0.0121          | 0.0123           |
| Example 18 | 0.0115         | 0.0110          | 0.0121          | 0.0153           |

## CLAIMS

1. A three-pack type dialysis agent used in the preparation of a bicarbonate dialysis fluid, comprising an agent S containing sodium chloride, an agent B containing sodium bicarbonate, and an agent A containing an electrolyte component other than sodium chloride and sodium bicarbonate and containing glucose, wherein  
the agent A contains acetic acid and acetate salt, and the molar ratio of acetic acid:acetate salt is 1:0.5 to 2, and  
the three-pack type dialysis agent is used for preparing a dialysis fluid having a total acetate ion concentration of 2 mEq/L or higher but less than 6 mEq/L.
2. The three-pack type dialysis agent according to claim 1, wherein the molar ratio of acetic acid:acetate salt in the agent A is 1:1 to 1.5.
3. The three-pack type dialysis agent according to claim 1 or 2, which is used in the preparation of a dialysis fluid having a total acetate ion concentration of 2 mEq/L or higher but less than 5 mEq/L.
4. The three-pack type dialysis agent according to any one of claims 1 to 3, wherein when the agent A is converted into a state of an aqueous solution that is concentrated to 175 times the concentration of each component in the finally prepared dialysis fluid, the aqueous solution has a pH of 3.9 to 4.7.
5. The three-pack type dialysis agent according to any one of claims 1 to 4, wherein the acetate salt is an alkali metal salt of acetic acid.
6. The three-pack type dialysis agent according to any one of claims 1 to 5, wherein the agent A further contains a physiologically available electrolyte component other than acetic acid, acetate salt, sodium chloride, and sodium bicarbonate.
7. The three-pack type dialysis agent according to claim 6, wherein the electrolyte includes potassium chloride, magnesium chloride, and calcium chloride.

8. The three-pack type dialysis agent according to claim 6 or 7, wherein the agent A further contains an organic acid salt other than acetate salt as the electrolyte and/or contains an organic acid other than acetic acid as a pH adjusting agent.
9. The three-pack type dialysis agent according to any one of claims 1 to 8, wherein the agent A is in the form of a solid.
10. The three-pack type dialysis agent according to claim 6, wherein the agent A is in the form of a solid and the magnesium chloride and/or calcium chloride is a dry material or an anhydride.
11. The three-pack type dialysis agent according to claim 9 or 10, wherein the acetic acid and acetate salt are contained as a mixture thereof.
12. The three-pack type dialysis agent according to any one of claims 9 to 11, wherein at least some of the acetic acid and acetate salt are contained in the form of an alkali metal diacetate.
13. The three-pack type dialysis agent according to claim 12, wherein the alkali metal diacetate is sodium diacetate and/or potassium diacetate.
14. The three-pack type dialysis agent according to claim 8, wherein the organic acid salt is at least one kind selected from the group consisting of sodium lactate, sodium gluconate, sodium citrate, sodium malate, and sodium succinate.
15. The three-pack type dialysis agent according to claim 8, wherein the organic acid is at least one kind selected from the group consisting of lactic acid, gluconic acid, glucono- $\delta$ -lactone, citric acid, malic acid, and succinic acid.
16. The three-pack type dialysis agent according to any one of claims 9 to 15, wherein:

the agent A comprises a first material containing a mixture of acetic acid and acetate salt, and a second material containing a composition including a physiologically

available electrolyte other than acetic acid and acetate salt,

all of the acetate salt in the dialysis agent A are contained in the first material, or some of the acetate salt in the dialysis agent A are also contained in the second material, and

glucose is contained in the composition of the second material, and/or a third material containing glucose separately from the first material and the second material is contained.

17. The three-pack type dialysis agent according to claim 16, wherein the second material contains potassium chloride, magnesium chloride, and calcium chloride as an electrolyte.

18. The three-pack type dialysis agent according to claim 16 or 17, wherein the second material further contains as an electrolyte an organic acid salt other than acetate salt.

19. The three-pack type dialysis agent according to any one of claims 9 to 18, wherein the agent S, agent B, and agent A are accommodated in a packaging container having a water vapor transmission of  $0.5 \text{ g/m}^2 \cdot 24\text{h}$  or less.

20. The three-pack type dialysis agent according to any one of claims 9 to 19, wherein the agent S, agent B, and agent A are accommodated in the packaging container together with a desiccant.

21. The three-pack type dialysis agent according to any one of claims 1 to 20, which is used by adjusting the addition amount of the agent S, agent B, and agent A so that the bicarbonate ion concentration and/or the sodium concentration in the dialysis fluid is changed.

22. A method for preparing a dialysis fluid, comprising the step of mixing an agent S containing sodium chloride, an agent B containing sodium bicarbonate, and an agent

A with water in such an amount that the dialysis fluid has total acetate ion of 2 mEq/L or higher but less than 6 mEq/L, wherein

the agent A contains an electrolyte component other than sodium chloride and sodium bicarbonate and contains glucose, acetic acid and acetate salt, wherein the molar ratio of acetic acid:acetate salt is 1:0.5 to 2.

23. The method for preparing a dialysis fluid according to claim 22, wherein the dialysis fluid is prepared so as to change the bicarbonate ion concentration and maintain the sodium ion concentration at a constant level during dialysis according to a disease state of a patient, in the mixing step.

24. The method for preparing a dialysis fluid according to claim 22, wherein the dialysis fluid is prepared so as to change the bicarbonate ion concentration and at the same time change the sodium ion concentration during dialysis according to a disease state of a patient, in the mixing step.