RED BLOOD CELL COMPOSITION

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ABSTRACT
The present invention provides an improved aqueous solution for suspending and storing red blood cells. The solution includes sodium citrate, a combination of sodium biphosphate and sodium phosphate dibasic, adenine, and mannitol. The solution is formulated at a low osmolarity and has a physiological pH of approximately 7.4. The solution simultaneously maintains stored red cells ATP and 2,3-BPG.
FIG. 2

% Hemolysis vs. Days

DAYS

- AS 1% H
- AS 2% H
- AS 3% H
- AS 4% H
- AS 5% H
- AS 6% H
- SAG-M REFERENCE * (n = 12)
RED BLOOD CELL COMPOSITION

[0001] The present invention relates generally to the storage of blood cell components. More specifically, the present invention relates to the storage of the red blood cell component of blood.

[0002] It is known to centrifuge collected blood to remove plasma and the Buffy-coat layer. The residue is a mass of red cells that is substantially separated from the plasma referred to as “packed red cells.” The separation of the red cells from the plasma is desirable for a number of reasons. By separating the red cells, it is possible to collect the plasma and use the plasma for separate therapeutic uses.

[0003] Additionally, it is desirable in many disease states to administer red blood cells in a purified or semipurified form, thereby avoiding to transfer to the recipient such constituents of blood as plasma and white cells, when these are unsuitable.

[0004] Accordingly, it is known to store packed red cells separately and apart from at least a substantial portion of plasma. These red cells are later administered to a patient during major surgery and the like.

[0005] Although it is desirable to separately store and utilize the red cell component of whole blood, it was discovered that, unless special precautions are taken, packed red cells do not survive as well as red cells that are stored in the presence of an increased amount of plasma. Accordingly, to promote the long term storage of packed red cells, it has been suggested to admix packed red cells with at least a small amount of blood plasma.

[0006] It is known to store packed red cells in a 100 ml of a protein-poor solution containing for each unit of packed red cells, 877 mg of sodium chloride, 16.9 mg of adenine, and 900 mg of glucose (SAG) to increase the storage life of the red cells. See, Hogman et al, New England Journal of Medicine, Dec. 21, 1978; 229 (25), 1377-82.

[0007] It has also been suggested to use mannitol as a reagent to improve the viability of: stored blood cells and create a storage solution. See, U.S. Pat. No. 4,082,509. The patent discloses a storage solution which includes both glucose (in an amount of 990 mg/ml) and mannitol (in an amount of 500 mg/ml). The solution provides an improved viability of the packed red cells stored in contact therewith.

[0008] European Published Patent No. 0444864 discloses a storage solution that provides improved storage time. Pursuant to the solution disclosed, the concentration of glucose (or fructose) is increased and mannitol is added to a conventional SAG solution. In an embodiment, an aqueous red blood cell storage solution is provided that contains per 100 ml of solution, substantially from 1500 to 2500 mg of sugar comprising glucose and/or fructose; from 500 to 1500 mg of mannitol; from 20 to 30 mg of adenine; and from 500 to 1000 mg of sodium chloride.

[0009] One difficulty that is encountered with storage solutions is the sterilization of the solutions. Glucose is known to degrade under autoclaving (heat) sterilization conditions unless it is maintained in an acidic medium. If glucose is not in an acidic medium, when heated, glucose will carmelize.

[0010] In collecting blood, specifically red cells, it is known to add to the whole blood collected from the donor an anticoagulant. The anticoagulant typically includes citrate. After the anticoagulant is added to the whole blood, the blood can be separated into components, including plasma and red blood cells. An example of an anticoagulant is citrate phosphate dextrose (CPD). During the separation process of the whole blood, typically much of the citrate separates with the plasma, leaving the red blood cells, with lower citrate levels when they are then mixed with a storage solution.

[0011] It is known to include in the anticoagulant a surplus of citrate in order to obtain good binding of ionized calcium which otherwise may initiate plasma coagulation at blood collection or blood storage. However, a disadvantage with this procedure is poor stability of Factor VIII and reduced yield of this factor in subsequent blood component preparation.

[0012] It is known that reduction of the concentration of citrate in the anticoagulant improves the stability of Factor VIII, provided conditions during collection are optimal. This is away to improve the yield of Factor VIII in plasma, when separation of the blood into components has to be carried out after a delay of several hours. Reduction of citrate in the anticoagulant has the additional advantage, when the red cells are stored in an additive solution based on citrate, that the citrate load in a recipient of massive volumes of both red cells and plasma will not be disturbingly high.

[0013] There is therefore a need for an improved red blood cell storage solution.

SUMMARY OF THE INVENTION

[0014] The present invention provides an improved aqueous solution for suspending and storing red blood cells. The solution includes sodium citrate, a combination of sodium biphosphate and sodium phosphate dibasic, adenine, and mannitol.

[0015] Preferably, the solution has been adjusted to a physiological pH of about 7.4.

[0016] Preferably, the solution is formulated at a low osmolality. To this end, the solution preferably does not include sodium chloride.

[0017] In an embodiment, the solution can be utilized with an anticoagulant solution having a reduced citrate concentration. For example, the anticoagulant solution can include, approximately 50% less citrate concentration than is typically utilized in a CPD anticoagulant solution.

[0018] In a preferred embodiment, the present invention provides an aqueous red blood cell storage solution comprising sodium citrate, sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol. The solution has a pH of approximately 7.4 and an osmolality of less than 300 mOsM/L. In an embodiment, the aqueous red blood cell storage solution includes guanosine.

[0019] In an embodiment, the present invention provides an aqueous red blood cell storage solution that is added to a plasma depleted collection of red blood cells, comprising in millimolar, concentration (mmol/L): approximately 20 mmol/L to about 140 mmol/L of at least one sugar chosen from the group consisting of dextrose and fructose; approximately 1 mmol/L to about 2.2 mmol/L of adenine; approximately 20 mmol/L to about 110 mmol/L mannitol; approximately 2.2 mmol/L to about 90 mmol/L sodium citrate;
approximately 1 mmol/l to about 10 mmol/l sodium biphosphate; approximately 5 mmol/l to about 25 mmol/l sodium phosphate dibasic and approximately 0 to about 2 mmol/l guanosine; per 100 ml of solution.

[0020] Preferably a two part aqueous red blood cell storage solution is provided. The solution includes a first part including sodium citrate, sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol, and no sodium chloride. A second part including a sugar chosen from, the group consisting of dextrose and fructose.

[0021] The present invention also provides a method of storing red blood cells comprising the step of combining a plasma depleted collection of red blood cells with an aqueous storage solution comprising sodium citrate, sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol, and having a pH of approximately 7.4 and an osmolality of less than 300 mOsm/l. In an embodiment, an anticoagulant having a reduced citrate concentration is utilized.

[0022] Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments and from the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 illustrates a perspective view of a first, second and third container for housing, respectively, a sugar medium, the storage solution, and plasma depleted red blood cells.

[0024] FIG. 2 illustrates graphically percent hemolysis versus days for red cells stored in examples of the solution of the present invention and in a SAG-M reference solution.

[0025] FIG. 3 illustrates graphically ATP mol/mol Hb versus days for red cells stored in examples of the solution of the present invention and in a SAG-M reference solution.

[0026] FIG. 4 illustrates graphically 2,3-BPG mol/mol Hb versus days for examples of the solution of the present invention and a SAG-M reference solution.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

[0027] The present invention provides an aqueous solution for suspending and storing red cells. The solution includes sodium citrate, a combination of sodium biphosphate and sodium phosphate dibasic, adenine, and mannitol. Preferably, the solution has been adjusted to a physiological pH of about 7.4. The solution is stable on steam sterilization in PVC containers. The solution is also formulated at low osmolality. Accordingly, the solution preferably does not include sodium chloride.

[0028] Because dextrose, or fructose, is necessary for the maintenance of red cell metabolism, dextrose or fructose is preferably provided to the collection of red blood cells. In an embodiment of the invention, the dextrose, or fructose, is provided separately from the basic formulation in the form of an acid concentrate solution.

[0029] For example, the basic formulation can be contained in a first container or compartment, and mixed with dextrose which is in a separate container or compartment. After the components are mixed they can then be added to the red cells obtained from whole blood. To this end, as illustrated in the embodiment of the invention set forth in FIG. 1, two containers 10 and 12 are provided. The sugar component can be housed in the first container 10 and the solution in the second container 12. A further container 14, that houses the red blood cells is also provided.

[0030] Alternatively, a blood bag system such as that disclosed in U.S. Pat. No. 4,608,178 can be used, the disclosure of which is incorporated by reference herein.

[0031] By maintaining the sugar component separate from the remaining solution, pursuant to the present invention, the solution can be maintained at a physiological pH of approximately 7.4. On the other hand, the sugar medium can be maintained at an acidic pH. Although the sugar will be maintained at an acidic pH, the solution has sufficient buffer capacity so that when the sugar is added to the solution, and then the red blood cells, the pH remains fairly constant at around 7.4. Additionally, by so separately the component, the solution and sugar can be maintained in PVC containers reducing costs.

[0032] Typically, when the red cells obtained from whole blood are collected they are collected with an anticoagulant solution. An example of such a solution is citrate phosphate dextrose formulation. In an embodiment, of the solution of the present invention, the red blood cell storage solution is used with an anticoagulant having a reduced citrate level. For example, a CPD solution that includes only 50% of the typical citrate concentration of a CPD solution.

[0033] Examples of a CPD and a CPD 50% citrate are as follows (in grams per liter):

<table>
<thead>
<tr>
<th></th>
<th>CPD</th>
<th>50% CITRATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Citrate Dihydrate</td>
<td>26.30</td>
<td>13.15</td>
</tr>
<tr>
<td>Citric Acid Hydrate</td>
<td>3.28</td>
<td>1.64</td>
</tr>
<tr>
<td>Dextrose Monohydrate</td>
<td>25.50</td>
<td>25.50</td>
</tr>
<tr>
<td>Sodium Biphosphate Monohydrate</td>
<td>2.22</td>
<td>2.22</td>
</tr>
</tbody>
</table>

[0034] The solution of the present invention, including dextrose, when added to red cells enables the cells to be stored for at least 42 days. The solution has been found to have the equivalent of efficacy for ATP maintenance and limitations of hemolysis to that of currently used saline-adenine-glucose-mannitol (SAG-M) or solution such as that set forth in European Patent No. 0 044 864, the disclosure of which is incorporated, herein by reference.

[0035] In an embodiment, the solution that is used for the storage of red blood cells comprises in millimolar concentration: approximately 20 to 140 mmol/l dextrose (and/or fructose); approximately 1 to about 2.2 mmol/l adenine; approximately 20 to about 110 mmol/l mannitol; approximately 2.2 to about 90 mmol/l sodium citrate; approximately 1 to about 10 mmol/l sodium biphosphate; approximately 0.5 to about 25 mmol/l sodium phosphate dibasic; and approximately 0 to about 2 mmol/l guanosine.

[0036] Preferably, 50 to about 200 ml of solution is used. Most preferably, 75 to about 150 ml of solution is used.

[0037] It has been found that the most preferable ranges are as follows for a 100 ml volume of solution in a
millimolar concentration: approximately 30 to about 60 mmol/l dextrose and/or fructose; approximately 1.2 to about 1.7 mmol/l adenine; approximately 30 to about 50 mmol/l mannitol; approximately 4.5 to about 55 mmol/l sodium citrate; approximately 2 to about 5 mmol/l sodium bisphosphate; approximately 8 to about 18 mmol/l sodium phosphate dibasic; and approximately 0 to about 1.5 mmol/l generally poorly maintained in known solutions for red cell storage dropping to levels of about 5 to about 10 percent of the initial value within 14 to 21 days of refrigerated storage. As set forth in detail below, with the solution of the present invention, 2,3-BPG remains at about 80 to about 110 percent of initial concentration after 21 days and about 30 percent after 42 days.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED CELL ADDITIVE SOLUTIONS</td>
</tr>
<tr>
<td>MILLIMOLAR CONCENTRATION (mol/l) IN</td>
</tr>
<tr>
<td>SOLUTION A + B (100 ML)</td>
</tr>
<tr>
<td>TYPE</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>5</td>
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<td>6</td>
</tr>
</tbody>
</table>

| TYPE | Mannotol \(\text{C}_6\text{H}_{12}\text{O}_6\) | Adenine \(\text{C}_6\text{H}_{12}\text{N}_4\) | Guanosine \(\text{C}_6\text{H}_{12}\text{N}_5\text{O}_7\) | Dextrose \(\text{C}_6\text{H}_{12}\text{O}_6\cdot \text{H}_2\text{O} \) | pH after 42 days |
| 1 | 40.0 | 1.5 | — | 45.4 | 7.46 |
| 2 | 40.0 | 1.5 | — | 45.4 | 7.44 |
| 3 | 40.0 | 1.5 | — | 45.4 | 7.42 |
| 4 | 40.0 | 1.5 | — | 45.4 | 7.41 |
| 5 | 40.0 | 1.5 | — | 45.4 | 7.46 |
| 6 | 40.0 | 1.5 | — | 45.4 | 7.44 |

[0044] Table 1, above, sets forth the detailed formulations expressed in millimolar concentration, mmol/l for 100 milliliter final volume of red cell additive solutions. Citrate, phosphate, mannitol, adenine, and some formulations with sodium glucuronate or guanosine were sterilized in PVC containers and housed in an 80 ml volume (container A). Dextrose was sterilized separately in small capacity PVC containers filled with 10 milliliter solution (container B).

[0045] Physiological pH (approximately 7.4) was achieved in container A by using an adequate balance of sodium, bisphosphate and sodium phosphate dibasic. The pH of container B was not adjusted but was naturally acidic (pH 5.8). The mixture of the two containers after steam sterilization resulted in a solution having a pH ranging from 7.41 to 7.46 depending on the formulations (see Table 1).

[0046] The test variables and experiments were as follows: a low (solutions 1, 3, 5) versus a high (solutions 2, 4, 6) phosphate level; and the effect of sodium glucuronate (solutions 3, 4) or guanosine (solutions 5, 6).

[0047] Four series of six units of whole blood were drawn on a citrate formation having a reduced citrate concentration, CPD 50%. Citrate. Plasma and the buffy coat layer were removed from centrifuged units. Each group of red cell concentration (RCC) were pulled together then subdivided into six containers containing each of the tested solutions (set forth above as 1-6).

[0048] Suspended RCC were stored at ±4°C for 50 days. Referring now to the Figures, the graphs illustrate the evolution of hemolysis, ATP, and 2,3-BPG, respectively, in guanosine. Preferably, the sugar component is housed in a separate container or compartment at an acidic pH. The remaining constituents are then maintained at a pH of approximately 7.4.

[0038] The above solution provides a red cell storage solution with a low osmolality. Preferably the osmolality is less than 300 mOsM/l. It is believed that an osmolality of less than 300 mOsM/l reduces the concentration of H⁺ inside the red blood cells that are stored in the solution and better approximates the physiological H⁺ concentration. Furthermore, the above solution can be utilized with a low citrate anticoagulant.

[0039] In an embodiment for use with a reduced citrate CPD anticoagulant, citric acid can be added to the solution. In an embodiment, in millimolar concentration, approximately 0.4 to about 1.5 mmol/l of citric acid is added. It has been found that the most preferable ranges for citric acid are 0.8 to about 0.5 mmol/l.

[0040] Although, preferably the sugar component is housed in a separate container, constituents that are not effected by an acidic environment can be housed with the sugar component. For example, mannitol, adenine, and sodium citrate.

[0041] By way of example, and not limitation, examples of the invention will now be given.

[0042] A series of six solutions were tested.

[0043] The concentration in the red cells of 2,3-BPG is related to oxygen delivery capacity of the cells. 2,3-BPG is
the tested formulations (see FIGS. 2, 3 and 4). As a comparison, the evolution of the same parameters for SAG-M resuspended red cell storage in the same plastic containers and tested in the same laboratory is shown in broken lines in FIGS. 2, 3, and 4 (from Hogan, C. F. et al., Storage of SAG-M Suspended Red Cells in a New Plastic Container: PVC Plasticized with Butylrub-in-Triethyl-Citrate, In Press, Transfusion). The SAG-M mixture was as follows in grams per liter: 9.00 dextrose monohydrate, 8.77 sodium chloride, 0.169 adenine, 5.25 mannitol, and an osmolality of 376.

[0049] From these experiments, it was demonstrated that all six tested formulations limit hemolysis during RCC storage to very low levels (about 50% of SAG-M reference solution). ATP is at least as well maintained as in reference SAG-M solution. 2.3-BPG is far better maintained than in the SAG-M reference solution especially in high phosphate formulations. The presence of guanosine also seems beneficial to 2,3-BPG maintenance.

[0050] Although it is desirable to include a sufficient amount of dextrose in the solution to supply sufficient nutrients to the red cells for prolonged storage, it is possible to supply sufficient dextrose to the red cells by increasing the concentration of dextrose in the anticoagulant formula. Accordingly, the solution of the present invention can be utilized with no dextrose in the red cell additive solution by using a high dextrose anticoagulant formulation. For example, it is anticipated that if the dextrose in the CPD anticoagulant is increased by 100% then the additive solution can be used without the further addition of a sugar.

[0051] Preferably the solution includes no sodium chloride. However, in order to provide a slightly more physiological osmolarity, it is possible that a minimal amount of sodium chloride could be present in the solution.

[0052] It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

We claim:

1. An aqueous red blood cell storage solution comprising sodium citrate, sodium biphosphate; sodium phosphate dibasic, adenine, and mannitol, and having a pH of approximately 7.4.
2. The aqueous red blood cell storage solution of claim 1 having an osmolality of less than 300 mOsm/l.
3. The aqueous red blood cell storage solution of claim 1 including guanosine.
4. The aqueous red blood cell storage solution of claim 1 including citric acid.
5. An aqueous red blood cell storage solution comprising sodium citrate, sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol, and having an osmolality of less than 300 mOsm/l.
6. The aqueous red blood cell storage solution of claim 5 including dextrose.
7. The aqueous red blood cell storage solution of claim 5 including citric acid.
8. The aqueous red blood cell storage solution of claim 5 including citric acid.

9. An aqueous red blood cell storage solution: comprising a first distinct solution and a second distinct-solution wherein:

- the first solution includes in millimolar concentration (mmol/l) approximately 20 mmol/l to about 140 mmol/l of at least one sugar chosen from the group consisting of dextrose and fructose;
- the second solution includes in millimolar concentrations:
  - approximately 1 mmol/l to about 2.2 mmol/l adenine;
  - approximately 20 mmol/l to about 110 mmol/l mannitol;
  - approximately 2.2 mmol/l to about 90 mmol/l sodium citrate;
  - approximately 1 mmol/l to about 10 mmol/l sodium biphosphate;
  - approximately 5 mmol/l to about 25 mmol/l sodium phosphate dibasic; and
  - approximately 0 mmol/l to about 2 mmol/l guanosine.
10. The aqueous red blood cell solution of claim 9 wherein the second solution includes approximately 0.4 to about 15 mmol/l of citric acid.
11. The aqueous red blood cell solution of claim 9 wherein the second solution has a pH of approximately 7.4.
12. The aqueous red blood cell solution of claim 9 wherein the total volume of solution is approximately 50 to about 200 ml.
13. A two part aqueous red blood cell storage solution comprising:

- a first part including sodium citrate, sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol; and
- a second part including a sugar chosen from the group consisting of dextrose and fructose.
14. The two part aqueous red blood cell storage solution of claim 13 wherein the first part includes guanosine.
15. The two part aqueous red blood cell storage solution of claim 13 wherein the first part is stored in a first container and the second part is stored in a second container.
16. The two part aqueous red blood cell storage solution of claim 13 wherein the first and second parts are stored in separate elements of a multiple element container.
17. The two part aqueous red blood cell storage solution of claim 13 wherein the pH of the first part is approximately 7.4.
18. An aqueous red blood cell storage solution comprising in millimolar concentration (mmol/l): approximately 30 mmol/l to about 60 mmol/l of at least one sugar chosen from the group consisting of dextrose and fructose;

- approximately 1.2 mmol/l to about 1.7 mmol/l adenine;
- approximately 30 mmol/l to about 50 mmol/l mannitol;
- approximately 4.5 mmol/l to about 55 mmol/l sodium citrate;
- approximately 2 mmol/l to about 5 mmol/l sodium biphosphate;
- approximately 8 mmol/l to about 18 mmol/l sodium phosphate dibasic; and
- approximately 0 mmol/l to about 1.5 mmol/l guanosine.
19. The aqueous red blood cell storage solution of claim 18 wherein the total volume of solution is approximately 75 to about 150 ml.
20. The aqueous red blood cell storage solution of claim 18 including approximately 0.8 to about 9.5 mmol/l of citric acid.

21. An aqueous red blood cell storage solution comprising in millimolar concentration (mmol/l):
- approximately 1.0 mmol/l to about 2.2 mmol/l adenine;
- approximately 20 mmol/l to about 110 mmol/l, mannitol;
- approximately 2.2 mmol/l to about 90 mmol/l sodium citrate;
- approximately 1 mmol/l to about 10 mmol/l sodium biphosphate;
- approximately 5 mmol/l to about 25 mmol/l sodium phosphate dibasic; and
- approximately 0 mmol/l to about 2.0 mmol/l guanosine; and
- having a pH of approximately 7.4.

22. The aqueous red blood cell storage solution of claim 21 wherein the osmolality is less than approximately 300 mOsm/l.

23. A method for storing red blood cells comprising the steps of combining a plasma-depleted collection of red blood cells with an aqueous storage solution comprising sodium citrate, sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol, and having an osmolality of less than 300 mOsm/l.

24. The method of claim 23 wherein the storage solution includes guanosine.

25. The method of claim 23 wherein the storage solution comprises in millimolar concentration (mmol/l):
- approximately 20 mmol/l to about 140 mmol/l of at least one sugar chosen from the group consisting of dextrose and fructose;
- approximately 1 mmol/l to about 2.2 mmol/l adenine;
- approximately 20 mmol/l to about 110 mmol/l mannitol;
- approximately 2.2 mmol/l to about 90 mmol/l sodium citrate;
- approximately 1 mmol/l to about 10 mmol/l sodium biphosphate;
- approximately 5 mmol/l to about 0.2 mmol/l sodium phosphate dibasic; and
- approximately 0 mmol/l to about 2 mmol/l guanosine; per 160 ml of solution.

26. The method of claim 23 wherein the storage solution comprises in millimolar concentration (mmol/l):
- approximately 1.0 mmol/l to about 2.2 mmol/l adenine;
- approximately 20 mmol/l to about 110 mmol/l mannitol;
- approximately 2.2 mmol/l to about 90 mmol/l sodium citrate;
- approximately 1 mmol/l to about 10 mmol/l sodium biphosphate;
- approximately 5 mmol/l to about 25 mmol/l sodium phosphate dibasic; and
- approximately 0 mmol/l to about 2 mmol/l guanosine; per 100 ml of solution.

27. A method for storing red blood cells comprising the steps of:
- adding an anticoagulant to collected whole blood having a sufficient level of dextrose to provide a nutrient supply to separated red blood cells;
- separating the red blood cells from the whole blood; and
- adding to the separated red blood cells an aqueous storage solution comprising sodium citrate sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol.

28. The method of claim 27 wherein the pH of the storage solution is 7.4.

29. The method of claim 27 wherein the storage solution comprises in millimolar concentration (mmol/l):
- approximately 1 mmol/l to about 2.2 mmol/l adenine;
- approximately 20 mmol/l to about 110 mmol/l mannitol;
- approximately 2.2 mmol/l to about 90 mmol/l sodium citrate;
- approximately 1 mmol/l to about 10 mmol/l sodium biphosphate;
- approximately 5 mmol/l to about 25 mmol/l sodium phosphate dibasic; and
- approximately 0 mmol/l to about 2 mmol/l guanosine; per 100 ml of solution.

30. The method of claim 27 wherein the anticoagulant has a reduced citrate level.

31. The method of claim 27 wherein the solution includes citric acid.

32. The method of claim 27 wherein the aqueous storage solution has an osmolality of less than 300 mOsm/l.

33. A method of storing red blood cells comprising the steps of combining a plasma depleted collection of red blood cells with an aqueous storage solution comprising sodium citrate, sodium biphosphate, sodium phosphate dibasic, adenine, and mannitol, and having a pH of approximately 7.4.

34. The method of claim 33 wherein the storage solution includes guanosine.

35. The method of claim 33 wherein the storage solution comprises in millimolar concentration (mmol/l):
- approximately 1 mmol/l to about 2.2 mmol/l adenine;
- approximately 20 mmol/l to about 110 mmol/l mannitol;
- approximately 2.2 mmol/l to about 90 mmol/l sodium citrate;
- approximately 1 mmol/l to about 10 mmol/l sodium biphosphate;
- approximately 5 mmol/l to about 25 mmol/l sodium phosphate dibasic; and
- approximately 0 mmol/l to about 2 mmol/l guanosine; per 100 ml of solution.

36. A two part aqueous red blood cell storage solution comprising:
- a first part including at least, sodium biphosphate and sodium phosphate dibasic;
- a second part including at least a sugar chosen from the group consisting of dextrose and fructose; and
- at least one of the first and second parts including mannitol, sodium citrate, and adenine.

* * * * *