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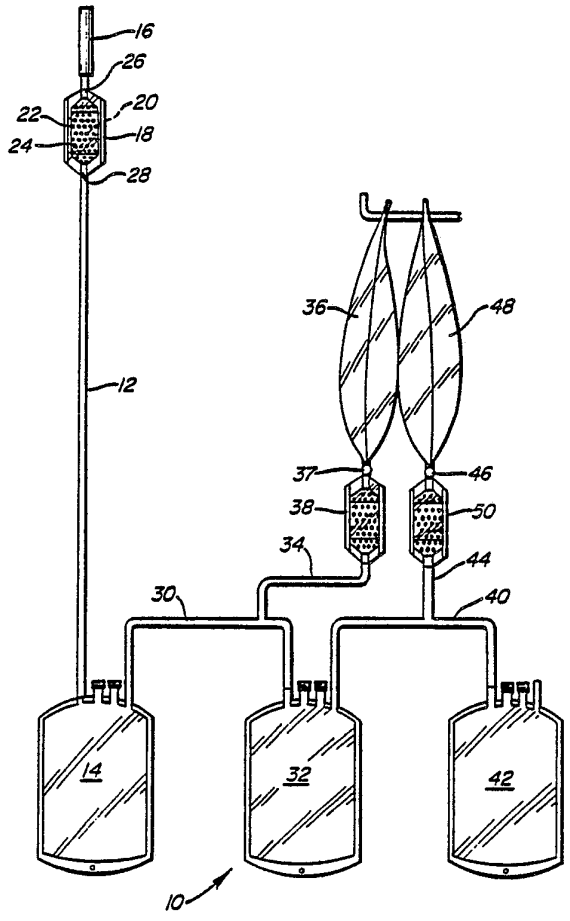
(54) Title: MULTIPLE BAG SYSTEM

(57) Abstract

A multiple bag system (10) for preparation of blood components. Donated blood tubing (12) communicates at one end with a first blood bag (14). A first compartment (18) is in flow communication with the donated blood tubing (12) the first compartment (18) containing a physiologically-acceptable, dry anticoagulant (20) for blood. Thus, blood may flow through the first compartment (18) to receive a predetermined amount of the anticoagulant (20) and pass through the donated blood tubing (12) to the first blood bag (14). Second blood tubing (30) communicates between the first blood bag (14) and a second blood bag (32). First branch tubing (34) communicates between the first bag (14) and a second compartment (38). The second compartment (38) contains another physiologically-acceptable dry material, for example for reconstituting into a red blood cell preservative solution, for reconstituting into a platelet preservative solution, by addition of sterile, aqueous liquid. Means are provided permitting aseptic passage of sterile, aqueous liquid through the second compartment (38) to receive a predetermined amount of the dry material, to reconstitute it into the desired solution, and permitting passage thereof into one of the blood bags.



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MULTIPLE BAG SYSTEM

TECHNICAL FIELD

In the United States Patent Application entitled Controlled Administration of Beneficial Agent to Blood, assigned to Baxter Travenol Laboratories, Inc. and filed on the same day as this present application, a technique and apparatus is provided for providing a dry anticoagulant system which is reconstituted by blood passing through the anticoagulant. Such a system has numerous advantages. For example, each aliquot of the blood may be exposed to a relatively uniform concentration of anticoagulant. To the contrary, in conventional blood bags which contain a small amount of anticoagulant solution, the initial aliquots of blood which enter the bag are exposed to an undesirably high concentration of anticoagulant.

Additionally, with the use of a dry anticoagulant which is reconstituted by the blood, sterilization procedures for the blood bags may be greatly simplified, and the additional moisture barrier packing used with conventional blood bags may be eliminated.

By this invention, an improvement is provided in which blood is not just placed into anticoagulated form by means of a dry anticoagulant, but blood components may be collected and stored, making use of more than one dry beneficial agent for the blood. Nevertheless, the system may retain the significant advantages of easier sterilization because of the initial absence of water from the system in certain embodiments of the invention. Thereafter, an aqueous solution may be used to reconstitute beneficial agents that are used in conjunction with separated blood components.

DESCRIPTION OF THE INVENTION

In accordance with this invention a multiple bag system is provided for preparation of blood components. The system comprises donated blood tubing to be in communicating relation with one end with a first blood bag, and typically carrying a donor needle at its other end. A first compartment is positioned in flow communication with the donated blood tubing, with the first compartment containing a physiologically-acceptable, dry anticoagulant for blood.

Thus, blood may flow through the first compartment to receive a predetermined amount of the anticoagulant, and pass through the donated blood tubing to the first blood bag, carrying such anticoagulant in a generally predetermined and desired concentration.

Second blood tubing is provided, communicating between the first blood bag and a second blood bag. First branch tubing communicates between the first bag and a second compartment. The second compartment may contain a physiologically-acceptable dry material which may be reconstituted into a red blood cell preservative solution by addition of sterile, aqueous liquid. Means are provided to permit aseptic passage of sterile, aqueous liquid through the second compartment to receive a predetermined amount of the dry material into solution to form the preservative solution and permitting passage thereof into the first bag.

The means permitting aseptic passage of sterile aqueous liquid may include a conventional aseptic or sterile connection device positioned on the end of the first branch tubing to provide connection with a desired sterile solution container which holds, for example, normal saline solution or any other desired aqueous solution for reconstitution of the dry material into

a red blood cell preservative solution. For example, the dry material in the second compartment may be reconstituted into a solution having a formulation similar to ADSOL$^{T.M.}$, which is a commercially available packed red cell storage solution sold by Baxter Health-care Corporation of Deerfield, Illinois. However, any other red blood cell reconstitution solution may be used as desired.

Specifically, the branch tubing described above may connect to the second blood tubing, to communicate with the first bag via such second blood tubing. Alternatively, the branch tubing may connect directly with the first bag. Additionally, added blood tubing may communicate between the second blood bag and an added blood bag, with added branch tubing communicating between the second bag and a second compartment. The second compartment, in turn, may contain a physiologically acceptable dry material which may be reconstituted into a platelet preservative solution by addition of sterile, aqueous liquid such as normal saline solution. Also, means are provided permitting aseptic passage of such sterile aqueous liquid through the second compartment to transfer a predetermined amount of the dry material into the solution, to form the preservative solution, and permitting passage thereof to pass typically to the second bag. This dry precursor for platelet preserving solution found in the second compartment may be formulated so that, upon reconstitution with a sterile aqueous liquid, an effective platelet storage solution may be provided. One example of such a platelet storage solution is Seligmann balanced salt solution as described in U.S. Patent No. 4,447,415.

The second branch tubing may connect to the added blood tubing and thus communicate with the first bag via such added blood tubing. Alternatively,

the second branch tubing may directly connect with the second blood bag.

It is generally preferable for all of the tubes and bags of the system to be permanently, integrally interconnected with each other. However, alternatively, the tubes and bags may be initially in several separate sections, being connectable by means of conventional sterile connector technology of a type well known in the art.

By the above-described bag system, it is possible for the system to be initially dry for ease of manufacture and other advantages. Then, blood may be collected, passing through the first compartment and the donated blood tubing to pick up a desired amount of anticoagulant-nutrient and to be conveyed to the first bag. Then, the system may be centrifuged in conventional manner, following which platelet-rich plasma is expressed through the second blood tubing into the second bag. Following this, an aqueous solution may be passed through the second compartment and the first branch tubing to form a packed red cell preservative solution. This preservative solution is then passed into the first bag to reconstitute the packed red cells and to place them into a mode appropriate for storage.

Following this, the first bag may be aseptically removed in conventional manner for storage, and the second bag is once again centrifuged, if desired, to separate platelets from the plasma. The platelet-poor plasma may be expressed through the added blood tubing from the second bag to the added blood bag. After this has taken place, the second branch tubing, connected to a source of sterile solution, may receive such sterile solution which passes through the added or third compartment to form a platelet preservation solution by dissolution of the dry contents of the

third compartment. This solution may be directed to the second bag, to resuspend the platelets for storage purposes.

The platelet poor plasma-containing bag may then be aseptically separated by conventional heat sealing and cutting of the appropriate blood tubing, so that each bag is separated from the others and conveyed to its separate use.

Thus, by this invention, blood components may be drawn and separated into blood bags which are initially dry, under circumstances where the blood does not enter even transiently into contact with excess concentrations of any of the beneficial agents used. The respective branch tubings may, if desired, be connected at the site of use with a bag or other container of appropriate aqueous solution by means of known sterile connector technology, to provide the desired storage solutions for use in accordance with this invention.

In another preferred embodiment, one or more solution containers may be manufactured as an integral unit with the compartment having the dry agent, separated by a frangible connector.

DESCRIPTION OF DRAWING

Fig. 1 is a partially diagrammatic plan view of a multiple bag container made in accordance with this invention.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Referring to the drawings, a multiple bag system is provided for preparation of blood components.

System 10 comprises donated blood tubing 12 which communicates at one end with first blood bag 14 and typically carries at its other end a conventional blood donation needle 16. However, needle 16 is not a necessary part of the invention, in that the blood may be received from another container, from a plasmapheresis apparatus, a blood collecting machine, or the like, where a different type of connector other than needle 16 might be used.

First compartment 18 is positioned intermediately along the length of tube 12 in direct flow relation at both ends therewith. First compartment 18 contains a dry anticoagulant in such a form that when blood passes through compartment 18, it picks up by dissolving action the components of the dry anticoagulant present, carrying the dissolved components along with itself throughout tube 12 into first bag 14.

Specifically, first compartment 18 contains a tablet 20 of rectangular, thin shape. Tablet 20 is made of a glassy, solid mass of dry blood storage anticoagulant preparation, typically having a water content on the order of no more than about 2 percent by weight. The inner walls of both sides of first compartment 18 define an array of small projections 22 which project inwardly to define flow passages between the inner walls 24 of both sides of first compartment 18 and the surface of anticoagulant tablet 20. Alternatively, separate portions of screening or the like may be used as a spacing member to define such flow passages, as a substitute

for the small inwardly extending projections 22.

As shown, first compartment 18 has an inlet 26 and an outlet 28 that respectively communicate with length of donated blood tubing 12.

Specifically anticoagulant preparation tablet 20 may comprise, for example, a dried mixture of:

	Weight Percent Present
Dextrose	44
Sodium Citrate	46
Citric Acid	6
Sodium Biphosphate	4

The above dextrose is dissolved as a near saturated solution in water by heating to boiling. Then water is removed by boiling under a vacuum of about 2 inches of mercury at about 70°, increasing to about 295°F. at the end of the process, until the dextrose reaches the desired water content of 2 weight percent or less (as defined by its temperature at the air pressure obtained by the vacuum system). The viscous mass is then cooled to avoid crystalization, to obtain a supercooled solution.

The other ingredients are added when the temperature of the molten dextrose falls to about 200°F., with vigorous stirring or alternatively in a twin screw extruder, to form a homogeneous mass. This material is molded into the desired shape and allowed to solidify, to form a white, glassy mass in the shape of tablet 20, which may be then placed in compartment 18.

Blood bag 14 may be initially free of any anti-coagulant. The entire system, including tablet 20, is typically radiation sterilizable, since it is substantially free of moisture. Additionally, no overpouch or other outer package is required to prevent the loss of water from a liquid anticoagulant present,

which constitutes a significant advantage over the conventional, present blood collection equipment.

Thus, as blood flows into bag 14, it picks up from first compartment 18 the desired amount of anticoagulant material. As another example, the anticoagulant may simply be a mixture of about 50 parts by weight of sodium citrate and about 10 parts by weight of citric acid, to form a short term anticoagulant for the blood.

After the blood has been collected into first bag 14, it may be centrifuged in conventional manner to settle the red cells. Then, the platelet-rich plasma is expressed through second blood tubing 30 into second bag 32, leaving behind in first bag 14 the packed red cells.

To resuspend the packed red cells, one may connect a branch tubing 34, having a sterile connector 37 utilized in commerical operations of the Fenwal Division of Baxter Travenol Laboratories, Inc. and disclosed, for example in U.S. Patent No. 4,340,097, connecting with a collapsible container 36 of aqueous solution. The nature of the aqueous solution depends upon the formulation in second compartment 38. For example, sterile water might be used, or, if desired, a dilute sugar or saline solution, with the formulation of the dry ingredient in second compartment 38 being appropriately modified in that circumstance to account for the added presence of sugar or saline.

Second compartment 38 in branch tubing 34 may be of construction similar to compartment 18, containing dry, soluble material. The dry material within second compartment 38 may also be similar to tablet 20, but generally of different formulation. Specifically, the tablet of the dissolvable material in compartment 38 may be formulated to reconstitute a red cell storage

solution when liquid passes through compartment 38 and tube 34, such reconstituted storage solution containing 27 mg./dl. of adenine, 2,000 mg./dl. of d-glucose, 750 mg./dl. of mannitol, and 550 mg./dl. of sodium chloride, this solution being substantially like ADSOL packed red cell preservative solution as described above.

After the platelet rich plasma has been expressed into second bag 32, the reconstituted red cell preservative solution may pass through tubings 34, 30 to resuspend the red cells in bag 14.

Following this, one may heat seal and cut tube 30 in conventional manner, to take first bag 14, with the resuspended packed red cells, away for cold storage.

Second blood bag 32 is then centrifuged to cause separation of platelets from the plasma. After the platelets have been so separated, as is conventional, the platelet poor plasma is expressed through added blood tubing 40 into added bag 42. Bag 42 may then be clamped off, and second branch tubing 44 may be connected by means of another sterile connector 46 or the like, similar to sterile connector 37, to another container 48 of aqueous solution. After sterile connection has been made, the solution flows through added compartment 50 (similar to compartment 38) and second branch tubing 44 into second bag 32, picking up dry solutes to become a reconstituting solution to resuspend the platelets in bag 32 for storage purposes. As stated previously, a typical platelet reconstituting solution which may be used is Seligman balanced salt solution having a formula as described in U.S. Patent No. 4,447,415. The dry materials in compartment 50 would be appropriately formulated to form such solution. Added blood tube 40 may then

then be sealed and severed in a conventional manner, so that the respective, sealed bags 32 and 42, containing their respective contents, may be conveyed to different storage sites.

As an alternative and preferred embodiment, referring to Fig. 1, collapsible container 36 and second compartment 38 may be made as a single, integral unit, with integral, frangible connector 37 being placed between them to limit the flow of aqueous solution from container 36 into second compartment 38, which contains a dry material for dissolution into the liquid. The same relationship may apply with respect to container 48 and added compartment 50, being manufactured in integral manner and separated by integral connector 46. Numerous frangible connectors are well-known to the art. One design of an integral, two-compartment system separated by a frangible connector is disclosed in Richmond, et al. U.S. Patent No. 4,465,488. Apart from the above modifications, this embodiment may be as previously described with respect to Fig. 1.

Such a multiple bag system has significant advantage in that it is relatively inexpensive to manufacture, when compared with systems that utilize corresponding sterile connectors, where a sterile connection must be made to connect originally separate, respective parts of the system. As an additional advantage, it becomes possible to gamma ray sterilize such a multiple bag system, since the liquid in bags 36, 48 is isolated from the solids of compartments 38, 50, 18. Thus the multiple bag system described above is not only relatively inexpensive to manufacture, but it is easy to sterilize, for large-scale, commercial mass production.

Accordingly, by this invention a system is provided having interconnected blood bags that are initially water free, for advantages as described above. The system may be used to not only collect blood, but to break it down into its respective components, and to store the components with artificial suspension solutions. Additionally, white cells may be separately collected and treated in a four bag assembly, if desired.

The above has been offered for illustrative purposes only, and is not intended to limit the scope of the invention of this application, which is as defined in the claims below.

THAT WHICH IS CLAIMED IS:

1. A multiple bag system for preparation of blood components, which comprises:

donated blood tubing communicating at one end with a first blood bag, a first compartment in flow communication with said donated blood tubing, said first compartment containing a physiologically-acceptable, dry anticoagulant for blood, whereby blood may flow through said first compartment to receive a predetermined amount of said anticoagulant and pass through said donated blood tubing to said first blood bag;

second blood tubing communicating between said first blood bag and a second blood bag, first branch tubing communicating between said first bag and a second compartment, said second compartment containing a physiologically-acceptable dry material which may be reconstituted into a red blood cell preservative solution by addition of sterile, aqueous liquid, and means permitting aseptic passage of sterile, aqueous liquid through said second compartment to receive a predetermined amount of said dry material into solution to form said preservative solution and permitting passage thereof to said first bag.

2. The multiple bag system of Claim 1 in which said branch tubing connects to said second blood tubing and communicates with said first bag via said second blood tubing.

3. The multiple bag system of Claim 1 in which added blood tubing communicates between said second blood bag and an added blood bag, second branch tubing communicating between said second bag and an added compartment, said added compartment containing a

physiologically-acceptable dry material which may be reconstituted into a platlet preservative solution by addition of sterile aqueous liquid, and means permitting aseptic passage of sterile, aqueous liquid through said added compartment, to receive a predetermined amount of said dry material to form said platlet preservative solution, and permitting passage thereof to said second bag.

4. The multiple bag system of Claim 3 in which said second branch tubing connects to said added blood tubing and communicates with said first bag via said added blood tubing.

5. The multiple bag system of Claim 3 in which said tubes and bags are all permanently integrally interconnected with each other.

6. A multiple bag system for preparation of blood components, which comprises:

donated blood tubing communicating at one end with a first blood bag, a first compartment in flow communication with said donated blood tubing, said first compartment containing a physiologically-acceptable, dry anticoagulant for blood, whereby blood may flow through said first compartment to receive a predetermined amount of said anticoagulant and pass through said donated blood tubing to said first blood bag; second blood tubing communicating between the first blood bag and a second blood bag, first branch tubing communicating between said first bag and a second compartment, said second compartment containing a physiologically-acceptable dry material which may be reconstituted into a red blood cell preservative solution by addition of sterile, aqueous liquid,

and means permitting aseptic passage of sterile, aqueous liquid through said second compartment to receive a predetermined amount of said dry material to form said perservative solution and permitting passage thereof to said first bag, said branch tubing connecting to said second blood tubing and communicating with the first bag via said second blood tubing;

added blood tubing communicating between said second blood bag and an added blood bag; second branch tubing communicating between the second bag and an added compartment; said added compartment containing a physiologically-acceptable dry material which may be reconstituted into a platelet preservative solution by addition of sterile aqueous liquid, and means permitting aseptic passage of sterile, aqueous liquid through said added compartment to receive a predetermined amount of said added compartment dry material into solution to form said platelet preservative solution and permitting passage thereof to said second bag, said second branch connecting with said added blood tubing and communicating with the second bag via said added blood tubing.

7. The multiple bag system of Claim 6 in which all tubes and bags are permanently, integrally interconnected with each other.

8. A multiple bag system for preparation of blood components, which comprises:

donated blood tubing communicating at one end with a first blood bag, a first compartment in flow communication with said donated blood tubing, said first compartment containing a physiologically-acceptable, dry anticoagulant for blood, whereby blood may flow through said first compartment to receive a predetermined amount of said anticoagulant and pass through said

donated blood tubing to said first blood bag;

added blood tubing communicating at least indirectly between said first blood bag and an added blood bag, branch tubing communicating between said first bag and an added compartment, said added compartment containing a physiologically-acceptable dry material which may be reconstituted into a platelet preservative solution by addition of sterile, aqueous liquid, and means permitting aseptic passage of sterile, aqueous liquid through said added compartment to receive a predetermined amount of said dry material into solution to form said preservative solution and permitting passage thereof to one of said blood bags.

9. The method which comprises passing blood through a tubing communicating at one end with the first blood bag and also passing said blood through a first compartment in flow communication with said tubing, the first compartment containing a physiologically-acceptable, dry anticoagulant for blood, whereby blood flowing through the first compartment receives a predetermined amount of the anticoagulant and passes through the donated blood tubing to the first blood bag;

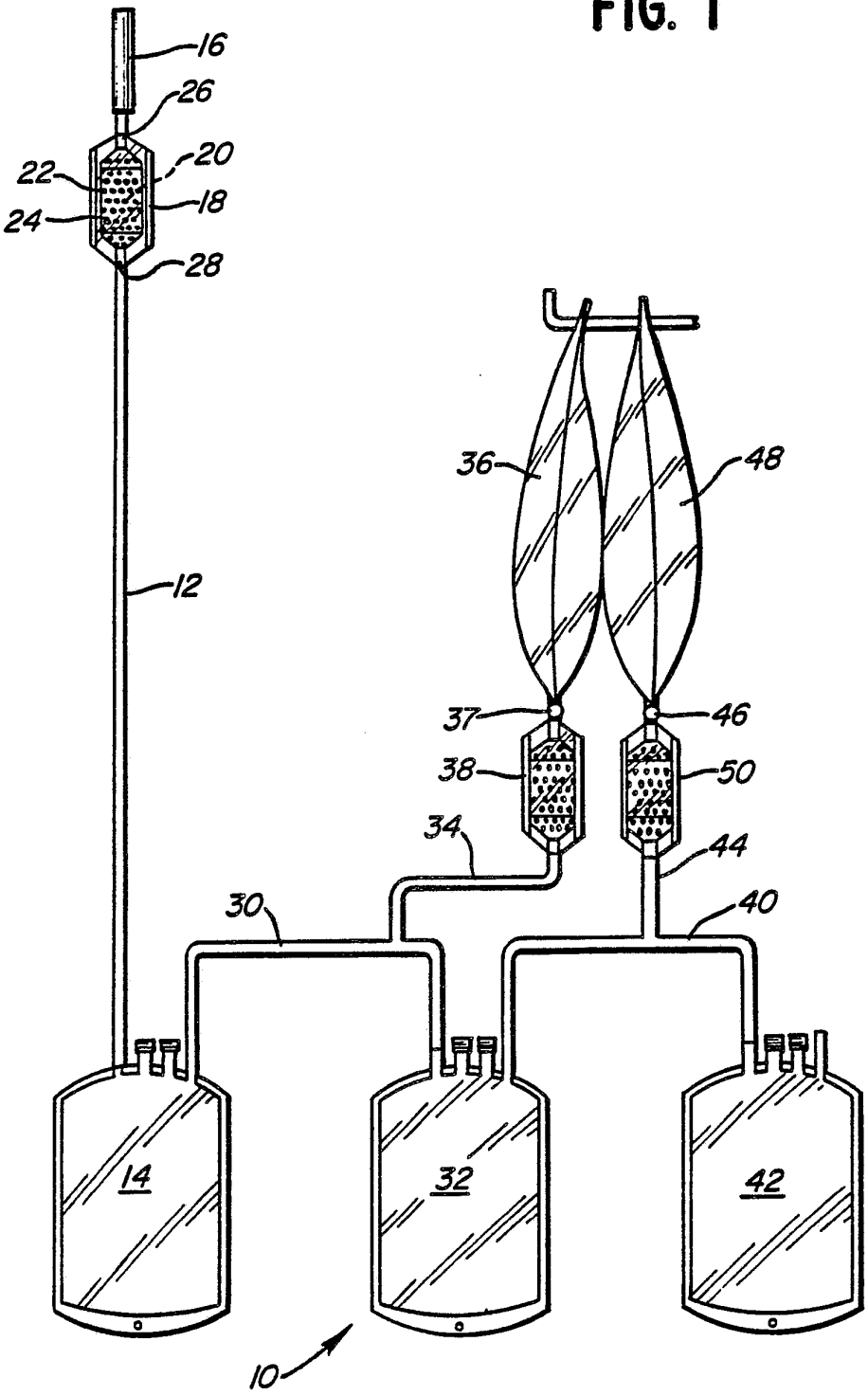
centrifuging said blood in the first blood bag to form packed red cells and plasma; passing said plasma through second blood tubing from said first blood bag to a second blood bag to leave the packed red cells behind in the first blood bag; connecting first branch tubing to a source of aqueous solution, said branch tubing communicating between said first bag and a second compartment which contains a physiologically-acceptable dry material which may be reconstituted into a red blood cell preservative solution by addition of sterile, aqueous liquid; passing said aqueous solution through said second compartment and first branch tubing

to produce said preservative solution; and conveying said preservative solution to the first bag to resuspend said packed red cells.

10. The method of Claim 9 including the further steps of centrifuging the second bag to separate platelets and plasma; conveying said plasma through second blood tubing from said second bag to an added bag while leaving said platelets behind; opening a flow passage between a source of sterile aqueous solution and a second branch tubing plus an added compartment in flow communication with said second branch tubing, said added compartment containing physiologically-acceptable dry material which may be reconstituted into a platelet preservative solution by addition of sterile, aqueous liquid; and allowing said aqueous liquid to flow through said added compartment and second branch tubing to the second bag, whereby said newly formed platelet storage solution enters said second bag to resuspend and facilitate storage of said platelets.

11. The method of Claim 10 in which connections between the respective bags are sealingly aseptically severed to separate said bags.

FIG. 1



INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03982

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61B 19/00
~~U.S.CL: 604/410~~

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	604/4, 6, 56, 82-85, 92, 185, 251, 252, 262, 408-410, 890, 892 424/467, 477

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US,A, 4,609,372 (CARMEN ET AL) 02 September 1986, see Fig. 1 and column 4, lines 40-60	1-11
Y	US,A, RE 25,129 (WALTER) 27 February 1962, see column 4, lines 15-35	1-11
Y	US,A, 4,235,236 (THEEUWES) 25 November 1980, column 5, line 21	1-11
Y	US,A, 4,680,025(KRUGER ET AL) 14 July 1987, see column 2, lines 42-54, column 3, lines 6-12, column 15, lines 29-49	1-11
A	US,A, 4,511,353 (THEEUWES) 16 April 1985, see abstract, see Figs. 1, 10	1-11

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31 January 1989	07 MAR 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Mark O. Polutta

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US,A, 4,381,776 (LATHAM) 03 May 1983, see column 1, lines 22-27	1
A	US,A, 4,223,675 (WILLIAMS) 23 September 1980, see Figs. 1-6, see abstract	1
A	CH, 497,181 (FUKIANOS) 30 November 1970, see Fig. 1, see column 3, lines 5-11	1

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ...., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.