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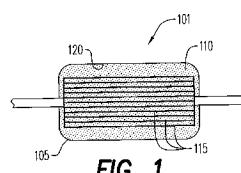


FIG. 1

(57) Abstract: An oxygen depletion device. The device has a cartridge; a plurality of hollow fibers extending within the cartridge from an entrance to an exit thereof; an amount of an oxygen scavenger packed within the cartridge and contiguous to and in between the plurality of hollow fibers. The hollow fibers are adapted to receiving and conveying red blood cells. There is another embodiment of an oxygen depletion device and method for removing oxygen from red blood cells.

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OXYGEN DEPLETION DEVICES AND METHODS FOR REMOVING OXYGEN FROM RED BLOOD CELLS

BACKGROUND OF THE INVENTION

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1. FIELD OF THE INVENTION

The present invention relates to devices for depleting oxygen from red blood cells to enhance storage life. The present invention relates to methods for depleting oxygen from red blood cells.

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2. BACKGROUND OF THE ART

Adequate blood supply and the storage thereof is a problem facing every major hospital and health organization around the world. Often, the amount of blood supply in storage is considerably smaller than the need therefor. This is especially true during crisis periods such as natural catastrophes, war and the like, when the blood supply is often perilously close to running out. It is at critical times such as these that the cry for more donations of fresh blood is often heard. However, unfortunately, even when there is no crisis period, the blood supply and that kept in storage must be constantly monitored and replenished, because stored blood does not maintain its viability for long.

Stored blood undergoes steady deterioration which is, in part, caused by hemoglobin oxidation and degradation and adenosine triphosphate (ATP) and 2,3-biphosphoglycerate (DPG) depletion. Oxygen causes hemoglobin (Hb) carried by the red blood cells (RBCs) to convert to met-Hb, the breakdown of which produces toxic products such as hemichrome, hemin and free Fe³⁺. Together with the oxygen, these products catalyze the formation of hydroxyl radicals (OH.cndot.), and both the OH.cndot. and the met-Hb breakdown products damage the red blood cell lipid membrane, the membrane skeleton, and the cell contents. As such, stored blood is considered unusable after 6 weeks, as determined by

the relative inability of the red blood cells to survive in the circulation of the transfusion recipient. The depletion of DPG prevents adequate transport of oxygen to tissue thereby lowering the efficacy of transfusion immediately after administration (levels of DPG recover once in recipient

5 after 8-48 hrs). In addition, these deleterious effects also result in reduced overall efficacy and increased side effects of transfusion therapy with stored blood before expiration date, but possibly older than two weeks are used.

10 There is, therefore, a need to be able to deplete oxygen levels in red blood cells prior to storage on a long-term basis without the stored blood undergoing the harmful effects caused by the oxygen and hemoglobin interaction.

15 **SUMMARY OF THE INVENTION**

Accordingly, the present disclosure provides for a disposable device that is able to remove oxygen from red blood cells.

20 The present disclosure provides for an oxygen depletion device. The device has a cartridge; a plurality of hollow fibers extending within the cartridge from an entrance to an exit thereof; an amount of an oxygen scavenger packed within the cartridge and contiguous to and in between the plurality of hollow fibers. The hollow fibers are adapted to receiving 25 and conveying red blood cells.

The present disclosure provides for an oxygen depletion device. The device has a receptacle of a solid material having an inlet and an outlet adapted to receiving and expelling a flushing gas and a plurality of 30 hollow fibers extending within the receptacle from an entrance to an exit thereof. The hollow fibers are adapted to receiving and conveying red blood cells.

The present disclosure provides for a method for removing oxygen from red blood cells. The method has the step of passing the red blood cells through an oxygen device. The device has a cartridge; a plurality of hollow fibers extending within the cartridge from an entrance to an exit thereof; and an amount of an oxygen scavenger packed within the cartridge and contiguous to and in between the plurality of hollow fibers. The hollow fibers are adapted to receiving and conveying red blood cells

The present disclosure provides for a method for removing oxygen from red blood cells. The method has the step of passing the red blood cells through an oxygen device. The device has a receptacle of a solid material having an inlet and an outlet adapted to receiving and expelling a flushing gas; and a plurality of hollow fibers films extending within the receptacle from an entrance to an exit thereof. The hollow fibers are adapted to receiving and conveying red blood cells.

The present disclosure and its features and advantages will become more apparent from the following detailed description with reference to the accompanying drawings.

20 BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 illustrates a pre-storage oxygen depletion device of the present invention.

25 Figs. 2a through 2c illustrate an embodiment of a depletion device that depletes oxygen from red blood cells prior to storage by a flushing inert gas around a hollow fiber inside the assembly.

30 Figs. 3a through 3c illustrate another embodiment of a depletion device that depletes oxygen from red blood cell prior to storage.

Figs. 4a through 4c illustrate another embodiment of a depletion device that depletes oxygen from red blood cells prior to storage wherein oxygen is scavenged by scavenger materials in the core of the cylinder, surrounded by hollow fibers.

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Figs. 5a through 5c illustrate another embodiment of a depletion device that depletes oxygen from red blood cells wherein oxygen is scavenged by scavenger materials surrounding cylinders of hollow fibers.

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Fig. 6 illustrates a plot of flow rate of RBC suspension per minute versus oxygen partial pressure for the depletion devices of Figs. 2a through 2c, Figs. 3a through 3c, Figs. 4a through 4c and Figs. 5a through 5c.

15

DETAILED DESCRIPTION OF THE DISCLOSURE

Referring to Fig. 2, an oxygen depletion device (ODD) 101 contains an oxygen sorbent 110. ODD 101 is a disposable cartridge 105 containing oxygen sorbent 110 and a series of hollow fibers 115. Oxygen sorbent 110 is a mixture of non-toxic inorganic and/or organic salts and ferrous iron or other materials with high reactivity toward oxygen. Oxygen sorbent 110 is made from particles that have significant absorbing capacity for O₂ (more than 5 ml O₂/g) and can maintain the inside of cartridge 105 to less than 0.01%, which corresponds to PO₂ less than 0.08 mmHg. Oxygen sorbent 110 is either free or contained in an oxygen permeable envelope. ODD 101 of the present disclosure can deplete approximately 100 mL of oxygen from a unit of blood.

RBCs pass through hollow porous fibers 115. Porous fibers are capable of high oxygen permeability rates. Suitable materials for porous fibers include polyolefins, Teflon, polyesters, PVDF, polysulfone, and other hydrophobic polymers as well as inorganic materials (ceramics). Oxygen

depletion takes place as RBCs pass through membrane 115. ODD provides a simple structure having a large surface area to remove oxygen and maintain constant flow of blood therethrough. The oxygen depletion or removal is accomplished by irreversible reaction of ferrous ion in oxygen 5 sorbent 110 with ambient oxygen to form ferric oxide. ODD 101 does not need agitation for oxygen removal and can be manufactured easily to withstand centrifugation as part of a blood collection system as necessary.

Referring to Figs. 2a through 2c and Figs. 3a through 3c, examples 10 of flushing depletion devices are disclosed. The depletion devices function to deplete O₂ by supplying appropriate composition of flushing gas. Gases appropriate for depletion devices include, for example, Ar, He, CO₂, N₂.

Figs. 4a through 4c and 5a through 5c, also disclose scavenging 15 depletion devices. Depletion takes place with the use of scavengers or sorbents and without the use of external gases. In both types of depletion devices however, oxygen depletion is effective to enhance DPG and ATP, respectively, prior to storage in blood storage bags.

20 Referring to Figs. 2a through 2c, a depletion device 20 is shown. Depletion device 20 includes a plurality of fibers 25, approximately 5000 in number, through which red blood cells flow. Plurality of fibers 25 are surrounded by a plastic cylinder 30. Plastic cylinder 30 contains a gas inlet 35 and a gas outlet 40 through which a flushing gas or a combination of 25 flushing gases, such as those mentioned above, are supplied to remove oxygen from blood. Specifications for depletion device 20 are shown in Table 1 below.

Table 1

Prototype Specification	Eternal Gas Pathways	External Gas Pathways
Prototype Serial #:	Device 20	
Fiber Type:	Celgard 200/150-66FPI	Celgard 200/150-66FPI
Number of Fibers:	5000	5000
Active Length of Fibers (cm):	13	28
Fiber OD (microns):	200	200
Fiber ID (microns):	150	150
Total Length of Fibers	15	30
Active Fiber Surface Area (m ²):	0.4084	0.8796

Referring to Figs. 3a through 3c, a depletion device 45 is shown.

Depletion device 45, like device 20 of Figs. 2a to 2c, includes a plurality of fibers 50, approximately 5000 in number, through which red blood cells flow. Plurality of fibers 50 are surrounded by a plastic cylinder 55. Plastic cylinder 55 contains a gas inlet 60 and a gas outlet 65 through which a gas or a combination of gases, such as those mentioned above are supplied to remove oxygen from blood. Specifications for depletion device 45 are shown in Table 2 below. The active surface area of depletion of device 45 is twice that of device 20 because device 45 is twice as long as device 20.

Table 2

Prototype Specification	Eternal Gas Pathways	External Gas Pathways
Prototype Serial #:		Device 45
Fiber Type:	Celgard 200/150-66FPI	Celgard 200/150-66FPI
Number of Fibers:	5000	5000
Active Length of Fibers (cm):	13	28
Fiber OD (microns):	200	200
Fiber ID (microns):	150	150
Total Length of Fibers	15	30
Active Fiber Surface Area (m ²):	0.4084	0.8796

15 Figs. 4a through 4c disclose a depletion device 70 having a core 75 containing scavenging materials for O₂. Core 75 is packed by a gas permeable film with very low liquid permeability. Hollow fibers 80 are

wound around core 75, and a plastic cylinder 82 contains and envelopes hollow fibers 80. In this particular embodiment, the active surface area for depletion is approximately 0.8796m^2 as shown in Table 3 below.

5

Table 3

Prototype Specification	Center Core 125 grams Sorbent	10 individual Bundles200 grams Sorbent
Prototype Serial #:	Device 70	
Fiber Type:	Celgard 200/150-66FPI	Celgard 200/150-66FPI
Number of Fibers:	5000	5000
Active Length of Fibers (cm):	13	28
Fiber OD (microns):	200	200
Fiber ID (microns):	150	150
Total Length of Fibers	15	30
Active Fiber Surface Area (m^2):	0.8796	0.8796

Figs. 5a through 5c disclose a depletion device 85 containing fiber bundles 87 enclosed in gas permeable film with very low liquid permeability. Fiber bundles 87 are surrounded by scavenger materials 89 for O_2 . Fiber bundles 87 and scavenger materials 89 are contained within a plastic cylinder 90. The active surface area for depletion is approximately 0.8796m^2 as shown in Table 4 below.

10

Table 4

Prototype Specification	Center Core 125 grams Sorbent	10 individual Bundles200 grams Sorbent
Prototype Serial #:		Device 85
Fiber Type:	Celgard 200/150-66FPI	Celgard 200/150-66FPI
Number of Fibers:	5000	5000
Active Length of Fibers (cm):	13	28
Fiber OD (microns):	200	200
Fiber ID (microns):	150	150
Total Length of Fibers	15	30
Active Fiber Surface Area (m^2):	0.8796	0.8796

Fig. 6 is a plot of the performance of flushing depletion devices 20 and 45 and scavenging depletion devices 70 and 85. The data of Fig. 6 was plotted using the following conditions: Hematocrit, 62% (pooled 3 units of pRBC), and 21°C at various head heights to produce different flow rates.

5 Oxygen scavenger (Multisorb Technologies, Buffalo, NY) was activated with adding 5% and 12% w/w water vapor for device 79 and device 85, respectively. Data are plotted with flow rate (g RBC suspension per min) vs. pO_2 (mmHg).

10 In the oxygen depletion devices disclosed herein, the hollow fibers may be packed in any suitable configuration within the cartridge, such as linear or longitudinal, spiral, or coil, so long as they can receive and convey red blood cells.

15 Fig. 6 shows that lowest oxygen saturation is achieved using devices 45 and 85. Device 45 exhibits a larger active surface area exposed to gases along length of fibers 50. Device 85 also has a long surface area of exposure to scavenging materials. Device 85 has bundles 87 surrounded by scavenging materials 89. The space occupied by 20 scavenging materials 89 between bundles 87 promotes dispersion of oxygen from red blood cells contained in fiber bundles 87, thus aiding scavenging of oxygen from red blood cells.

A further use of the depletion devices is to add back oxygen prior 25 to transfusion by flushing with pure oxygen or air. This use is for special cases, such as massive transfusions, where the capacity of the lung to reoxygenate transfused blood is not adequate, or sickle cell anemia.

30 Similarly, depletion devices can be used to obtain intermediate levels or states of depletion of oxygen depending needs of the patient to obtain optimal levels in the transfused blood depending upon the patients needs.

It is within the scope of the present invention to remove oxygen from the RBCs or to strip oxygen from the blood prior to storage in the storage bags. An oxygen scavenger can be used to remove the oxygen from the RBCs prior to storage in the blood bags. As used herein, "oxygen scavenger" is a material that irreversibly binds to or combines with oxygen under the conditions of use. For example, the oxygen can chemically react with some component of the material and be converted into another compound. Any material where the off-rate of bound oxygen is zero can serve as an oxygen scavenger. Examples of oxygen scavengers include iron powders and organic compounds. The term "oxygen sorbent" may be used interchangeably herein with oxygen scavenger. For example, oxygen scavengers are provided by Multisorb Technologies (Buffalo, NY). Such materials can be blended to a desired ratio to achieve desired results.

It will be appreciated that scavengers can be incorporated into storage receptacles and bags in any known form, such as in sachets, patches, coatings, pockets, and packets.

Although the present invention describes in detail certain embodiments, it is understood that variations and modifications exist known to those skilled in the art that are within the invention. Accordingly, the present invention is intended to encompass all such alternatives, modifications and variations that are within the scope of the invention as set forth in the disclosure.

WHAT IS CLAIMED IS

1. An oxygen depletion device, comprising:
 - a cartridge;
 - 5 a plurality of hollow fibers extending within the cartridge from an entrance to an exit thereof, wherein the hollow fibers are formed of an oxygen-permeable membrane and are adapted to receiving and conveying red blood cells; and
 - 10 an amount of an oxygen scavenger packed within the cartridge and contiguous to and in between the plurality of hollow fibers.
2. The device of claim 1, wherein the hollow fibers are substantially parallel and longitudinally disposed within the cartridge from the entrance to the exit.
- 15 3. An oxygen depletion device, comprising:
 - a receptacle of a solid material having an inlet and an outlet adapted to receiving and expelling a flushing gas;
 - 20 a plurality of hollow fibers extending within the receptacle from an entrance to an exit thereof, wherein the hollow fibers are adapted to receiving and conveying red blood cells.
- 25 4. The device of claim 3, wherein the hollow fibers are substantially parallel and longitudinally disposed within the cartridge from the entrance to the exit.
5. The device of claim 3, further including a source of flushing gas in communication with the inlet of the receptacle.

6. A method for removing oxygen from red blood cells, comprising: passing the red blood cells through an oxygen device, wherein the device includes

a cartridge;

5 a plurality of hollow fibers extending within the cartridge from an entrance to an exit thereof, wherein the hollow fibers are adapted to receiving and conveying red blood cells; and

an amount of an oxygen scavenger packed within the cartridge and contiguous to and in between the plurality of hollow fibers.

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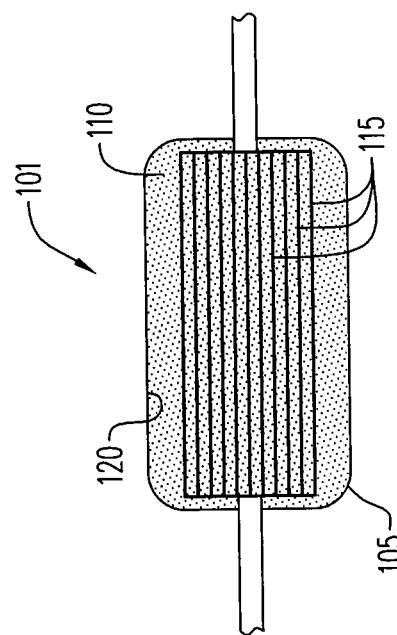
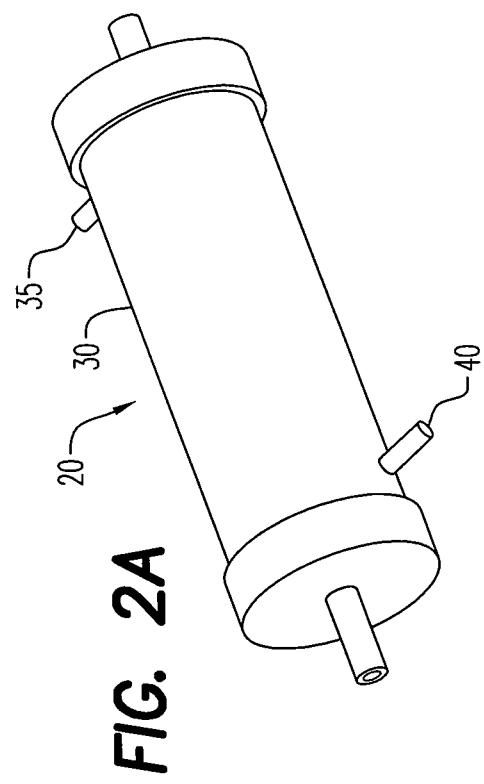
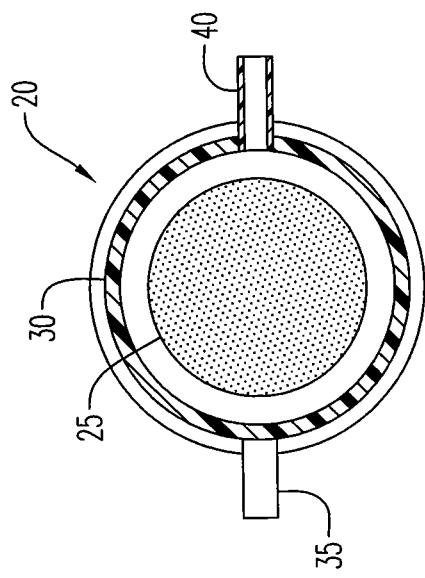
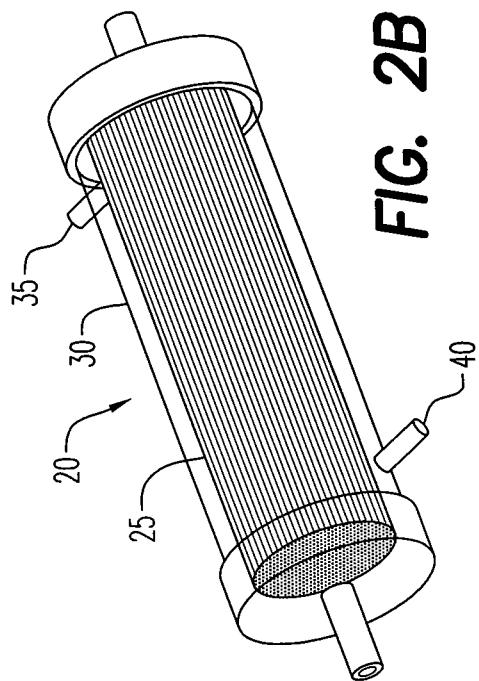
7. A method for removing oxygen from red blood cells, comprising: passing the red blood cells through an oxygen depletion device, wherein the device includes

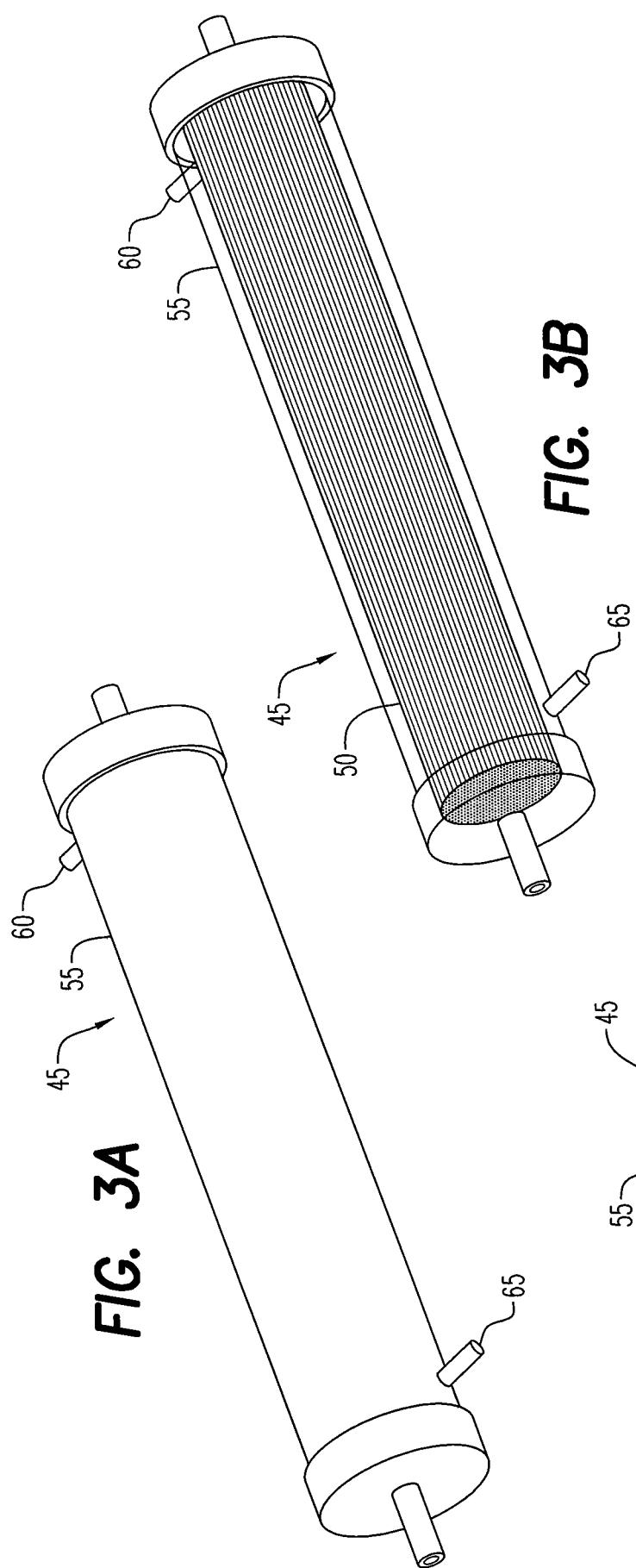
a receptacle of a solid material having an inlet and an outlet

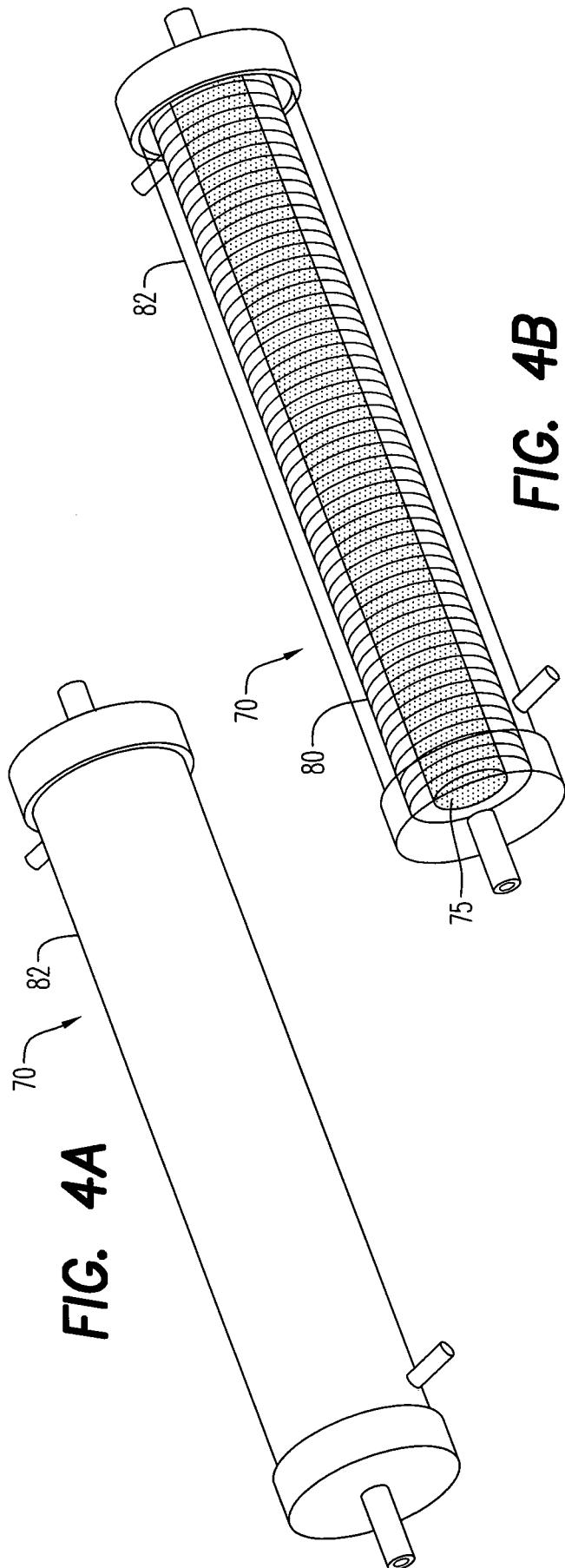
15 adapted to receiving and expelling a flushing gas;

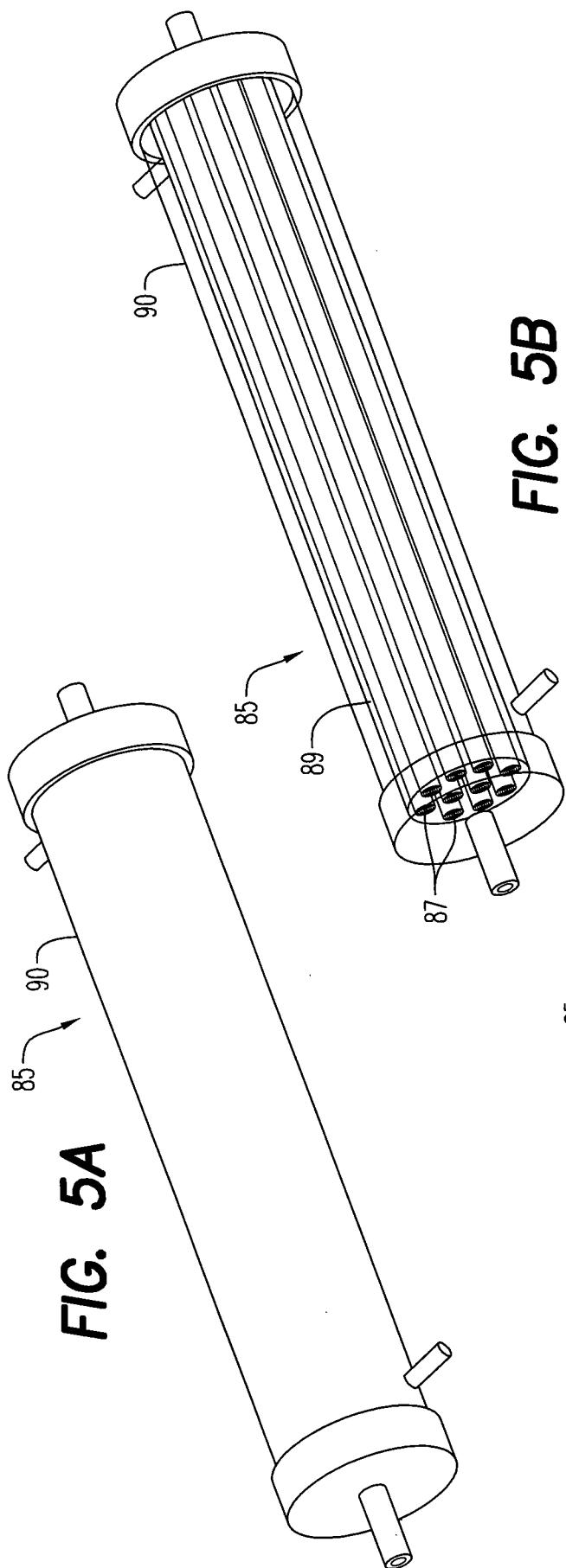
a plurality of hollow fibers films extending within the receptacle from an entrance to an exit thereof, wherein the hollow fibers are adapted to receiving and conveying red blood cells.

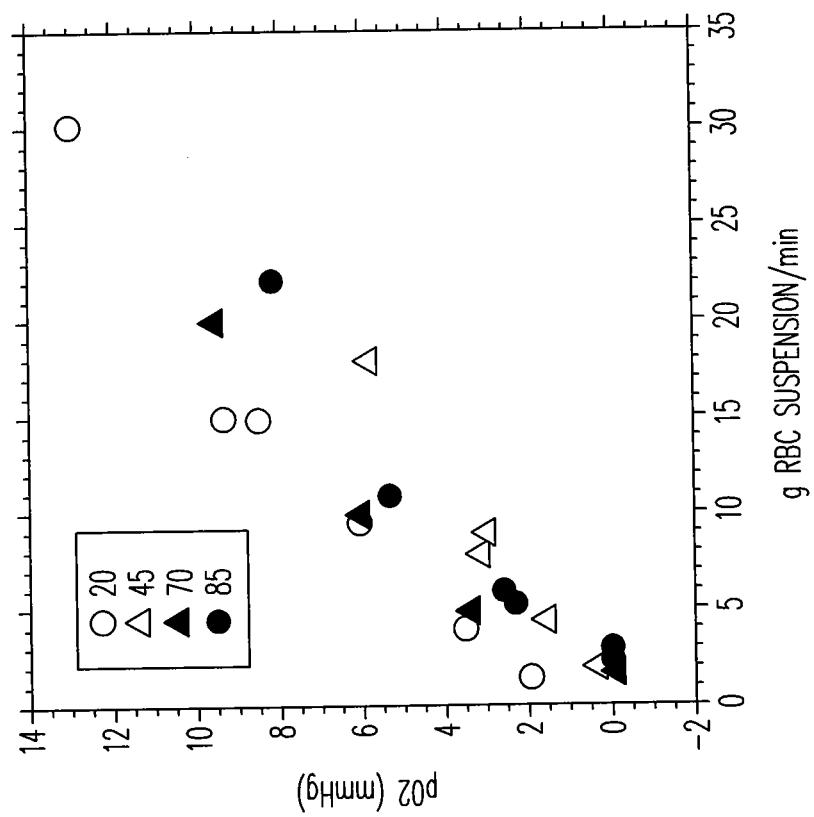
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**FIG. 6**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2010/052376

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 1/02 (2010.01)

USPC - 435/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A01N 1/02; A61M 1/00, 37/00; C10J 1/08 (2010.01)

USPC - 261/122.1; 435/2; 604/4, 5.04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0230856 A1 (PAREKH et al) 20 October 2005 (20.10.2005) entire document	1-7
Y	US 2008/0243045 A1 (PASQUALINI) 02 October 2008 (02.10.2008) entire document	1-5
Y	US 5,624,794 A (BITENSKY et al) 29 April 1997 (29.04.1997) entire document	6-7
A	EP 0,890,368 A1 (PORRO et al) 13 January 1999 (13.01.1999) entire document	1-7

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

22 November 2010

Date of mailing of the international search report

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