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(54) **OXYGEN DEPLETION DEVICES AND METHODS FOR REMOVING OXYGEN FROM RED BLOOD CELLS**

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(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.

18 Claims, 5 Drawing Sheets

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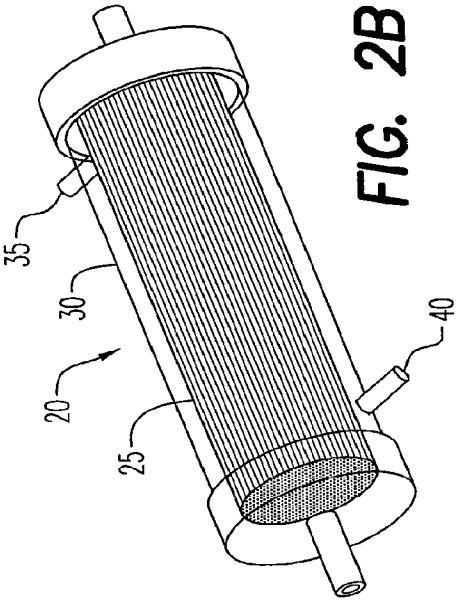

FIG. 2B

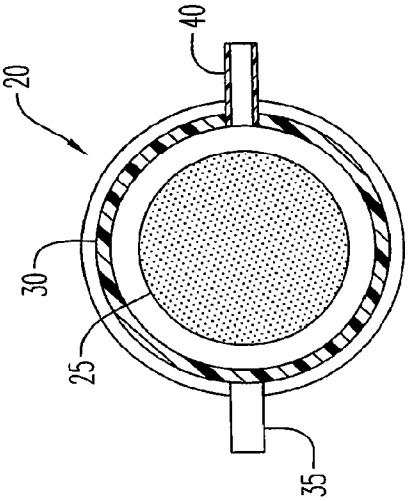

FIG. 2C

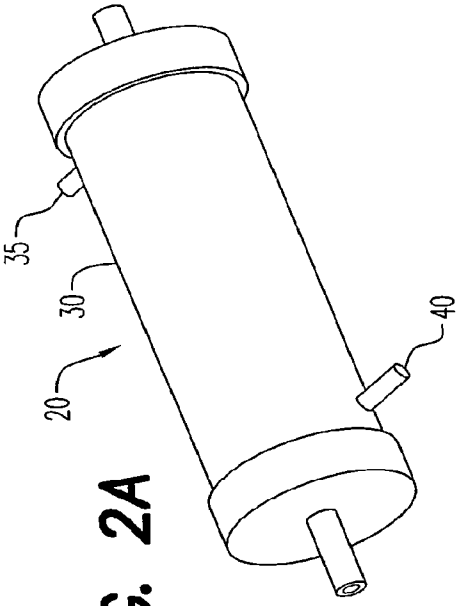

FIG. 2A

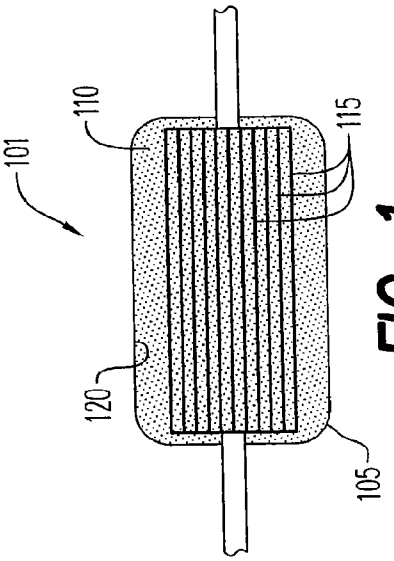

FIG. 1

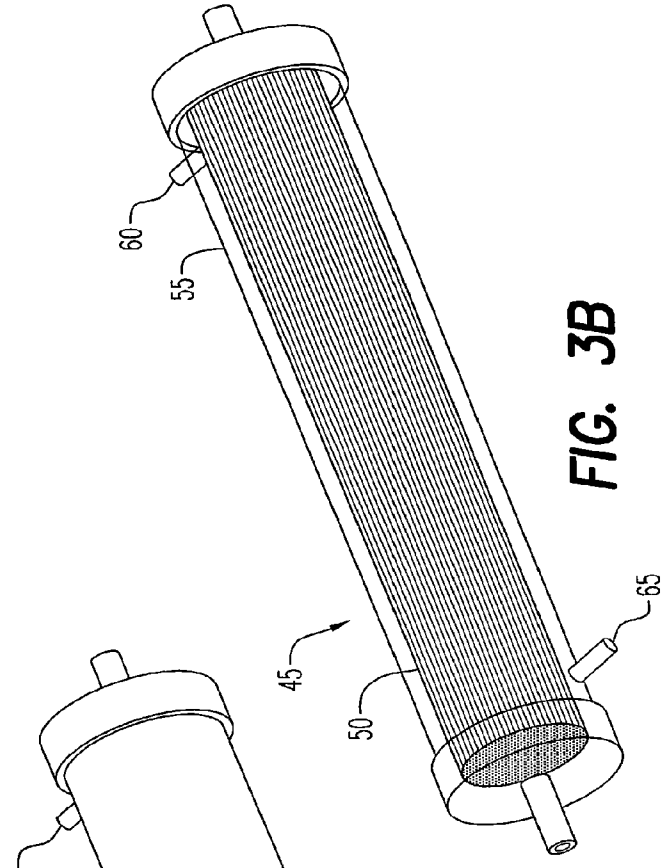

FIG. 3B

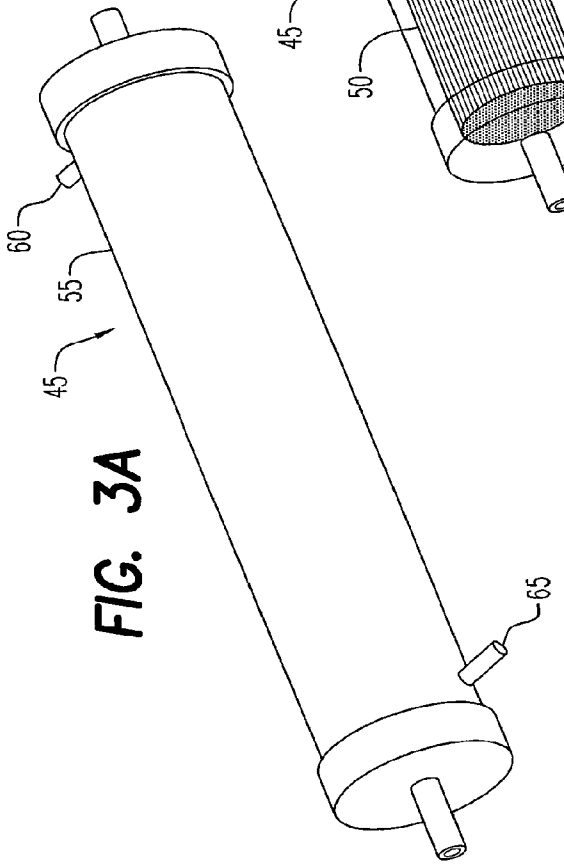

FIG. 3A

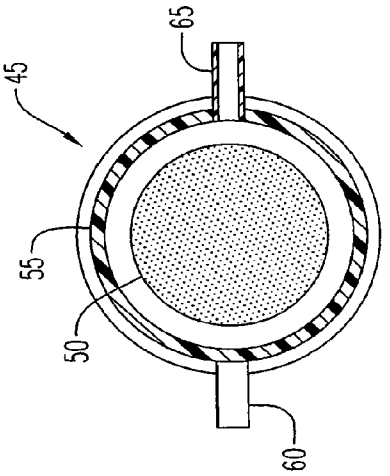

FIG. 3C

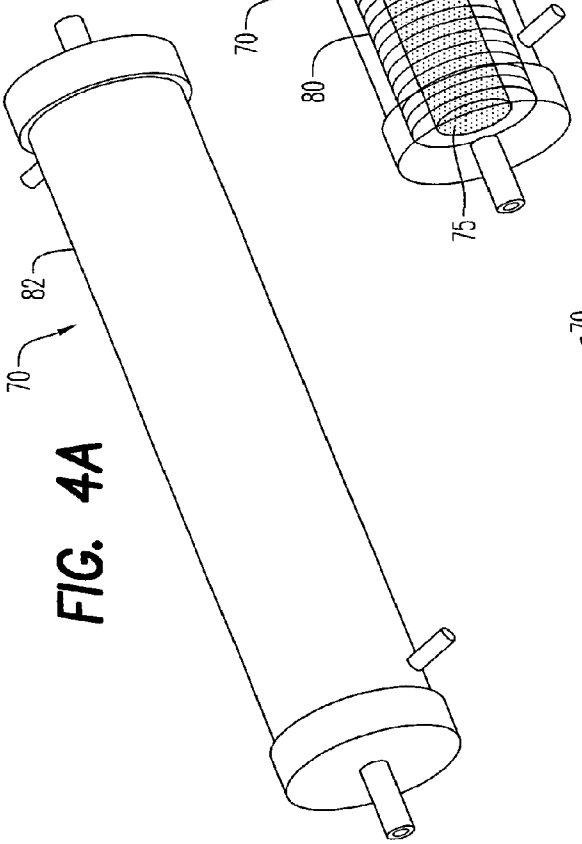

FIG. 4A

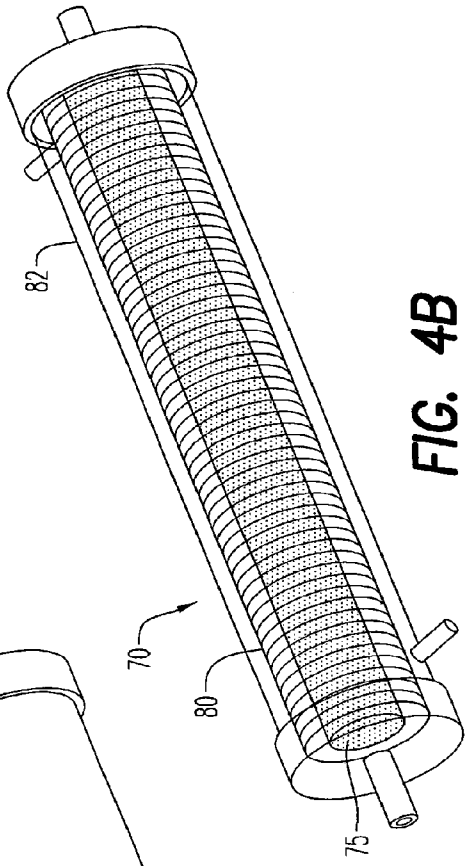

FIG. 4B

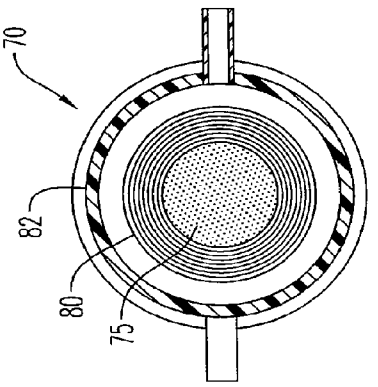

FIG. 4C

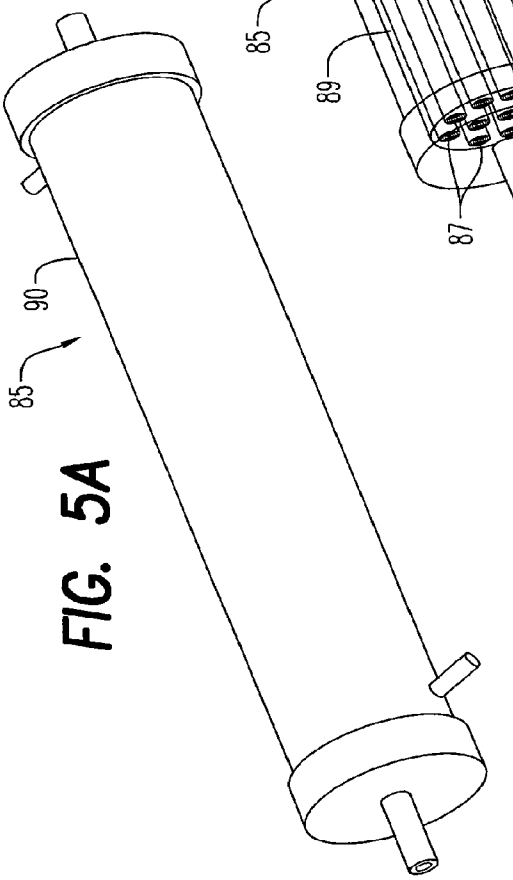

FIG. 5A

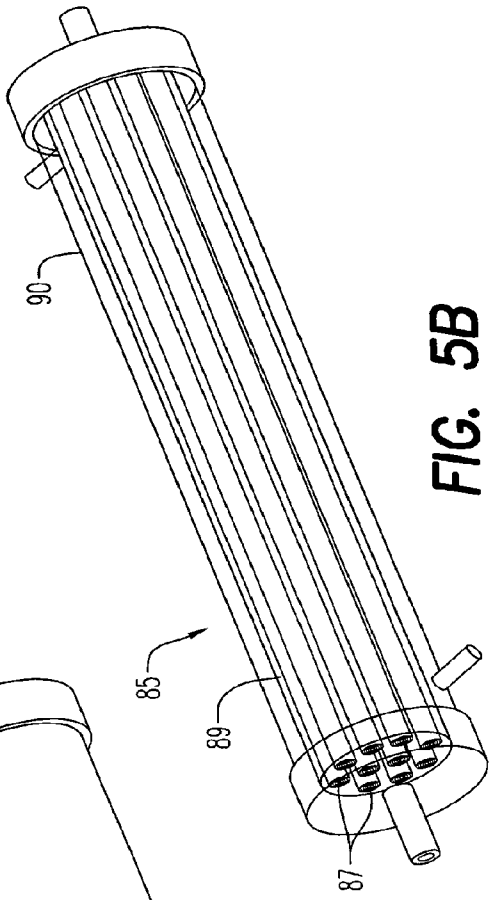

FIG. 5B

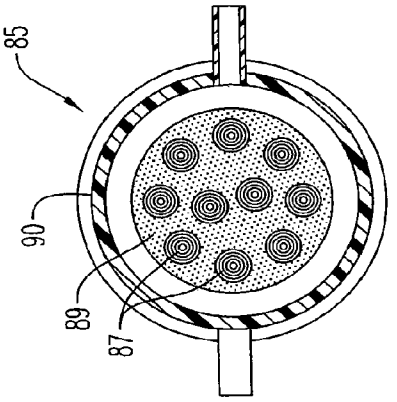

FIG. 5C

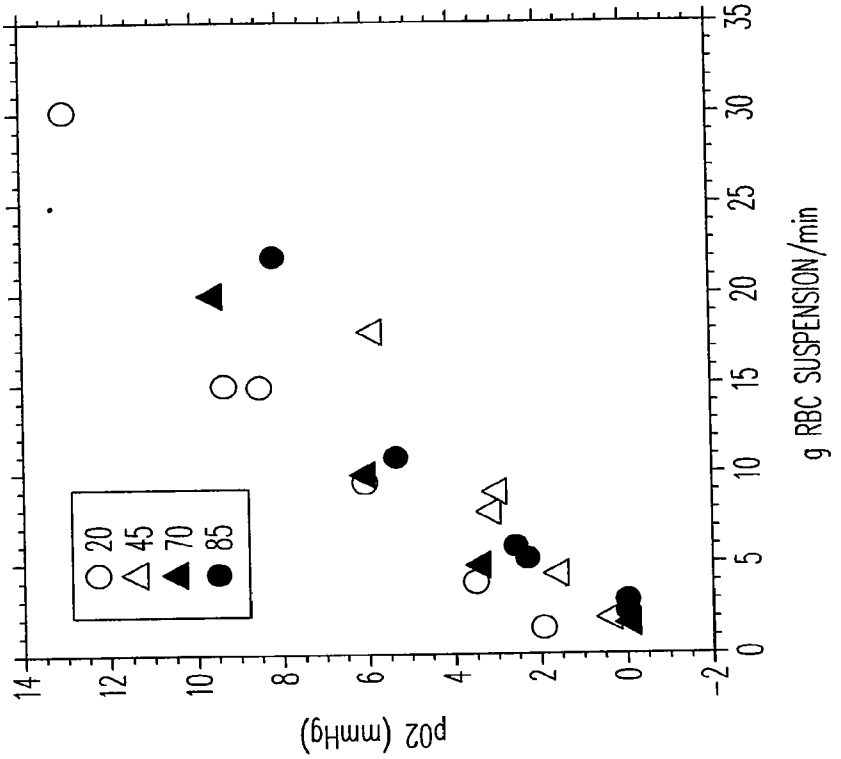
pO2 (mmHg)
14
12
10
8
6
4
2
0
-2
0
5
10
15
20
25
30
35
g RBC SUSPENSION/min
20
45
70
85

FIG. 6

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

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 13/115,532, filed May 25, 2011, now U.S. Pat. No. 8,569,052, issued Oct. 29, 2013, which claims the benefit under 35 U.S.C. §119(e) to U.S. application Ser. No. 12/903,057, filed on Oct. 12, 2010, which claims priority to U.S. Provisional Application No. 61/250,661, filed Oct. 12, 2009. All of the foregoing applications are hereby incorporated by reference in their entireties.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grants awarded by the National Institutes of Health (NIH) and the National Heart Lung and Blood Institute (NHLBI). The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

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.

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 Fe^{3+}. 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 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.

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.

SUMMARY OF THE INVENTION

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

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 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 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.

BRIEF DESCRIPTION OF THE FIGURES

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

FIG. **2***a* illustrates 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.

FIG. **2***b* illustrates 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.

FIG. **2***c* illustrates 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.

FIG. **3***a* illustrates another embodiment of a depletion device that depletes oxygen from red blood cells prior to storage.

FIG. **3***b* illustrates another embodiment of a depletion device that depletes oxygen from red blood cells prior to storage.

FIG. **3***c* illustrates another embodiment of a depletion device that depletes oxygen from red blood cells prior to storage.

FIG. **4***a* illustrates 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.

FIG. **4***b* illustrates 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.

FIG. **4***c* illustrates 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.

FIG. **5***a* illustrates 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.

FIG. **5***b* illustrates 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.

FIG. **5***c* illustrates 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.

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

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 O_2 (more than 5 ml O_2/g) and can maintain the inside of cartridge **105** to less than 0.01%, which corresponds to PO_2 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® (polytetrafluoroethylene), polyesters, polyvinylidene fluoride (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 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. **2***a* through **2***c* and FIGS. **3***a* through **3***c*, examples of flushing depletion devices are disclosed. The depletion devices function to deplete O_2 by supplying appropriate composition of flushing gas. Gases appropriate for depletion devices include, for example, Ar, He, CO_2, N_2.

FIGS. **4***a* through **4***c* and **5***a* through **5***c*, also disclose scavenging 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.

Referring to FIGS. **2***a* through **2***c*, 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 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 (m2):	0.4084	0.8796

Referring to FIGS. **3***a* through **3***c*, a depletion device **45** is shown. Depletion device **45**, like device **20** of FIGS. **2***a* to **2***c*, 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 (m2):	0.4084	0.8796

FIGS. **4***a* through **4***c* disclose a depletion device **70** having a core **75** containing scavenging materials for O_2. 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 0.8796 m^2 as shown in Table 3 below.

TABLE 3

Prototype Specification	Center Core 125 grams Sorbent	10 individual Bundles 200 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 (m2):	0.8796	0.8796

FIGS. **5***a* through **5***c* 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 0.8796 m^2 as shown in Table 4 below.

TABLE 4

Prototype Specification	Center Core 125 grams Sorbent	10 individual Bundles 200 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. Oxygen scavenger (Multisorb Technologies, Buffalo, N.Y.) 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).

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.

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 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 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.

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, N.Y.). 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:

1. A method for adding oxygen to red blood cells comprising: passing red blood cells through an oxygen addition device, wherein said device comprises:

a receptacle of a solid material having an inlet and an outlet receiving and expelling a gas; and

a plurality of hollow fibers extending within said receptacle from an entrance to an exit thereof, wherein said plurality of hollow fibers receive and convey said red blood cells, wherein said red blood cells are passaged within said hollow fibers.

2. The method of claim **1**, wherein said red blood cells entering said oxygen addition device are oxygen-depleted red blood cells.

3. The method of claim **1**, wherein said gas is pure oxygen.

4. The method of claim **1**, wherein said gas is air.

5. The method of claim **1**, wherein said plurality of hollow fibers are formed from an oxygen-permeable material selected from the group consisting of polyolefin, polytetrafluoroethylene, polyester, polyvinylidene fluoride (PVDF), and polysulfone.

6. The method of claim **1**, wherein said plurality of hollow fibers are formed from a hydrophobic polymer.

7. The method of claim **1**, wherein said plurality of hollow fibers are formed from an inorganic ceramic.

8. The method of claim 1, wherein said plurality of hollow fibers are configured as a linear spiral, a longitudinal spiral, or a coil.

9. A method for preparing red blood cells for transfusion into a subject in need thereof, comprising: passing red blood cells through an oxygen addition device and transfusing re-oxygenated red blood cells to said subject, wherein said device comprises:

a receptacle of a solid material having an inlet and an outlet receiving and expelling a gas; and

a plurality of hollow fibers extending within said receptacle from an entrance to an exit thereof, wherein said plurality of hollow fibers receive and convey said red blood cells, wherein said red blood cells are passaged within said hollow fibers.

10. The method of claim 9, wherein said subject is a patient with inadequate lung capacity to re-oxygenate transfused blood.

11. The method of claim 9, wherein said subject is a patient with sickle cell anemia.

12. The method of claim 9, wherein said red blood cells entering said oxygen addition device are oxygen-depleted red blood cells.

13. The method of claim 9, wherein said gas is pure oxygen.

14. The method of claim 9, wherein said gas is air.

15. The method of claim 9, wherein said plurality of hollow fibers are formed from an oxygen-permeable material selected from the group consisting of polyolefin, polytetrafluoroethylene, polyester, polyvinylidene fluoride (PVDF), and polysulfone.

16. The method of claim 9, wherein said plurality of hollow fibers are formed from a hydrophobic polymer.

17. The method of claim 9, wherein said plurality of hollow fibers are formed from an inorganic ceramic.

18. The method of claim 9, wherein said plurality of hollow fibers are configured as a linear spiral, a longitudinal spiral, or a coil.

* * * * *