



A REVIEW ON ARTIFICIAL BLOOD

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Account Information	ABSTRACT
Original Review article	Artificial blood products, including hemoglobin-based oxygen carriers (HBOCs) and Perfluorocarbons (PFCs), have been developed as potential substitutes for human blood. These products aim to address critical shortages, provide blood transfusion alternatives in emergencies, and overcome risks associated with human blood, such as disease transmission. Despite considerable progress, artificial blood products face challenges in oxygen-carrying capacity, biocompatibility, and regulatory approval. This review examines the current state of artificial blood development, explores the benefits and limitations of available products, and discusses ongoing research in the field.
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1. INTRODUCTION

Artificial blood refers to substances designed to perform the same critical functions as natural human blood, particularly in carrying oxygen to tissues and facilitating the removal of carbon dioxide. Artificial blood has the potential to replace human blood in emergencies, during surgeries, and in situations where blood donations are unavailable or insufficient. Despite extensive research and development, artificial blood has not yet fully replicated the broad array of functions that human blood performs, but significant advancements are being made. This detailed review explores the key types of artificial blood, their potential benefits, challenges, and the ongoing research aimed at improving these products.

The need for blood substitutes has been a long-standing issue in medical practice, particularly in emergency situations, surgeries, and regions with blood supply shortages. While human blood remains the gold standard for transfusion, the demand often exceeds supply, and there are concerns about the safety of blood donations, including the risks of transmitting infectious diseases. Artificial blood, designed to perform similar functions to natural blood—such as oxygen and carbon dioxide transport—has garnered significant attention. The development of artificial blood substitutes aims to address these issues, but challenges remain in achieving an ideal product that mimics the complex functions of human blood. (1)

Blood transfusions are essential in medicine, particularly in trauma care, surgery, and for patients with chronic blood conditions (e.g., Anemia). However, there are significant challenges related to the availability, safety, and compatibility of human blood donations. Artificial blood products, designed to simulate the functions of natural blood, could overcome many of these issues. HBOCs and PFCs are potential blood substitutes for transfusion therapy. However, despite progress, artificial blood substitutes still face many hurdles in terms of effectiveness, safety, and regulatory approval. (2)

Types of Artificial Blood

1. Hemoglobin-Based Oxygen Carriers (HBOCs):

These products use purified and sometimes modified hemoglobin—the protein found in red blood cells that is responsible for carrying oxygen. HBOCs work by binding to oxygen in the lungs and releasing it in tissues with low oxygen levels, similar to how natural red blood cells function. HBOCs are designed to efficiently carry oxygen to tissues, mimicking the function of natural red blood cells. Unlike human blood, which must be refrigerated and has a limited shelf life, HBOCs can be stored at room temperature for extended periods (weeks to months), making them highly convenient for emergency and military use. Since HBOCs do not rely on human blood, they do not require matching blood types, making them universally compatible.

Examples: Hemopure (derived from bovine hemoglobin), Polyheme (human hemoglobin-based).

HBOCs are associated with several side effects, including vasoconstriction (narrowing of blood vessels), which can lead to high blood pressure and tissue damage. Other worries are kidney damage, oxidative stress, and immune responses. HBOCs may have a higher oxygen affinity than natural red blood cells, which could impair the ability to release oxygen in low-oxygen tissues, a critical aspect of their function. HBOCs do not perform other essential functions of red blood cells, such as immune defence and clotting, which makes them insufficient as a complete replacement for blood.

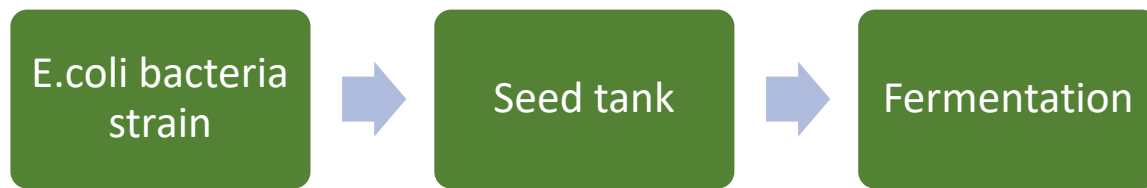
2. Perfluorocarbons (PFCs):

PFCs, are synthetic chemical compounds that can dissolve large amounts of different gases, including oxygen and carbon dioxide. PFCs can thus function as oxygen carriers, although they do not rely on haemoglobin. PFCs dissolve oxygen from the lungs and release it to tissues. Unlike HBOCs, PFCs do not carry oxygen through haemoglobin binding but rely on the gas solubility of the compounds themselves. PFCs have the ability to carry both oxygen and carbon dioxide, making them useful in a variety of medical conditions. Like HBOCs, PFCs are universally compatible because they do not depend on human blood or blood type matching. PFCs can carry oxygen in environments where oxygen levels are low (hypoxic conditions), making them useful in critical situations.

Examples: Fluosol (one of the first PFC-based products), Oxygent (another PFC-based oxygen carrier).(3)

To optimize oxygen transport, patients need to breathe pure oxygen when using PFCs. This requirement limits the application of PFCs, as the technology is not suitable for patients in environments without controlled oxygen levels (e.g., in emergency or trauma situations). The administration of PFCs can lead to lung-related side effects, as the body processes large amounts of oxygen in the lungs. While PFCs can carry oxygen, their ability to deliver it to tissues is still not as effective as human blood, particularly in critically ill or injured patients who require rapid oxygenation.

Artificial blood can be prepared in various methods from synthesized production, chemical isolation to using recombinant biochemical technology. Synthetic hemoglobins-based products are manufactured from hemoglobin factored from an E. coli bacteria strain. Then the hemoglobin is made in a seed vessel and fermented.(4)



4. History of Artificial Blood

Early Concepts and Theoretical Foundations (1900s - 1940s)

The idea of artificial blood can be traced back to the early 20th century. Scientists began exploring the need for blood substitutes due to the challenges of blood storage, the risk of disease transmission, and blood shortages. One of the early theoretical concepts for oxygen carriers was based on the discovery of the importance of hemoglobin, the protein in red blood cells responsible for carrying oxygen. In the 1930s, researchers began experimenting with synthetic solutions to replace blood during surgery. The early solutions were mostly saline or colloidal solutions designed to restore blood volume rather than oxygen-carrying capacity.

Mid-20th Century: Early Developments in Hemoglobin-Based Blood Substitutes (1940s - 1960s)

During World War II, the need for blood substitutes became especially urgent. Researchers started investigating blood volume expanders, which could maintain blood pressure and circulation during emergencies. These early products were mainly saline solutions that were not designed to carry oxygen but were a step toward creating blood substitutes.

After World War II, the idea of using hemoglobin (the oxygen-carrying molecule in red blood cells) as a basis for artificial blood began to gain traction. In the 1950s and 1960s, scientists started experimenting with purified hemoglobin from animals and humans, attempting to create solutions that could carry oxygen as red blood cells do. (5)

1970s-1980s: Hemoglobin-Based Oxygen Carriers (HBOCs)

First Hemoglobin-Based Products: In the 1970s and 1980s, significant progress was made in developing hemoglobin-based oxygen carriers (HBOCs), which were designed to mimic the oxygen-carrying ability of red blood cells. These products were made by isolating hemoglobin from animal or human blood and then modifying it to improve its stability and function in the bloodstream.

One of the earliest artificial blood substitutes was Fluosol, a perfluorocarbon-based blood substitute, developed in the 1960s and 1970s. This product was able to dissolve large amounts of oxygen and could carry oxygen in a manner similar to red blood cells, though it required high concentrations of oxygen to be effective. Hemoglobin-based products faced several challenges, including toxicity due to free hemoglobin circulating in the bloodstream, the difficulty of stabilizing hemoglobin, and problems with oxygen release (hemoglobin's inability to release oxygen efficiently to tissues under low oxygen conditions).(6)

1990s: Perfluorocarbons and Commercial Trials

In the 1990s, perfluorocarbons (PFCs) emerged as an alternative to hemoglobin-based products. These are synthetic compounds that can dissolve large amounts of oxygen and carbon dioxide. They have the potential to transport gases without relying on hemoglobin, and are not affected by blood type compatibility. Unlike HBOCs, PFCs are more stable and do not cause immune reactions as easily. Products like Fluosol-DA (a perfluorocarbon-based product) were tested in clinical trials, and Oxygent became one of the more notable PFC-based blood substitutes developed during this time. These products were used in some clinical settings, such as surgery and trauma care, although they faced challenges related to the need for patients to breathe pure oxygen and lung toxicity from the high levels of dissolved gases.

Despite these promising developments, neither HBOCs nor PFCs received widespread approval. In 1996, the U.S. FDA approved Polyheme, a human hemoglobin-based product, for clinical trials, marking a major milestone. However, HBOCs faced significant issues with safety, particularly in terms of kidney function and vasoconstriction (narrowing of blood vessels).(7)

2000s: Advancements and Setbacks

In the early 2000s, multiple HBOCs entered clinical trials, but none gained FDA approval for widespread clinical use due to safety concerns. For instance, **Hemopure** (a bovine hemoglobin-based product) was tested in both humans and animals, but concerns about its effectiveness and safety, particularly its effect on blood pressure and kidney function, limited its approval.

Researchers began experimenting with **genetically engineered hemoglobin** and other novel blood substitutes. **Stem cell-derived blood substitutes** also became a focus of research, as scientists explored ways to create red blood cell-like products from stem cells.

2010s: Progress and New Approaches

In the 2010s, the development of artificial blood continued, with researchers investigating new materials, synthetic blood substitutes, and improving on older technologies. Some of the promising areas of research included the development of **synthetic red blood cells** and the use of **bioengineered hemoglobin**.

Beyond oxygen transport, researchers also began focusing on the development of **artificial platelets** and **blood clotting agents** that could be used in emergency situations, helping to address the other key functions of human blood.

Advances were made in improving the **storage stability** of artificial blood products, a critical factor in their widespread use. Some artificial blood products were developed to be stored at room temperature for extended periods, solving one of the major logistical issues with blood donations. (8)

2020s: Looking Forward

Research into **synthetic red blood cells** is at the forefront of artificial blood development. These synthetic cells are designed to more closely mimic the functions of natural red blood cells, including **oxygen-carrying capacity**, **carbon dioxide removal**, and **immune response**. Researchers are using advanced techniques, including gene editing, to create red blood cell substitutes that can more efficiently transport oxygen and withstand the conditions of the human body.

Stem cell-derived blood products are also being investigated, where stem cells can be induced to become red blood cells that can be used as substitutes for human blood. This approach could provide a potentially unlimited source of blood substitutes in the future, though challenges related to production scalability and cost remain.

some products like **Hemopure** and **Polyheme** are still undergoing clinical trials, the regulatory pathway for artificial blood is still complex. The challenge remains to create a product that is not only effective at oxygen transport but is also safe and compatible with the human body over the long term.(9)

Raw Materials

The use of different materials varies depending on the type of artificial blood used. Both natural isolated haemoglobin and synthetically produced hemoglobIN can be used to create products based on haeinointegrin. Amino acids: To synthesize haemoglobin, manufacturers rely on compounds called amino acids. These are the chemicals that plants and animals use to build the proteins that are necessary for life. There are 20 amino acids that are naturally occurring that might be used to make haemoglobin. These amino acid molecules have common chemical properties. An amino group, a carboxyl group and supplementary chain make up their structure. (10)

The side chain is what distinguishes the various amino acids. To synthesize hemoglobin, a certain kind of bacterium and the conditions necessary for its incubation are also needed. These consist of alcohols, urea, acetic acid, glucose, molasses, warm water, and liquid ammonia. The hemoglobin is taken from human blood for different kinds of hemoglobin-based artificial blood products. Typically, blood plasma is taken from donors whose blood has gone over its expiration date prior to transfusion. Hemoglobin can also be obtained from discarded animal blood. This hemoglobin needs to be altered before usage since it differs somewhat from human hemoglobin. (11)

The Manufacturing Process

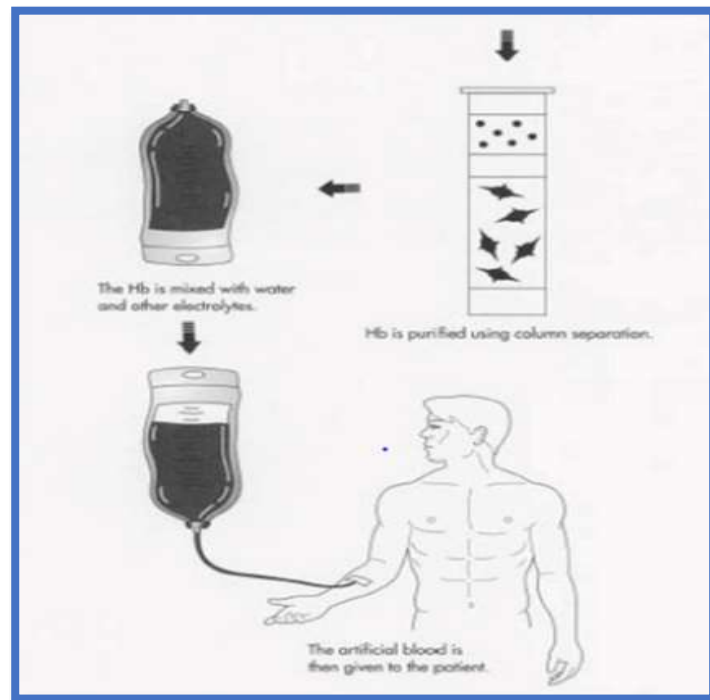
There are various techniques for creating artificial blood. This refers to the extraction or synthesis of hemoglobin, followed by cross-linking and reconstitution in an artificial blood solution in the case of hemoglobin-based products. A polymerization reaction creates PFC compounds. The manufacturing procedure for a synthetic hemoglobin-based product is described below. production of hemoglobin. This merely entails removing hemoglobin from E. coli bacterial strains that are capable of producing human hemoglobin. The protein is extracted and the bacteria are eliminated throughout the roughly three-day protein purification process. This is started by transferring a sample of the pure culture (of the bacteria) to a test tube that has all the nutrients the culture needs to develop. This first dose causes the bacteria to replicate.

They are moved to a seed tank once the population is sufficiently large. A seed tank is a sizable kettle made of stainless steel that offers the perfect conditions for bacterial growth. It contains food, warm water, and an ammonia source all necessary for the synthesis of hemoglobin. Vitamins, amino acids, and other trace nutrients are frequently supplied as growth factors. To keep the bacterial solution in the seed tank moving, compressed air is continuously pumped into it and mixed with it. The contents of the seed tank are transferred to the fermentation tank once a sufficient amount of time has elapsed. (12) An expanded seed tank is called a fermentation tank. It also comes with a growth medium, which is necessary for the bacteria to proliferate and produce hemoglobin. The tank is filled with ammonia water as needed because the pH is essential for optimal growth. Once there is enough hemoglobin produced, the tank is drained so that isolation can begin. To begin the process of isolation, the majority of the hemoglobin is separated using a centrifugal separator. Further separation and purification can be achieved by fractional distillation. The most common method of column separation is based on the boiling principle and uses vertical structures called fractionating columns to separate one or more liquid components.

Final processing

To make the fake blood, it is then mixed with water and additional electrolytes. After that, the synthetic blood can be pasteurized and put into an appropriate container. Compound quality is routinely verified during the

entire process. Especially frequent checking on the bacterial culture is crucial. Apart from them the different physical and chemical properties of the final product are also checked like pH, melting point, humidity content, etc. This method of production has been shown to be able to produce batches as large as 2,640 gal (10,000 L). (13)



- *To make usable artificial blood, the fermenting haemoglobin is cleaned and combined with water and additional electrolytes.*

Current Research and Future Directions

Research into artificial blood is on going of the most exciting areas of research involves engineering **synthetic red blood cells** that can carry oxygen as efficiently as natural red blood cells while also performing other functions like immune defence and clotting. Advances in genetic engineering and biotechnology may allow the development of artificial blood products that are better suited to the complex functions of natural blood. For example, scientists are exploring the potential of using stem cells to create more sophisticated blood substitutes. (14)

Researchers are working to improve the safety and efficacy of hemoglobin-based products, making them more compatible with the human body and less likely to cause adverse reactions. Bioengineering approaches are being explored to develop more advanced substitutes that mimic the full functionality of human blood, including the ability to regulate immune responses, support clotting, and respond to varying oxygen levels. (15) Blood shortages are a global issue, especially in emergencies, during surgeries, and in regions with underdeveloped healthcare infrastructure. Artificial blood could alleviate these shortages by providing a non-human, universally compatible alternative. Artificial blood products eliminate the risk of transmission of blood borne diseases like HIV, hepatitis, and bacterial infections, which is a significant advantage over human blood transfusions. (16)

Most artificial blood products have a much longer shelf life compared to human blood. This is especially important in remote areas, military settings, or disaster zones where fresh blood donations may not be

available. Both HBOCs and PFCs do not rely on blood type matching, which is a significant advantage in emergencies, making them immediately available for any patient, regardless of blood type.(17)

CONCLUSION

Artificial blood represents a promising frontier in medicine, especially in addressing global blood shortages and providing alternatives to human blood transfusions. While significant strides have been made, challenges remain in developing a product that can fully replace human blood. As research continues into synthetic blood, gene editing, and bioengineering, artificial blood may eventually become a safe, effective, and widely available solution for medical emergencies and blood supply shortages. However, overcoming the existing hurdles in oxygen delivery, biocompatibility, and long-term safety will require continued innovation and rigorous clinical testing.

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