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International Journal of Biochemistry & Physiology
ISSN: 2577-4360

Recent Innovations in Artificial Oxygen Delivery using Liposome Encapsulated Haemoglobin

Ashok V* and Padmini PJ

Department of Biochemistry, Sri Balaji Vidyapeeth Deemed to be University, India

***Corresponding author:** Dr. Ashok V, Associate Professor, Department of Biochemistry, Sri Balaji Vidyapeeth Deemed to be University, India, Tel: +917907352959; Email: dr.ashokmbbs1986@gmail.com

Review Article

Volume 8 Issue 1

Received Date: April 20, 2023

Published Date: May 17, 2023

DOI: 10.23880/ijbp-16000223

Abstract

The need for blood transfusion is one the rise because of rapid population growth, development of new infections, accidents and natural disasters. One of the future evolutionary innovations could be artificial blood substitutes which is the most important need in transfusion medicine. Encapsulation of hemoglobin within a liposome is one of the recent strategies in the production of artificial oxygen carriers. In this review we summarize the role of liposome encapsulated haemoglobin (LEH) as artificial oxygen carrier. In addition, the steps taken toward the development of LEH as artificial blood technology and some of their applications and limitations were highlighted.

Keywords: Artificial Blood; Oxygen Carrier; Hemoglobin; LEH

Abbreviations: LEH: Liposome Encapsulated Haemoglobin; EPC: Egg Phosphatidylcholinebrain BPS: Phosphatidylserine; DCP: Dicetyl Phosphate; DMPC: Dimyristoyl Phosphatidylcholine; PEG: Polymer Poly Ethylene Glycol.

Introduction

In developing countries there is a considerable inadequacy of blood supplies for the treatment of cancers, infections and trauma. Therefore, artificial blood substitutes would be of great value for bridging this gap. Blood loss can occur in the body due to trauma or due to surgery. The common side effects of blood transfusion are allergic reactions, circulatory overload and blood borne diseases transmission such as HIV and hepatitis. In surgical and medical emergencies there is a need of universally transfusable, nonallergic, oxygen-carrying blood replacement fluid to provide temporary life support until availability of adequate blood supply. Development of an agent similar to natural blood mimicking the oxygen-carrying capability of blood has been of great interest and many products have been developed based on this property. In this review we mainly discussed the artificial blood substitute- Liposome encapsulated haemoglobin (LEH) that mimics the oxygen-carrying capability of blood. In addition, the potential applications and hurdles against routine application of LEH in human were discussed.

Encapsulation of hemoglobin by a phospholipid layer is called as liposome encapsulated haemoglobin. LEH particles are much smaller than RBCs and are around 0.1 to 10 micron in diameter. LEH has a short circulation half-life due to rapid removal by reticuloendothelial system, which can be solved by a number of approaches for example by addition of polyethylene glycol (PEG) on the particle surface [1]. Modifying the surface of these liposomes with PEG can result in products with higher half-life, increased stability and solubility, as well as lower antigenicity and immunogenicity

[2,3]. In addition to the removal by reticuloendothelial system, another reason for low serum half-life of LEHs is shear induced liposome destruction in bloodstream. Hence, to minimise this issue, an actin matrix was introduced into the aqueous core of the LEH to increase their mechanical strength. This strategy caused increased half-life of the product known as LEAcHb [4].

1. Characteristics of LEH
2. LEH is similar in structure to the membrane enclosed red blood cells.
3. The addition of PEG increases the circulation half-life of LEH from 18 hours to 65 hours [5].
4. LEH is metabolised by RES (reticuloendothelial system) of the liver and spleen same as red blood cells [6].
5. The oxygen affinity of LEH can be controlled by co-encapsulation with allosteric modifiers [7].
6. To retain the hemoglobin in the oxy-hemoglobin state and prevent formation of methemoglobin various hemoglobin protectants can also be encapsulated in the liposomes [8].
7. Decreased vasoconstrictor activity, since physical properties of LEH are closer to red cells, it produces less of a hypertensive response than that observed with cell-free hemoglobin [9]. Recent studies demonstrate that the vasoconstrictor activity of LEH is significantly less than the unencapsulated hemoglobin [10].
8. Diffusion properties of LEH are similar to RBC. The rate of oxygen release from LEH is slower than cell-free hemoglobin i.e. closer to the rate of release from intact red blood cells [11]. Rapid oxygen release from unencapsulated hemoglobin may cause hypertension secondary to auto regulation at the level of the arterioles [12].
9. The protective lipid encapsulation of hemoglobin in LEH leads to decreased neurotoxic effects [13]. Preparation of LEH

Materials used for LEH preparation are Egg Phosphatidylcholine (EPC), Dimyristoyl Phosphatidylcholine (DMPC) and bovine Brain Phosphatidylserine (BPS), the sodium salt of diphosphoglyceric acid, tetramethylene phenylenediamine, cholesterol and Dicetyl Phosphate (DCP), purified haemoglobin. The various methods for preparation of LEH are

- Film hydration method
- Reverse-phase evaporation method
- Double emulsion method

Stability of LEH

The stability of LEH depends on liposome size, phospholipid concentration, total haemoglobin concentration, percent of methemoglobin, oxygen-binding capacity and sterility [14]. The half-life and stability of LEH can be improved by the inclusion of the synthetic polymer poly-ethylene glycol (PEG) in liposome composition. The presence of PEG on the surface of the liposomal carrier has been shown to extend blood-circulation time while reducing uptake by the mononuclear phagocyte system (stealth technology). LEH has less side effects compared to unmodified hemoglobin because unmodified hemoglobin have higher risks of myocardial infarction and death in the clinical trials [15].

Applications of LEH

1. LEH may be effective in acute brain ischemia, it improves oxygen delivery and reduces cerebral infarction in rats [16].
2. LEH with a high oxygen affinity act as an oxygen carrier in rat liver cell culture [17].
3. LEH accelerates gastric wound healing in rats [18].
4. LEH enhances chemotherapy to suppress metastasis in mice [19].
5. LEH inhibits release of tumor necrosis factor from rabbit alveolar macrophages by modification of posttranscriptional mechanism [20].
6. Sakai H et al conducted a phase I clinical trial to show the preclinical safety and efficacy of hemoglobin vesicles which can be used extensively as a transfusion alternative [21].

Advantages of LEH: They are

1. Nontoxic
2. Biocompatible
3. Biodegradable
4. Safe from blood borne pathogens

Limitations of LEH

The main limitation is the production cost of these liposomes. Human studies with LEH are minimal which describes its stability, adverse effects and clinical efficacy. The microencapsulation process can cause denaturation of haemoglobin. Another major obstacle is encapsulating sufficient haemoglobin with maintaining an acceptable viscosity [22].

Conclusion

LEH, the artificial blood substitute is a bigstep forward in mankind like landing on the moon. LEH can be used for delivery of oxygen as a red blood cell substitute. The addition of PEG to LEH has increased the circulation half-life of LEH

by slowly releasing of hemoglobin. LEH with a wide range of potential, its application must be explored throughout the world by encouraging active research in the field of artificial blood substitutes.

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