Conceptual Development of Nano Route Based Synthetic RBC using Chemical Composition Concepts

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Abstract
The significance of blood in sustaining and supporting human bodily functions cannot be understated. It is crucial for various medical procedures, particularly during surgeries, and a scarcity of blood supply poses significant challenges. In response to this global issue, the development of synthetic red blood cells (RBCs) using nano-technology has emerged as a promising solution. These artificial blood substitutes can serve as a viable alternative to human RBCs, addressing the shortage of blood for transfusions. The primary function of synthetic RBCs is to facilitate oxygen transport, mirroring the actions of their human counterparts, including clotting capabilities and pathogen responsiveness. This paper provides an overview of the recent advancements in the field of synthetic RBCs, highlighting their potential as a vital component in addressing the shortage of blood supply. The work done & presented in this paper is the result of the final year one year project work that has been done by the final year engineering students of the college and as such there is little novelty in it and the references are being taken from various sources from the internet, the paper is being written by the students to test their writing skills in the final stages of their engineering career and also to test the presentation skills during their final year project presentation and the work done & presented in this paper is the report of the undergraduate project work done by the students.

Keywords Artificial blood, Perfluorocarbons, Red Blood Cells (RBCs).

1. Introduction

Blood is an essential element for the sustenance of human life. The concept of utilizing artificial blood arose after William Harvey's pioneering description of blood circulation. However, early attempts to develop blood substitutes fell short in replicating all the functions and characteristics of natural blood. The creation of a fluid that fully emulates the multifaceted functions of blood remains an ongoing aspiration for the future. Throughout history, various substances have been explored as potential blood substitutes, ranging from simple liquids like urine, beer, and milk, to plant resins, which bear limited resemblance to the constituents of blood. In later years, advancements led to the utilization of biological cells derived from stem cells, offering greater similarity to natural blood. The emergence of the HIV virus in the 1980s heightened the demand for a suitable blood replacement due to the risks associated with blood transfusions. Despite these efforts, the development of a comprehensive liquid alternative to human blood continues to be a goal for future exploration.

Several challenges are faced by human beings in 21st century the rapid population growth, aging population, blood-borne pathogens new infectious diseases, and natural disasters are common threatening factors for the current state of blood transfusion. Artificial blood would greatly help the developing countries as the have increasing demands. Scientists and experts are expecting that artificial blood substitutes will act as innovation and will change the dynamics in medical field [1]. The study of the basics of Human blood such Composition of human blood RBC (Red blood cells), WBC (White blood cells), Platelets and plasma. The idea of classification

of the blood groups, history of blood transfusion classification of blood groups as A, B, AB, O E.coli based haemoglobin production by fermentation and purification substitute [2].

2. Literature Reviews / Surveys

In this section, recent status and progresses in artificial blood substitutes, focusing on red blood cells substitutes, are summarized in a nut shell. While the other methods were theoretical there was a need of more efficient way of transferring oxygen. The oxygen carrying function was very difficult to implement in practical. Use of Perfluorocarbon specially Perfluorodecalin it was observed that Pfc's do not readily combine with blood and they had to be used in the emulsion form [3]. The use of fulosol DA in a 65 year old haemorrhage patient when the human blood was not available showed a great improvement in the blood pressure it was infused during the operation , this PFC had a shelf life of nine days and washout time was around 3 months, this was a very early implementation which lead to the improvement in the research in PFCs as oxygen carriers [4].

Clinical trials started during the 1980's using Fluosol DA-20% (FDA), a mixture of perfluorodecalin and perfluorotripropylamine emulsified with Pluronic F68 . It was tested on 55 patients but it had flaws as it was functional only for about 12 hours it couldn't effectively perform due to low concentration and small shelf life but it emphasized on the use of improved emulsion design which would solve the shortcomings in future [5]. Life of PFC in the circulatory system is around 48 hours PFCs are white in colour. One of the drawback highlighted was a few research showed that PFC particles may cause influenza like side effects in certain patients when they breathe out these mixtures. These particles are equipped for dissolving many gases including oxygen and PFC products can't be utilized by the human body and should be eliminated; this cycle takes a time around 18-24 months. Their elimination process over-burden the reticulo-endothelial system and reduce its efficiency [6].

Spinal cord injury may lead to permanent damage of tissues due to the injury there might be reduced blood flow which reduces the oxygen delivery one of recent trails showed that using fluorocarbon (Oxycyte) increased parenchymal tissue oxygen levels during the l postinjury hypoxic phase, and fluorocarbon has been shown to be effective in stroke and head injury. The research carried out on rats indicated a faster recovery and improvement in the neuronal cells after severe brain injury. Also the experiment conducted on various animals with brain injury they showed great improvement and the oxygen content raised up to 6 times . And also the study indicates that a PFC emulsion can significantly increase cerebral oxygenation after TBI and enhance mitochondrial function at 4 hours after injury as compared with saline [7].

PFCs were compared with Normal saline solution (NSS) while the they both showed similar outcome there was a noticeable difference between men and women who were treated by PFCs the survival of male was around 30% higher than that of female [8]. Studies showed that the PFCs deviated from the oxygen binding curve hence they are not very effective in oxygen delivery at pO2 of 100mmHg (normal air). Therefore to utilize PFCs effectively, partial pressure of oxygen in the environment should be increased in vivo by ventilating the patient with oxygen, or in vitro, by oxygenating perfusion solutions and cell culture media [9]. PFCs gases can also dissolve C0 and N2 making it suitable to treat conditions like flue-gas poisonings or gas embolism/decompression sickness. But PFCs had side effects like decrease in the mean arterial pressure, lung damage, thrombocytopenia, and flue-like symptoms, it also had a poor emulsion stability and disadvantage that it remained in organs for a longer period of time [10].

Cytotoxicity screening proved that there was a minimal cytotoxicity of components, except in one of the PFCs used in the emulsion manufacturing, perfluorooctyl bromide (PFOB). Their studies found that particle size is determining factor which affects oxygen mass transfer, as increased micelle size resulted in reduced oxygen diffusion. It is very important to focus on the characterization of emulsification parameters to form a stable, reproducible emulsions with the desired bio-delivery properties which will ensure the proper functioning of PFC and increases the reliability. Research determined that Emulsions made with either lipid or Pluronic based surfactants with particle sizes ≥ 0.5 μm were not effective in oxygen mass transfer at conventional oxygen partial pressures. This is due to the relatively large particle sizes result in effective oxygen diffusivities that cancel out the benefit of the increased oxygen solubility inherent to the perfluorocarbon component [11]. The failure of perfluorocarbon emulsions to detrimentally improve management of blood and safely decrease the proportion of patients receiving allogeneic blood transfusion during traumatic surgical procedures does not appear to be the result of inability in enhancement of oxygen delivery [23].

When there is a greater impact in medical field oxygen-delivery benefit is discovered from the use of perfluorocarbon-based emulsions, it will likely be from the use of these agents to limit tissue damage and subsequent organ dysfunction during a reversible period of tissue hypoxia [12]. In the study of various

perfluorocarbons, Perftoran has been used the primarily, having more than 35,000 users, and seem to have the lowest side effects possibly due to its small size and unique surfactant–Proxanol 268. Data based on Russian research indicated that side effects ranged between 0% to 25% with an overall rate of 6.9% based on 912 patients receiving Perftoran . Perftoran has been rebranded as Vidaphor in America in 2017 and has been used since then [13]. The search for the suitable substitute for blood has been a complex journey and different research show varying results some also contradict the others [24]. The use of PFC emulsion and the size of the particle had a great impact in the effectiveness of carrying oxygen. There were many side effects witnessed during the initial stage primarily witnessed during the application of fulosol-DA and PFOB [5,9,11] which lead to advancements and also use of other PFCs which showed lesser and milder side effects use of compounds like Dodecafluoropentane (DDFP) C5F12 [13]. Extensive research lead to the evolution PFC nano-emulsions which have long organ retention time [13]. Like this, a large number of researchers have worked on the artificial blood [22].

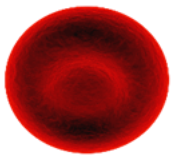

Fig. 1 : Human Red blood Cell (RBC)

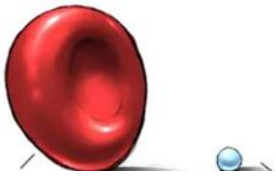

Fig. 2. Red Blood Cells(RBCs) size 7 microns(left) and Perfluorocarbons(PFCs) size 0.2 microns(200nm)

3. Scopes & objectives

The discovery of a flawless artificial blood substitute remains an ongoing quest, with significant advancements yet to be made in the field. This research paper aims to evaluate the existing literature on artificial blood, specifically focusing on perfluorocarbon (PFC) based oxygen carriers, while identifying gaps in knowledge for future experimentation. The paper compiles and compares different compounds and combinations of PFCs, examining their formulation, impacts, side effects, and potential for further research and improvement in terms of efficiency and broader medical applications. While an exhaustive analysis of patented works is unfeasible due to the extensive number of patents issued by educational institutions, research organizations, pharmaceutical companies, and medical management chains, this systematic review aims to assist researchers in the field. It highlights the current advancements in PFC-based artificial blood, along with the challenges that need to be overcome to achieve successful synthetic blood production. The structure of this review paper consists of an overview of the literature review approach in the second section, followed by an in-depth analysis of various PFCs and a comprehensive review of existing literature on oxygen carriers. The deliberations in the fourth section are concluded by the findings presented in the fifth section..

4. Proposed methodology

Literature accumulated from the digital databases. The databases protected “International Research Journal of Pharmacy”, “Elsevier” “IEEE Xplore” and “Google Scholar” “PubMed”. The keywords used for the quest had been “Artificial Blood”, “PFC”, “Synthetic blood”, “Perfluorocarbon’s”, “Blood substitutes”, “Artificial oxygen carriers”, “blood transfusion history” or a combination of those words. In addition to the literature search, we conducted a search for relevant patents using the terms "Artificial blood," "Perfluorocarbons," and "blood substitute" on PubMed and Google Scholar. This patent search aimed to identify ongoing commercialization efforts in the field rather than conducting a comprehensive analysis of individual patent works. Furthermore, we also searched for patents published from 2000 to 2021 using the terms "Artificial blood," "Artificial oxygen carriers," and "Perfluorocarbons" on PubMed and Google Scholar [21].

As mentioned earlier, the purpose of exploring patents was to gain insights into ongoing commercialization activities in the field rather than conducting an exhaustive assessment of all copyrighted works. Therefore, we focused on a sample of copyright works from pharmaceutical companies. The literature reviewed spans the past four decades, reflecting the continuous research and development in the field of synthetic blood synthesis. The

review specifically considered English language-based publications to ensure accessibility for a global audience. Additionally, relevant publications referenced in the collected literature were used to enhance the search process. The review also examines three commonly discussed perfluorocarbons used in these processes, ranging from the use of perfluorodecalin in surgical procedures in the 1980s to recent advancements such as perftoran. The oxygen carrying capacity, shelf life, composition, and side effects of these perfluorocarbons, as documented in the literature, are also reviewed [28].

5. Comparision

First ,we analysed different types comparison of synthesis of artificial blood we have compared the different PFCs used in Artificial blood synthesis. It is then followed up with an in-depth review of methods used for synthesis of artificial blood ,including the patented works.

6. PFC's Used

Perfluorocarbons are chemically inert, odourless compounds were used for different medical applications like nano imaging in the past due its properties it can dissolve huge amount of gases and can be potent oxygen carriers ere we make a detailed comparison of various groups of PFCs. Perfluorocarbons are used as artificial oxygen carriers in the synthetic blood to act as RBCs. Within the literature, the types of PFCs used to form the artificial blood are. The table indicates the evaluation of sensors. The table 1 gives the idea about the comparisons of the PFCs used their formulation, size and side effects.

PFC	Formulation	Mean droplet size	Major side effects
Fluosol-DA	14% PFD. 6% perfluorotripropylamine + 2.7% pluronic F-68 + 0.4% egg yolk phospholipid + 0.03% potassium oleate	0.12 μm	Transient drop in neutrophils and platelets, pneumonia
Perftoran	14% PFD. 6% perfluoromethylcyclohexylpiperidin + 6.5% proxanol 268 + egg yolk phospholipid	0.03–0.15 μm	Hypotension and pulmonary complications.
DDFPe	2% DDFP. 5% human serum albumin	0.2 μm	Coughing, hypertension
PFC	Formulation	Mean droplet size	Major side effects

Table 1 : The comparison

7. Fluosol-DA

This was the first oxygen carrier developed Fluosal-DA(20%) after the experiment of the survival of mammals breathing organic liquid was conducted which led to the revolution in the field of finding a suitable substitute to human blood, on comparison the Mice which was breathing the liquid fluorocarbon for 1 hour, with those breathing the silicone oils, survived for several weeks after removal from the fluid The diffusion of oxygen through the fluorocarbon is four times as fast as through saline [14]. Isolated in-situ pig model to analyse the affect in larger animals was conducted in 1981. This experiment proved that Fluosol-DA has sufficient oxygen-carrying capacity to maintain cardiac function during perfusion in larger animals. But to ensure the safety and to avoid the risk on myocardium, the carrier solution for the Fluosol-DA must be adjusted to appropriate electrolyte content [15,17]. Fluosol-DA appeared to be inefficient as did not make impact on anaemic patients. The storage requirements Fluosol led to its market withdrawal, as the product had to be kept at very low temperature, then thawed and mixed with additives before use [18].

8. Perftoran

Perftoran was developed in Russia as an oxygen-carrier for patients facing acute blood-loss due to anemia, It was approved in Russia in 1996 and used extensively for acute haemorrhagic anemia .It was tested on 964 people with different conditions like haemorrhagic anemia, trauma, sepsis, limb ischemia, cardiac surgery, and organ transplantation improved oxygenation and also reduced the need for allogenic blood .it was administered to 30,000 people ,all these results showed the useful effects with mild and manageable side effects. Perftoran infusions were accompanied by acceleration of platelet aggregation and disaggregation, diminution of acidosis, and inhibition of peroxidative waste production in the blood by 1.5-2.0 times It made Improvements in recovery and possibly reduction in mortality and morbidity [16].

9. DDFPe

The utilization of Dodecafluoropentane emulsion (DDFPe) as a technique for oxygen delivery has shown promise in addressing severe medical conditions such as haemorrhagic shock and traumatic brain injury (TBI) [19]. This innovative approach has the potential to save lives in battlefield scenarios and traumatic injuries by enabling its application in prehospital settings. By facilitating the early reversal of hypoxic conditions, DDFPe can reduce the severity of injuries and provide additional time for the successful transportation of injured patients. The emulsion, stabilized at a concentration of 2% weight/volume, contains DDFPe particles with a mean size of less than 260 nm. Once introduced into the bloodstream, DDFPe travels to the lungs to pick up oxygen and subsequently delivers it passively to hypoxic tissues. Dodecafluoropentane distinguishes itself from previously developed perfluorocarbons through its significantly lower boiling point, molecular weight, and enhanced oxygen-carrying capacity [20]. It is worth noting that the particle size of PFCs tends to increase over time and may be affected by deviations from standard temperature conditions. The shelf life of DDFPe is approximately 2 years when stored at a temperature of 4°C, and 1 year at room temperature. However, the shelf life decreases when exposed to higher temperatures. Despite several advantages over other PFCs, DDFPe failed to effectively treat decompression sickness in a rat model due to microbubble expansion [21].

10. Conclusions and Future Directions

Extensive research and trials have been conducted over the years to explore alternatives to human blood. In the 1980s, the use of Perfluorocarbons (PFCs) as oxygen carriers in emulsions showed promising results in animal experiments, sparking further investigations into their potential as artificial blood substitutes. In recent years, more efficient PFCs such as Dodecafluoropentane emulsion (DDFPe) have been utilized, and ongoing research aims to identify the optimal alternative with minimal side effects. As this field continues to advance, it is expected that superior alternatives will be discovered to meet the growing demand for blood and alleviate scarcity issues. It is crucial to enhance research efforts and expand the scope of review in order to address this challenge. The paper provides a concise overview of various Perfluorocarbons used in the development of synthetic blood. Additionally, it discusses the oxygen-carrying capacity, efficiency, and potential side effects associated with different Perfluorocarbons explored by researchers. Emphasizing the importance of investigating the latest PFCs like DDFPe and improving emulsion formulation, the aim is to create a more effective alternative. It is essential to thoroughly evaluate studies through proper trials in order to establish a viable alternative with enhanced safety and efficacy. The following are the future works.

- Research must be carried out to improvise the currently used PFCs.
- Importance should be given to nullify the side effects without affecting the oxygen carrying capacity
- Newer methods are to be tested to find a much efficient way to form Artificial blood.

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