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Opinion Article

Microfluidic-Engineered Red Blood Cell Mimetics for Sustained Oxygen Delivery in Acute Hemorrhagic Shock

Martin Porvaznik*

Department of Chemical Engineering and Biotechnology, University of Chicago, Chicago, USA

DESCRIPTION

Hemorrhagic shock remains a leading cause of preventable mortality in trauma patients, particularly in pre-hospital settings where blood products are unavailable. Existing hemoglobin-based oxygen carriers have been limited by short circulation times, vasoactive properties, and oxidative toxicity. We present a novel approach utilizing microfluidic manufacturing of biomimetic nanoparticles that recapitulate key structural and functional properties of red blood cells while overcoming limitations of previous artificial oxygen carriers. These Red Blood Cell Mimetics (RBCMs) were engineered with a multilamellar polymer architecture encapsulating purified hemoglobin and enzymes critical for redox homeostasis, creating a functional oxygen delivery system with extended circulation properties.

The RBCMs were fabricated using a continuous-flow microfluidic platform enabling precise control over size distribution (6μm-8μm diameter) and membrane composition. The outer membrane consists of a block copolymer incorporating phosphorylcholine groups to mimic the erythrocyte glycocalyx, providing protection against immune recognition and protein adsorption. Beneath this outer layer, a middle phospholipid region contains precisely oriented transmembrane proteins, including aquaporins for facilitated water transport and glucose transporters for metabolic substrate uptake. The innermost compartment contains hemoglobin co-encapsulated with catalase, superoxide dismutase, and carbonic anhydrase, creating an enzymatic network that maintains hemoglobin function while preventing oxidative damage. Additionally, the oxygen affinity was optimized through incorporation of allosteric modulators, achieving a P50 value (oxygen pressure at 50% saturation) of approximately 28 mmHg, closely matching native human erythrocytes.

Rheological characterization demonstrated deformability properties approaching those of natural erythrocytes, with successful passage through microchannels as small as 7μm without membrane disruption. Oxygen binding and release kinetics revealed rapid equilibration with environmental pO2, with full loading/unloading cycles completed within 200 milliseconds. Stability studies demonstrated maintenance of structural integrity and hemoglobin function for at least 42 days when stored at 4°C in an optimized preservation solution. Importantly, *in vitro* endothelial cell assays showed no significant induction of inflammatory markers or nitric oxide scavenging effects typically associated with cell-free hemoglobin products.

In a swine model of controlled hemorrhagic shock (40% blood volume removal), administration of RBCMs effectively restored oxygen delivery capacity as evidenced by normalization of mixed venous oxygen saturation and lactate clearance comparable to whole blood transfusion. Hemodynamic parameters, including mean arterial pressure and cardiac output, stabilized within 15 minutes of RBCM administration without requiring vasopressor support. Tissue oxygenation monitored by near-infrared spectroscopy demonstrated restoration of adequate oxygen delivery to critical organs, with brain and kidney tissue pO2 maintained above critical thresholds throughout the observation period. Importantly, repeat-dose toxicology studies in non-human primates revealed no evidence of organ dysfunction, inflammatory activation, or complement-mediated reactions following multiple administrations over a 14-day period.

CONCLUSION

Biodistribution studies utilizing non-invasive imaging confirmed an intravascular half-life of approximately 25 hours, significantly longer than previous hemoglobin-based oxygen carriers. Metabolism studies demonstrated gradual biodegradation of the polymeric components through hydrolytic and enzymatic processes, with complete clearance documented within 12 days and no evidence of bioaccumulation in any tissue. These microfluidic-engineered RBCMs represent a promising bridge therapy for hemorrhagic shock in settings where blood products are unavailable or impractical, potentially extending the critical window for definitive intervention while avoiding complications associated with previous generations of artificial oxygen carriers.

Correspondence to: Martin Porvaznik, Department of Chemical Engineering and Biotechnology, University of Chicago, Chicago, USA, E-mail: martinporvaznik08@gmail.com

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