Development of an oxygen carrier nanoemulsion for organ preservation

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INTRODUCTION

The current key development focus in organ preservation for transplant purposes is preservation of organs at normothermic or subnormothermic temperatures (i.e at or slightly below physiological temperature) as opposed to cold storage.

The current **gold standard** in organ preservation for transplant is to preserve harvested organs at low temperatures while circulating an organ preservation solution through the organ. The organs however, sustain some **damage** when exposed to such low temperatures, a phenomenon known as **'cold perfusion damage'**. It is therefore desirable to transport the organ at temperatures closer to normal **physiological conditions (i.e 25 to 37 °C)**. This however, substantially increases the organ's **oxygen requirement** levels.

A critical aspect of organ preservation at higher temperatures is thus the provision of a sufficient oxygen supply to the harvested organ so that the organ can maintain its metabolic rate and remain a viable candidate for transplant.

The CSIR has developed a synthetic **perfluorocarbon (PFC)** based nanoemulsion that serves as an oxygen carrier for the preservation of organs. Perfluorochemicals can be used as oxygen carriers due to their exceptionally high capacity to dissolve gasses[1,2]. Additionally, PFC's display high levels of chemical stability and biological inertness which makes them suitable for biological use[1,2]. Perfluorooctyl bromide (PFOB) is the particular PFC used in the CSIR oxygen carrier emulsion[1,2].

AIM

A collaboration between the Academic Medical Centre (AMC) in the Netherlands and the CSIR aims to combine the nutrient provision abilities of AMC's organ preservation fluid, 'Polysol', with the CSIR's oxygen carrier to serve as a novel organ preservation solution for normothermic or submormothermic organ storage. Polysol is a liquid that contains proteins, divalent ions, various amino acids and other ingredients designed to provide necessary nutrition to the organ that is being transported.

APPROACH

Initially, when combining Polysol and the nanoemulsion, the nutrients present in Polysol caused **accelerated** instability of the nanoemulsion in the form of **flocculation and phase separation**. Literature states that the addition of polyethylene glycol (PEG) to perfluorocarbon emulsions enhances stability[3]. A two-month stability trial was therefore conducted to investigate the effect of PEG addition on the emulsion and the Polysol-emulsion mixture stability.

The stability of the nanoemulsion was determined by measuring the droplet size and zeta potential of the emulsion through use of a Malvern Zetasizer.

RESULTS

It was found that sedimentation of the Polysol-PFOB emulsion mixture was largely decreased by the addition of PEG. It was also found that stability was achieved by adding PEG of a specific molecular weight of 20 kD range and specific concentration of 0.2% v/v.

INTRODUCTION OF A SILICONE-BASED EMULSION

Due to the high cost of the PFC (PFOB is approx. R16 000/kg), a more economically-viable option than the PFC emulsion was sought. A PDMS (poly(dimethylsiloxane)) emulsion was successfully developed for this purpose. When comparing the PFC and PDMS emulsion it is found that PDMS:

- has similar oxygen carrying capacity and similar cytotoxicity to the PFC emulsion with droplet sizes of 140 nm to 160 nm reported during the stability trials as compared to droplet sizes of 220 nm to 360 nm for the PFC emulsion
- emulsion is stable in the presence of Polysol or other protein/amino acid-based aqueous solutions without the addition of PEG
- emulsion costs 50 times less than the PFC emulsion.

CONCLUSIONS

- a stable Polysol-PFC emulsion mixture for organ preservation purposes can be formulated through the addition of 0.2% v/v 20 kD PEG
- a PDMS-based emulsion for organ preservation purposes is stable without the addition of PEG

A stable organ preservation solution with a high oxygen solubility capacity can potentially provide the nutrients and oxygen required for organ preservation at temperatures closer to normal physiological temperatures, thus increasing the chances of organs being viable for transplant.

FUTURE WORK

The project team is currently planning acute toxicity *in vivo* trials for the emulsion formulation, as well as the first *in vivo* efficacy studies in a rat model.

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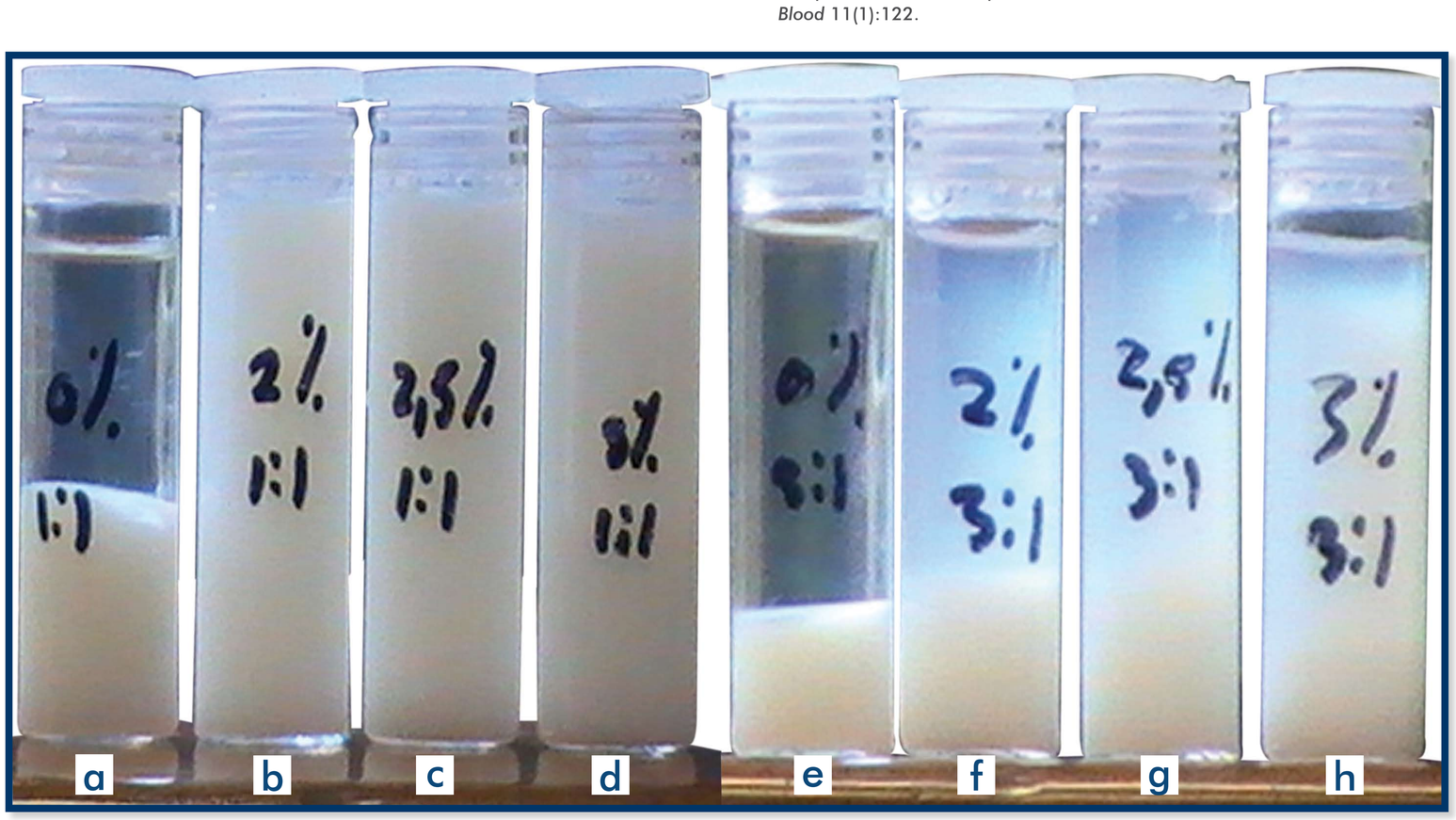

Figure 1: 40% PFOB-lecithin E80S emulsion and Polysol mixture with, from left to right, 0% PEG, 2% PEG, 2.5% PEG and 3% PEG with Polysol:emulsion ratio 1:1 for a) to d) and ratio 3:1 for e) to h)

Improving the viability of organs for transplant using nanotechnology