Nanoprobes for ^{1}H MRI based oximetry

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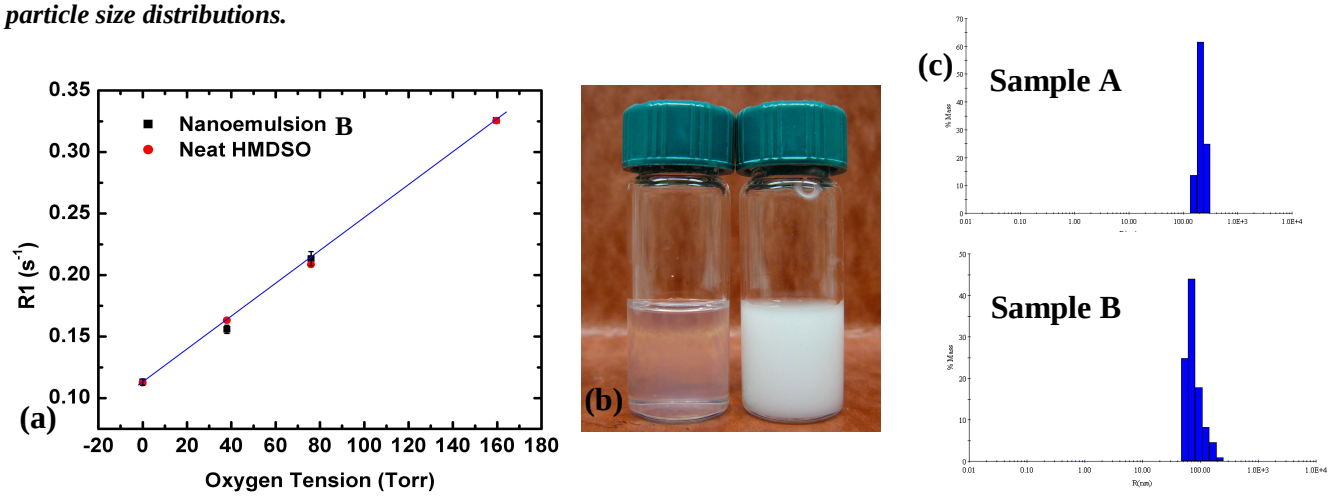
Introduction: There is increasing evidence for the importance of tissue oxygenation in development, progression, and response to cancer therapy. Oxygen is required for efficient function by most tissues and hypoxia leads to rapid cellular dysfunction and damage. Thus, measurements tissue oxygen tension (pO_2) non-invasively may be significant in understanding mechanisms of tissue function and in clinical prognosis. To date, applications of MR oximetry have used direct intra tissue injections or conventional microemulsions (1). Perfluorocarbon nanoemulsions have been synthesized for targeted plaque imaging and show promise for pO_2 measurements as well (2). The potential of hexamethyldisiloxane (HMDSO) as a ^{1}H based pO_2 reporter molecule (by analogy with fluorinated pO_2 reporters) has been studied by ^{1}H spectroscopy (3) and imaging (4) and it has been used to map tissue oxygenation in tissue in response to oxygen challenge (4). We present here synthesis, characterization and application of HMDSO based nanoemulsions suitable for intravenous delivery for ^{1}H MR oximetry applications.

Materials and Methods: The HMDSO nanoemulsion was prepared by ultrasonic emulsification of a mixture of HMDSO, Solutol® (BASF) as surfactant and de-ionised water. Two different synthesis methods were compared which used HMDSO/Solutol/water ratios A) 16/2/82 % by wt and B) 18/27/55 % by wt, respectively. Particle size was measured by dynamic light scattering (Wyatt Instruments). Samples were bubbled with different oxygen mixtures (0, 5, 10 and 21 % O_2) and $R_1(=1/T_1)$ was measured as a function of pO_2 . A spin-echo based pulse sequence used to measure T_1 values by spectroscopy using a Varian 4.7 T scanner. The sequence consisted of a) 20 non-selective saturation pulses followed by a delay *tau* for magnetization recovery, b) 3 CHESS pulses for selective saturation of water and fat immediately followed by c) spin-echo detection with and HMDSO frequency selective 90^o and 180^o pulses. T_1 datasets were obtained using this sequence by varying *tau*.

Figure: (a) R_1 vs pO_2 calibration curves for nanoemulsion B and neat HMDSO, (b) photo of nanoemulsions A and B and (c) dynamic light scattering data for the two nanoemulsions showing particle size distributions.



Results and Discussion: HMDSO based nanoprobes for ^{1}H MR oximetry were successfully synthesized and tested. Method A and B yielded nanoemulsions with mean particle radii of 216 and 82 nm, respectively. In both cases a linear dependence of R_1 on pO_2 was observed and the calibration curve matched that of neat HMDSO showing minimal effect of the surfactant. Method B provided emulsions that were stable over 7 days with nominal change in radius whereas nanoemulsions from method A coalesced to form ~ 1micron sized droplets in 3 hrs. Thus the nanoprobes show promise for in vivo measurements of pO_2 following intravenous delivery and studies are currently underway. The use of Solutol®, a polyethylene glycol derivative (PEG), as surfactant may impart stealth characteristics for the nanoprobes and improve blood pool lifetime and enable surface modification for potential use for targeted imaging of pO_2.

Acknowledgements: This work was supported by the Small Animal Imaging Resource (U24 CA126608) and BTRP P41 RR02584

References

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