Supporting Information

Micron-sized PFOB liquid core droplets stabilized with tailored-made perfluorinated surfactants as a new class of endovascular sono-sensitizers for focused ultrasound thermotherapy

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Experimental Part

1. Agar Based Gel

Proportions of the different ingredients used to reach a constant 290 ml of final gel including various emulsion concentrations and solid particles of silicon dioxide and SiO2 and benzalkonium chloride (BAL) are detailed in Table 2 and Table 3. It is noteworthy that the total volume of water (for emulsion-free gels) or of water+emulsion (for emulsion loaded gels) is constant and equal to 251,6 ml. According to the volume of emulsion to be added to obtain gels with various volume fractions of MSD, the volume of water to be added changes. Water was degassed overnight at 28 mbar. Silicon oxide was suspended in 50 ml of degassed water in a plastic beaker and cooled down with an iced bath, then the mixture was insonified with a 13 mm sonotrode at 60% amplitude for 2 min with a pulse width of 8 s and duty cycle of 12%. 285 mg of BAL was dissolved in 5 ml of water. The BAL solution, glycerol, the silicon oxide mixture and water were added to a 400 ml tared beaker and the mass was recorded. The mixture was homogenised and then placed in a desiccator under high vacuum (28 Mbar) for at least one hour. Then the beaker was placed under mechanical stirring and heated with an oil bath. At around 60-70°C, 9 g of agar was added. The solution was heated at above 90°C for one hour with at least 30 min above 96°C. The gel was set to cool down under magnetic stirring (the weight of the magnetic stirrer is known). At around 60-70°C, the beaker was weighed to ensure that no water was lost and if necessary it was compensated with degassed water. The mixture was set to cool down again until reaching 44°C and then the stirring bar was removed.

To the MSD emulsion, three drops of methylene blue were added aiming to control visually the homogeneity of the emulsion throughout the gel. Then the blue stained emulsion was added, according to the desired volume fraction (see table 3) and was gently homogenised manually using a large spatula for about 15 s and then placed immediately in an iced bath. The volume fraction of PFOB in TMM was used to describe the MSD concentration.

2. Gelatine based gel

The purpose of this section was to identify the dominant mechanism producing enhanced acoustic absorption among two hypotheses: 1) the MSD are directly converting the mechanical energy into thermal energy; 2) the MSD act as inelastic scatters producing mode conversion and re-emitting higher frequency than the incident one, with the higher frequencies being absorbed more effectively by the surrounding bulk gel.[52] If the second hypothesis is true, the efficiency of micro-particles should be significantly decreased in a non-absorbent gel. If the first hypothesis is true, their efficiency should be comparable when embedded in an absorbent or non-absorbent bulk gel.

A non-acoustic absorbent gel was prepared with water, gelatine and benzalkonium chloride and its acoustic properties were measured. Water was degassed during 2 hours at 28 mbar. Using a 500 ml RBF and a medium stirring bar, 9.04 g of gelatine in powder (brand Vahiné) was added to 255 ml of degassed water. 285 mg of BAL was dissolved in 5 ml of water and kept under high vacuum (28 mbar) until use. The gelatine/water mixture was stirred and put under vacuum with the bench vacuum. Then the mixture was heated at 45°C for 5-10 min to ensure complete dissolution of the gelatine and finally BAL was added. The mixture was left to cool down to 25°C in a desiccator under high vacuum (around 57 mbar). Then RBF was weighed to ensure that no water was lost and if necessary it was compensated with degassed water. To maintain the shape of this soft gel while enabling the propagation of focused ultrasound, we used a glass-made open cylinder, with its base closed by paraffin film, carefully avoiding trapped air bubbles between the gel and the film. Once the mixture reached 30°C, it was poured together with a stirring bar in the respective glass cylinder. Then 15 ml of emulsion was added and homogenised manually as described above. During this step, the cylinder was immersed in an iced cold bath and then placed in the fridge. For the control gel, we used the same protocol, but 285 ml of degassed water was added instead of 255 ml, and the gel was simply poured in a glass cylinder and put in the fridge.

Figure

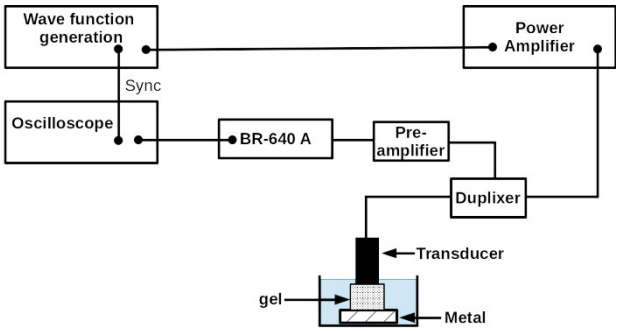

Figure S1 Experimental set up dedicated to the measurement of sound velocity by encoding the time of flight for an ultrasound wave to travel forward and back through a gel, whose thickness is determined by another measurement made in the absence of gel and for a known speed of sound of water.

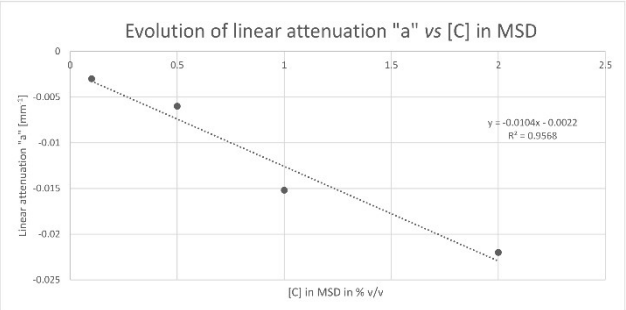

Figure S2 Linear fit of the linear attenuation coefficient “a” in ultrasound images *vs* MSD concentration

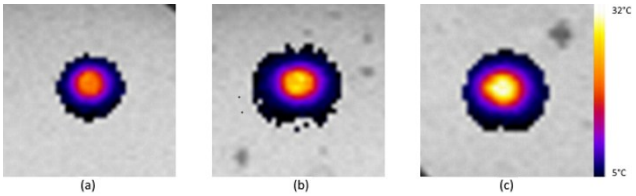

Figure S4 MR magnitude and overlaid PRF shift temperature elevation map at the end of HIFU exposure interval under identical sonication parameters in three TMM gels with (a) (b) (c); 0%, 0.1%, 0.5% MSD concentration respectively. Shown FOV is 30 mm