Microbubbles

Microbubbles are bubbles smaller than one millimetre in diameter, but larger than one micrometre. They have widespread application in industry, life science, and medicine. The composition of the bubble shell and filling material determine important design features such as buoyancy, crush strength, thermal conductivity, and acoustic properties.

They are used in medical diagnostics as a contrast agent for ultrasound imaging.

The gas-filled, e.g. air or perfluorocarbon, microbubbles oscillate and vibrate when a sonic energy field is applied and may reflect ultrasound waves. This distinguishes the microbubbles from surrounding tissues. In practice, because gas bubbles in liquid lack stability and would therefore quickly dissolve, microbubbles must be encapsulated with a solid shell. The shell is made from either a lipid or a protein such as Optison microbubbles which consist of perfluoropropane gas encapsulated by a serum albumin shell.

Microbubbles may be used for drug delivery, biofilm removal, membrane cleaning/biofilm control and water/waste water treatment purposes.

They are also produced by the movement of a ship’s hull through water, creating a bubble layer; this may interfere with the use of sonar because of the tendency of the layer to absorb or reflect sound waves.

Oddo et al. developed novel MBs conjugated to specific ligands to receptors which are overexpressed in brain tumors. These MBs are designed to target a tumor tissue, visualize it, and deliver therapeutic molecules into it. The objective of a study was to assess the biodistribution of the test items: They used MBs labeled with indocyanine green (MB-ICG) for visualization and MBs conjugated to a cyclic molecule containing the tripeptide Arg-Gly-Asp (RGD) labeled with ICG (MB-RGD-ICG) to target brain tumor integrins as the therapeutic tools. Male Sprague Dawley rats received a single dose of each MB preparation. The identification of the MB in various organs was monitored by fluorescence microscopy in anesthetized animals as well as real-time US for brain imaging. Equally sized control groups under identical conditions were used in this study. One control group was used to establish fluorescence background conditions (ICG), and two control groups were used to test autofluorescence from the test items (MBs and MB-RGD). ICG with or without MBs (naked or RGD-modified) was detected in the brain vasculature and also in other organs. The pattern, duration, and intensity of the fluorescence signal could not be differentiated between animals treated with ICG alone and animals treated with microbubbles MBs-ICG or MBs-RGD-ICG. Following MB injection, either naked or combined with RGD, there was a sharp rise in the Doppler signal within seconds of injection in the brain. The signal was mainly located at the choroid plexus, septum pellucidum, and the meninges of the brain. The signal subsided within a few minutes. Injection of saline or ICG alone to respective animals did not result in a similar raised signal. Following a single intravenous administration of MB-ICG and MB-RGD-ICG to rats, the MBs were found to be effectively present in the brain [1)].

Studies have demonstrated that circulating DNA-encapsulated microbubbles (MBs) combined with focused ultrasound (FUS) can be used for local blood brain barrier (BBB) opening and gene delivery. However, few studies focused on how to increase the efficiency of gene delivery to brain tumors after

the released gene penetrating the BBB.

Fan et al., proposed the use of folate-conjugated DNA-loaded cationic MBs (FCMBs). When combined with FUS as a trigger for BBB opening, FCMBs were converted into nanometer-sized vesicles that were transported to the brain parenchyma. The FCMBs can selectively aggregate around tumor cells that overexpressed the folate receptor, thus enhancing gene delivery via folate-stimulated endocytosis. Our results confirmed that FCMBs can carry DNA on the surface of the MB shell and have good targeting ability on C6 glioma cells. In addition, the optimized FUS parameters for FCMBs-enhanced gene delivery were confirmed by cell experiments (center frequency = 1 MHz; acoustic pressure = 700 kPa; pulse repetition frequency = 5 Hz; cycle number = 10000; exposure time = 1 min; FCMBs concentration = 4 × 107 MB/mL). In vivo data also indicated that FCMBs show better gene transfection efficiency than MBs without folate conjugation and the traditional approach of directly injecting the gene. This study described a novel development of multifunctional MBs for FUS-triggered gene delivery/therapy [2].

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Oddo L, Paradossi G, Cerroni B, Ben-Harush C, Ariel E, Di Meco F, Ram Z, Grossman R. In Vivo Biodistribution of Engineered Lipid Microbubbles in Rodents. ACS Omega. 2019 Aug 8;4(8):13371-13381. doi: 10.1021/acsomega.9b01544. eCollection 2019 Aug 20. PubMed PMID: 31460465; PubMed Central PMCID: PMC6704434.
2)
Fan CH, Chang EL, Ting CY, Lin YC, Liao EC, Huang CY, Chang YC, Chan HL, Wei KC, Yeh CK. Folate-conjugated gene-carrying microbubbles with focused ultrasound for concurrent blood-brain barrier opening and local gene delivery. Biomaterials. 2016 Aug 12;106:46-57. doi: 10.1016/j.biomaterials.2016.08.017. [Epub ahead of print] PubMed PMID: 27544926.