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Acoustic behavior of microbubbles and implications for drug delivery ☆

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ABSTRACT

Ultrasound contrast agents are valuable in diagnostic ultrasound imaging, and they increasingly show potential for drug delivery. This review focuses on the acoustic behavior of flexible-coated microbubbles and rigid-coated microcapsules and their contribution to enhanced drug delivery. Phenomena relevant to drug delivery, such as non-spherical oscillations, shear stress, microstreaming, and jetting will be reviewed from both a theoretical and experimental perspective. Further, the two systems for drug delivery, co-administration and the microbubble as drug carrier system, are reviewed in relation to the microbubble behavior. Finally, future prospects are discussed that need to be addressed for ultrasound contrast agents to move from a pre-clinical tool into a clinical setting.

Contents

Abbreviations: AALs, acoustically active lipospheres; $[Ca^{2+}]_i$, intracellular calcium ions; HUVEC, human umbilical vein endothelial cells; MI, mechanical index; PEG, polyethylene glycol; PRF, pulse repetition frequency; ROS, reactive oxygen species; P_, peak negative pressure; PI, propidium Iodide.

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1. Introduction

In 1968 it was discovered that following saline injection, small echogenic gas pockets were formed, thereby dramatically improving the contrast in the ultrasound imaging [1]. Since then, the gas pockets have evolved into clinically approved ultrasound contrast agents for diagnostic ultrasound imaging [2–8]. More recently, ultrasound contrast agents have been introduced as ultrasound-triggered agents for drug delivery and therapy [9–13]. The reader is referred to various reviews written about the use and different formulations of ultrasound contrast agents. [2–8,14]. For a recent overview of clinically approved ultrasound contrast agents, see [8] or [15].

Ultrasound contrast agents consist of gas microbubbles dispersed in a solution, and are administered intravenously. To improve stability and corresponding circulation lifetime of the agent in the vascular system, the following adaptations are made to the gas microbubbles. First, the gas bubbles are coated with lipid, polymer, sugar or protein material [8,10,15]. The coating reduces the surface tension, and corresponding capillary pressure which drives the gas into solution. Moreover, it provides a gas diffusion barrier. Secondly, the gas core is composed of a heavy molecular weight inert gas, for example SF_6, C_3F_8, or C_4F_{10}, which improves longevity as a result of its low solubility in the surrounding medium. The typical size of clinically approved microbubbles is between 1 and 10 μm in diameter. Because of their size, the microbubbles are contained within the vasculature and can therefore be considered true blood pool agents [7,16].

Microbubbles oscillate in a driving pressure field, and for imaging purposes, gas compressibility provides echogenicity with an improvement of several orders or magnitude compared to solid particles of the same size [17,18]. The bubble oscillations will set the surrounding fluid into motion. More intense oscillations will set up an acoustic streaming pattern which may assist in the mixing and delivery of co-administered drugs. Even higher amplitudes of oscillations lead to asymmetrical collapse and jet formation, which may further promote delivery of the co-administered drugs or incorporated payload. An even further increase of the driving pressure may lead to the spontaneous formation of vapor and gas cavities, termed cavitation. Key to the formation of such cavitation bubbles is the presence of pre-existing cavitation nuclei. Stabilized contrast microbubbles provide such nuclei. The 'strength' of the acoustic pressure field and the applied frequency is classified through the mechanical index (MI), and related to the stability of the microbubbles. This relation is based upon the early MI definition by Apfel [19] and is defined as $MI = \frac{P_-}{\sqrt{f}}$ with P_- the peak negative pressure of the ultrasound wave (in MPa), and f the center frequency of the ultrasound wave (in MHz). Even though the MI has a dimension, it is reported as a dimensionless number. A value of 1.9 is adopted by the US Food and Drug Administration as the safety limit for clinical ultrasound in the absence of microbubbles, as is based on the formation of cavitation bubble, as per the above. Based on the MI, a classification of microbubble behavior can be given [20]. First, a typical setting for contrast agent imaging (power modulation, pulse inversion, contrast pulsing schemes (CPS)) is an MI between 0.05 and 0.2. At higher MI, between 0.2 and 0.5, destruction of the contrast agent (gas loss, shell material loss, bubble dissolution) causes signal deterioration during a clinical exam. However, it is known that bubbles may sustain stable oscillations during acoustic driving caused by so-called rectified diffusion [17]. This regime is termed the stable cavitation regime. Most of these bubbles dissolve once ultrasound is stopped. An MI of above 0.5 is highly destructive for contrast agents [21]. In this review, the ultrasound settings are typically given in terms of frequency and pressure, which can then be converted to an MI value using the equation above.

Microbubbles need to be close to cells in order to trigger drug delivery. One delivery mechanism for drug uptake by cells is termed sonoporation, where pore formation in the cell membrane is induced through mechanical and fluid mechanical stress of the oscillating and/or collapsing bubbles (see also Section 3). Fig. 1 shows an illustration of the key possible mechanisms. Fig. 1a shows the setting where a microbubble is in contact with an endothelial cell. The microbubble oscillates volumetrically in the stable cavitation regime. In the compression phase of the microbubble (middle picture in Fig. 1a), the microbubble pulls on the cell membrane. Furthermore, the liquid neighboring the bubble-wall interface shears along the cell membrane, as denoted by the arrows. In the expansion phase (bottom picture), the microbubble exerts a normal force on the cell membrane, and the shear motion along the cell membrane is pointed outwards. Thus, the stable cavitation regime implies that the liquid and cell around the microbubble are stretched and sheared at the frequency of the incoming ultrasound wave. Since the microbubble oscillations are mild, the oscillations can be sustained over a long duration, potentially setting up an acoustic streaming pattern as illustrated in Fig. 1b. With increasing

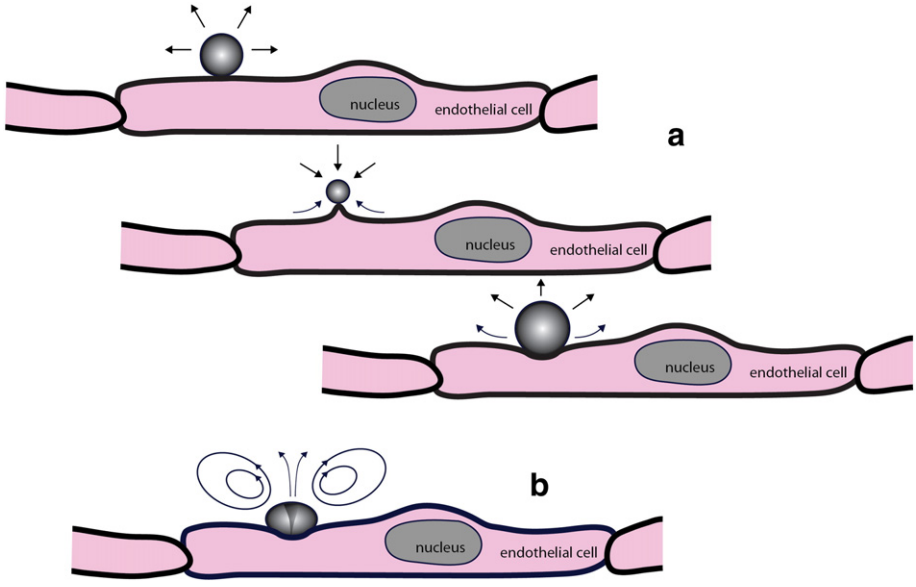

Fig. 1. Illustration of common microbubble phenomena nearby cells. (a) stable cavitation, in which the bubble massages the cell membrane; (b) transient cavitation, in which violent collapses and jets occur, and acoustic microstreaming around the bubble can become significant.