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State-of-the-art materials for ultrasound-triggered drug delivery ☆

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ABSTRACT

Ultrasound is a unique and exciting theranostic modality that can be used to track drug carriers, trigger drug release and improve drug deposition with high spatial precision. In this review, we briefly describe the mechanisms of interaction between drug carriers and ultrasound waves, including cavitation, streaming and hyperthermia, and how those interactions can promote drug release and tissue uptake. We then discuss the rational design of some state-of-the-art materials for ultrasound-triggered drug delivery and review recent progress for each drug carrier, focusing on the delivery of chemotherapeutic agents such as doxorubicin. These materials include nanocarrier formulations, such as liposomes and micelles, designed specifically for ultrasound-triggered drug release, as well as microbubbles, microbubble-nanocarrier hybrids, microbubble-seeded hydrogels and phase-change agents.

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1. Introduction

Early reports in the field of ultrasonic drug delivery demonstrated that the application of ultrasound energy alone may facilitate intracellular delivery of molecules [1–7]. Therefore, it stands to reason that ultrasound with ultrasound-responsive materials can be an effective tool for enhancing the therapeutic efficacy of a drug during therapy. In this review, we cast a selection of recent innovative materials for ultrasound-triggered drug delivery into the rational design paradigm in order to identify general design rules that scientists and engineers can use in their quest for more potent drug carriers. Our main focus is on ultrasound-targeted drug delivery; gene therapy has been recently reviewed elsewhere [8].

We start by defining the general rational design paradigm: that materials can be engineered for a specific application by understanding the key interrelationships between composition, processing, structure, property and performance. In drug delivery, the main performance criterion is the therapeutic index (TI), defined as the drug dose that produces a toxicity in 50% of the population (TD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50}).

$$TI = \frac{TD_{50}}{ED_{50}}. \quad (1)$$

Targeting increases TI by simultaneously increasing the dose required for toxicity and decreasing that for effective therapy. This is achieved by delivering a greater percentage of the drug to the target tissue and avoiding healthy tissue. For ultrasound-triggered drug delivery, the main properties that are necessary to achieve a significant increase in TI are (1) stable encapsulation of the drug compound prior to application of ultrasound, (2) release of the drug by ultrasound stimulation and (3) the ability to image the carrier and monitor delivery of the drug cargo. The adoption of the third criterion provides theranostic control capabilities to the drug delivery system and is ideally suited for ultrasound, which is widely used for both imaging and therapy.

Several types of nano, micro and macro structures have been developed with these properties in mind. These include microbubbles, liposomes, micelles, phase-change emulsions, microbubble-loaded hydrogels and other interesting structures. In this review, we illustrate a few promising structures by focusing on how they were synthesized and characterized, how they interact with ultrasound, and how they performed at ultrasound-triggered drug delivery.

2. Ultrasound triggers

As an ultrasound wave propagates through tissue in the body, several physical effects occur which can be used as triggers for ultrasound-mediated drug release. These physical effects include simple pressure variation, acoustic fluid streaming, cavitation and local hyperthermia. Rational design of an ultrasound-triggered drug carrier typically involves designing the material to respond to one or more of these triggers.

2.1. Pressure variation

In medical ultrasound, transducers are used to generate longitudinal pressure waves, which are transmitted into the body at varying frequency and amplitude. The broad ranges of biomedical ultrasound frequencies are 0.1–50 MHz and peak negative pressures are 0.01–10 MPa [9,10]. The acoustic waves are attenuated as they pass through tissue owing to absorption and scatter of the acoustic energy, and this effect typically increases with increasing transmit frequency. Near 1 MHz, however, this attenuation is minimal and deep-tissue imaging/therapy is possible. Ultrasound is also characterized by pulse length and shape, as well as pulse repetition frequency. For imaging, the reflections and scatter of acoustic waves are detected and used to generate an image. For drug delivery, on the other hand, acoustic waves are used to stimulate the carrier to release its cargo, and/or provide other bioeffects such as enhanced vascular permeability. The key mechanisms of drug carrier interactions with acoustic waves are cavitation, acoustic streaming and hyperthermia.

2.2. Cavitation

Compressible objects, such as microbubbles, contract and expand as they experience the compression and rarefaction cycles of passing acoustic waves. These volumetric oscillations can facilitate drug release, increased drug uptake and strong backscattered echoes that can be used for imaging. The type of cavitation depends highly on the amplitude and frequency of the ultrasound wave, as well as the size and material properties of the bubble. In many cases, the bubble activity can be divided into "stable" or "inertial" cavitation regimes depending on the mechanical index (MI) [11]. The MI is defined as the derated *in situ* peak negative pressure (PnP) divided by the square root of the center frequency (F_c) [11,12]:

$$MI = \frac{PnP}{\sqrt{F_c}} \quad (2)$$

where the units of PnP and F_c are MPa and MHz respectively. The MI is by no means a perfect measure or predictor of biological consequence and does not account well for the presence of ultrasound-sensitive materials in the body, which are discussed in this review. In general, diagnostic imaging occurs at MI levels below 1.9, which is the maximum allowable MI for clinical imaging applications without microbubbles [12]. A maximum MI of 1.9 would likely apply for imaging incompressible drug carriers, such as micelles and liposomes. Microbubbles, on the other hand, interact strongly with ultrasound by acting as "cavitation nuclei" [13], and the maximum allowable MI when using microbubbles is 0.8 [14]. Below an MI of 0.8, microbubbles undergo stable cavitation, in which the microbubble is stable over many acoustic cycles, and which is often characterized as a backscattered signal centered at the fundamental and harmonic frequencies. It is unclear what the maximum allowable MI would be for imaging phase-change agents.

Therapeutic ultrasound, in which biological effects are desired, uses higher MI values. High MI ultrasound can result in the violent collapse of gas bubbles, a phenomenon known as "inertial cavitation" [15]. This high energy event is associated with extreme, localized pressures and temperatures that can disrupt the drug carrier and enhance drug uptake. In addition to acting on preformed microbubbles, inertial cavitation can be nucleated in the aqueous phase adjacent to a drug carrier. Alternatively, cavitation can be nucleated within the hydrophobic portion of a drug carrier, such as within the lipid bilayer of a liposome, due to weaker intermolecular cohesive forces compared to water. These latter mechanisms are important for drug targeting using micelles and liposomes. The biological consequences from acoustic phenomena are discussed in detail elsewhere [12,16–19]. For comprehensive reviews on the physical effects of ultrasound on compressible microbubbles, please see articles by Qin et al. [20] and Postema et al. [21].

2.3. Acoustic streaming

Radiation forces experienced by reflectors and scatterers in the ultrasound field can lead to localized particle displacements and fluid currents, termed "acoustic streaming" [15]. Acoustic streaming may involve "bulk streaming", where fluid is moved in the direction of the propagating sound wave, or "microstreaming" wherein localized eddies or currents are generated next to cavitating bodies [22]. Bulk streaming produces a "radiation force" that can move particles in the direction of the propagating ultrasound wave. For stably cavitating microbubbles, radiation forces are maximal at driving frequencies near the microbubble resonance frequency. Radiation forces can be used to displace particles in blood [23], to facilitate adhesion between circulating agents and the endothelium, and to drive particles into target tissue [24,25]. Microstreaming is another