Ultrasound-Induced Drug Release from Stimuli-Responsive Hydrogels

Subjects: Engineering, Biomedical

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Stimuli-responsive hydrogel drug delivery systems are designed to release a payload when prompted by an external stimulus. These platforms have become prominent in the field of drug delivery due to their ability to provide spatial and temporal control for drug release. Among the different external triggers that have been used, ultrasound possesses several advantages: it is non-invasive, has deep tissue penetration, and can safely transmit acoustic energy to a localized area.

hydrogels polymers stimuli-responsive ultrasound drug delivery tissue engineering cancer therapy controlled drug release thermoresponsive materials

1. Introduction

Stimuli-responsive drug delivery systems enable the delivery of payloads on-demand, at a specific time, and at a specific location [1][2][3][4]. These platforms can be designed to respond to a variety of different stimuli, either internal such as redox, pH, or enzymes, or external physical triggers such as magnetic field, ultrasound, light, electricity, or temperature [5][6][7][8][9][10].

For the past 70 years, ultrasound has been extensively used as a diagnostic tool [11][12]. However, it has recently been applied to a broad range of therapeutic applications such as the treatment of vascular thrombosis by dissolving clots, the ablation of tumors, and the healing of bone fractures [12][13][14]. Ultrasound has proven to be both safe and ethical for in vivo use in a variety of applications [15][16]. Ultrasound also induces biological effects that are beneficial for therapeutic applications. It enhances transdermal drug delivery, enhances uptake in cells and tissues, and facilitates wound healing [13][17][18][19][20][21]. Ultrasound provides the capability for a wide variety of applications in the biomedical field including imaging [22], clinical diagnosis [23], therapeutics delivery [20][24][25], detection [26], sensing [27][28], the initiation of chemical and biological processes [29][30][31], and the release of signaling molecules [32].

2. Acoustics

The developing field of responsive hydrogels is reaching new intersection points with external stimulus triggers. Recent developments have brought stimuli-responsive hydrogels into the field of acoustics and ultrasound. In this case, the acoustics field can be defined as the use of mechanical waves for energetic transfer in materials such as

solids, liquids, or gases [33][34]. The transfer of energy into and through materials is then converted into specific acoustic responses for each hydrogel. These acoustic responses include payload delivery, modulation of material properties, initiation of biochemical processes, directed assembly, actuation, locomotion, or sensing [33][35][36][37][38].

The positive characteristics of ultrasound acoustics are frequency, wavelength, time, and transmission loss [39]. While acoustic frequencies range anywhere from 1 Hz to over 100 GHz, ultrasound frequencies only make up the range of 20 kHz to 50 MHz [33][34]. This range of frequencies is particularly interesting since it is outside of the range of human hearing [33]. Additionally, these ultrasound frequencies have generally small wavelengths in water, making them extremely compatible with responsive systems used within the human body [40]. The short time scales of ultrasound frequencies also make them extremely efficient in energy exchange [41]. Another positive characteristic is the low amount of transmission loss within the human body in this frequency range [33]. Due to these positive characteristics, ultrasound is an ideal external trigger for stimuli-responsive hydrogels.

3. Acoustic Mechanisms

When using ultrasound acoustics on stimuli-responsive hydrogels, acoustic mechanisms are the pathway in which energy is transferred to induce a response. Acoustic responses typically involve work that is not directly correlated to acoustic waves. The acoustic waves are instead used for energetic transfer through both thermal and non-thermal mechanisms within a responsive hydrogel.

The thermal mechanism is the pathway in which acoustic energy is transferred into thermal energy. The increase in temperature caused by ultrasound irradiation enhances drug diffusion and increases cell permeability [42]. Positive results have been observed with ultrasound-triggered drug release in thermosensitive hydrogels containing colloids such as nanoparticles [43], liposomes [44], and micelles [45]. While the power of high-intensity focused ultrasound is proven to be useful for drug delivery, damage to surrounding cells should be accounted for when considering long-term hyperthermia [46][47][48].

The non-thermal mechanism is the pathway in which acoustic energy is transferred into mechanical energy in the form of oscillation and force [46]. This mechanical energy can take the form of acoustic cavitation. Cavitation is the formation of bubbles within a material, in which the bubble rapidly oscillates and then collapses within itself [49]. Cavitation has been used for drug delivery for chemotherapy [50] and bone regeneration [51][52]. Mechanical energy can also take the form of ultrasonic mechanical force. This mechanical force can be used to cleave unstable bonds [46]. Acoustic radiation force is another form of mechanical energy derived from ultrasound. The forces created by the acoustic waves act on the particles suspended within a fluid, these particles then move, cluster, and interact with one another [53]. The movement and interaction of these particles create acoustic radiation forces, which when paired with low-intensity focused ultrasound can be used for drug delivery and bone regeneration [54][55].

High-intensity focused ultrasound and low-intensity focused ultrasound prove to be effective in drug delivery using both thermal and non-thermal mechanisms in stimuli-responsive hydrogels. High-intensity focused ultrasound is extremely effective when inducing drug release, however possible damages and challenges may occur for

sensitive biological systems [33][56]. While low-intensity focused ultrasound may be less powerful, it is at lower risk of damaging sensitive biological systems [57][58]. In scenarios using thermo-responsive hydrogels with hyperthermia as the thermal mechanism, high-intensity focused ultrasound would be ideal [46]. While both forms of focused ultrasound have respective challenges, it is seen that each can be useful for different applications.

Thermo-responsive and ultrasound-responsive hydrogels respond positively to ultrasound acoustics, making focused ultrasound an excellent external trigger for both systems. Both types of hydrogels prove to be responsive to ultrasound stimulation due to the combination of hyperthermia and sonoporation induced by focused ultrasound [46][47][59]. While different mechanisms exist for both types of hydrogels, each transfers acoustic energy into a form of work proven to be useful for drug delivery. Specifically, drug delivery for the purpose of cancer therapeutics and tissue engineering. Thermo-responsive materials paired with focused ultrasound have been used for both cancer treatments [60][61] and tissue repair [62]. Ultrasound-responsive materials paired with focused ultrasound have been used for both chemotherapy [63] and bone tissue engineering [52][64].

4. Designing Hydrogels for Drug Delivery

Rationally designing stimuli-responsive hydrogels to be used for ultrasound-triggered drug delivery requires a thorough understanding of the parameters that affect hydrogel response. These key factors are: bond strength, molecular weight, degree of polymerization, chain units, polymer structure, shape, and molecular assembly [46][65][66]. Rationally designing hydrogels to be as sensitive to ultrasound as possible is critical, as it will greatly decrease the chances of adverse biological effects [12][47].

These parameters are crucial when rationally designing stimuli-responsive hydrogels. Drug release from polymer systems requires relatively low amounts of energy to break, when paired with weaker bonds [67][68][69]. Molecular weight distribution also affects the responsiveness and location of mechanical force acting along a polymer chain [70][71][72]. The degree of polymerization and chain units influence the mechanochemical activity of polymeric materials [73][74][75]. Polymer structure and shape both play a role in the sonomechanical effects of ultrasound on materials [76][77][78]. The designed molecular assembly can also influence the mechanochemical activity of the materials [79][80][81]. The amount of energy used will be lowered by implementing these factors into the design of hydrogel matrices, which will also decrease the chances of surrounding tissue damage.

The factors involving the structure of a stimuli-responsive hydrogel have large effects on drug delivery, but another important parameter is the embedded payload or carrier within the hydrogel matrix. Possible embedded nanocarriers include microbubbles [82], nanoparticles [83][84][85], liposomes [82], loaded nanodroplets [62][86], and micelles [87][88]. Cells can be placed into hydrogel matrices for direct diffusion into the surrounding area [54] or aided by nanocarriers for increased targeting specificity [62]. Proteins have been diffused from hydrogels without direct targeting [89][90][91], or aided by nanocarriers in drug delivery systems [92]. Payloads such as drugs can also be directly diffused from hydrogels [93], or aided by nanocarriers for targeted drug delivery [94]. The rational design of hydrogels for ultrasound-triggered drug release is dependent on both the structural factors of the matrix and the embedded materials within the hydrogel.

While hydrogel matrices affect the response to focused ultrasound, the specific parameters of the applied ultrasound also influence the outcome. Two types of ultrasound can be used, either High-Intensity Focused Ultrasound (HIFU) or Low-Intensity Focused Ultrasound (LIFU), each being beneficial for different applications [33][55][58]. LIFU is advantageous for applications involving reversible cellular effects [15] and increased tissue regeneration [95]. For instance, Kearney et al. [83] and Levingstone et al. [96] used LIFU at 2.5 min per hour for 5 h with an intensity of 9.6 mW/cm^2 to induce bone regeneration aided by BMP-2 release. For applications involving irreversible cell death or tissue ablation, HIFU would most likely be preferred [97]. For example, HIFU was used by Meng et al. [98] and Zhu et al. [99] at a 50% duty cycle with intensities of 6 W/cm^2 and 1 W/cm^2, respectively, to promote release and uptake in tumor systems.

Ultrasound has proven to be both safe and ethical for in vivo use in a variety of applications [15][16]. The Food and Drug Administration (FDA) has defined safety guidelines for ultrasound exposure [15]. Criteria such as the mechanical index, thermal index, spatial peak pulse average intensity, and spatial peak temporal average intensity have been defined to stipulate the maximum allowed ultrasound exposure [47][100][101]. Adverse biological effects can be avoided during in vivo ultrasound studies when following these.

Drug delivery applications must be fully understood to rationally design hydrogels specific for each application. The two main applications for ultrasound drug delivery via hydrogel systems are tissue engineering and cancer therapy. Each application features a variety of hydrogel systems, ultrasound parameters, delivery methods, and drugs used.

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