Ultrasound-Modulated Shape Memory and Payload Release Effects in a Biodegradable Cylindrical Rod Made of Chitosan-Functionalized PLGA Microspheres

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ABSTRACT: Minimally invasive implants and/or scaffolds integrated with multiple functionalities are of interest in the clinical settings. In this paper, chitosan (CTS) functionalized poly(lactic-co-glycolic acid) (PLGA) microspheres containing a model payload, lysozyme (Lyz), were prepared by a water-in-oil-in-water emulsion method, from which cylindrical shaped rod (5 mm in diameter) was fabricated by sintering the composite microspheres in a mold. High-intensity focused ultrasound (HIFU) was then employed as a unique technique to enable shape memory and payload release effects of the three-dimensional (3-D) structure. It was found that incorporation of CTS into PLGA microspheres could regulate the transition temperature \( T_{\text{trans}} \) of the microsphere from 45 to 50 °C and affect shape memory ratio of the fabricated cylindrical rod to some extent. Shape memory test and drug release assay proved that HIFU could modulate the shape recovery process and synchronize the release kinetics of the encapsulated Lyz in the rod in a switchable manner. Moreover, the two processes could be manipulated by varying the acoustic power and insonation duration. Mechanical tests of the microspheres-based rod before and after ultrasound irradiation revealed its compressive properties in the range of trabecular bone. Examination of the degradation behavior indicated that the introduction of CTS into the PLGA microspheres also alleviated acidic degradation characteristic of the PLGA-dominant cylindrical rod. With HIFU, this study thus demonstrated the desired capabilities of shape recovery and payload release effects integrated in one microspheres-based biodegradable cylindrical structure.

INTRODUCTION

In the clinical settings of tissue repair and regeneration, there is currently a growing demand for minimally invasive implants and scaffolds with multiple capabilities such as biodegradability, biocompatibility, suitable mechanical properties, and delivery of therapeutic drugs in a spatially and temporarily controlled manner. Thermal-responsive shape memory polymers (SMPs) integrated with multifunctionality hold promise for such purposes of use by starting with a small, compact material and then switching over to a more voluminous structure in the body, upon exposure to an external stimulus (trigger). So far, various SMP-based medical devices have been explored for different uses such as stent for cardiovascular system and self-tightening sutures, which all demonstrated the potential of SMPs in biomedical applications.

The shape-memory effect of SMPs is typically triggered by increasing, through direct heating, the environmental temperature above the switching transition temperatures \( T_{\text{trans}} \). However, this is not always practical for the situation of SMPs used in vivo. A variety of indirect stimulation methods through applying external stimuli such as magnetic field, electrical resistance heating, laser, or light have been proposed and examined experimentally. However, as extra components (e.g., magnetic particles) are usually required to be introduced into an SMP matrix to realize the intended stimulation, it is likely to give rise to concerns in biodegradability and biocompatibility. As a consequence, apart from a need to use accepted biodegradable polymers with shape memory effect (SME), finding a safer and effective stimulus other than direct heating in the body to accomplish remotely controllable triggering on shape recovery, and the integrated functions should be another pivotal factor for consideration when SMPs are designed for uses in physiological conditions.

Ultrasound, especially with high-intensity focused ultrasound (HIFU), has been researched and applied in the clinical settings for many years. As a noninvasive surgical tool, HIFU has demonstrated its therapeutic capability by causing selective tissue necrosis in a defined volume at a variable distance from the transducer. The underlying mechanism is that the ultrasound energy absorbed by tissue causes molecular vibrations, which results in heat energy and a rapid rise in temperature in the focal zone but with minimal effects to surrounding tissues. This suggests that if the acoustic waves are directed to interact with the polymer chains in a selected region, the generated heat can be, in a similar manner, otherwise used to trigger the shape recovery effect of SMPs. On the other hand, ultrasound has been considered as one of the most powerful physical modalities for spatiotemporal control of...
pulsatile drug delivery in an "on-off switch" manner. Thus, it would be a natural and reasonable choice to use HIFU as the trigger for realizing both SME and on-demand drug delivery functionalities in the biomedical engineering scenarios. However, despite the wealth of research and application in the field of HIFU, its use as a remotely controllable stimulus for simultaneously triggering shape recovery effect and the integrated drug release capabilities in biodegradable SMPs is still sporadically investigated.

Herein, we first develop a microspheres-based biodegradable cylindrical rod or scaffold, and then demonstrate its synchronized capabilities in SME and on-demand drug delivery, solely regulated by HIFU. Microspheres are established drug delivery vehicles for sustained releases and are also used as building blocks with substantial spatiotemporal designability for constructing integral macroscopic scaffolds in bone tissue engineering. As a proof-of-concept, we used poly(lactic-co-glycolic acid) (PLGA), one of the most used synthetic biodegradable polymers in the fields of tissue engineering and drug delivery, to prepare lysozyme (Lyz) protein loaded microspheres, in which a biodegradable polysaccharide chitosan (CTS), was introduced to modify the physical, mechanical and biological properties of the PLGA microspheres.

**MATERIALS AND METHODS**

**Materials.** PLGA (50:50 lactic to glycolic ratio, MW = 31,000 Da) was purchased from Daigang Biomaterials (Jinan, China). Lyz (MW = 14,400 kDa, 6800 IU/mg), dimethyl sulfoxide (DMSO) and CTS (derived from crab shells, degree of deacetylation >85%) were obtained from Sigma. Fluorescein isothiocyanate (FITC) and poly(vinyl alcohol) (PVA, 98–99% hydrolyzed, MW = 146,000–186,000 Da) were purchased from Aladdin Chemicals. Acetone and dichloromethane (DCM) were commercial products from Changshu Yang-Park Chemicals. All of these chemicals were used as received.

**Preparation of Lyz-Laden Microspheres.** Lyz was chosen as the model protein due to its similar size with most growth factors and structural stability. PLGA microspheres containing Lyz were prepared by a water-in-oil-in-water (W1/O/W2) emulsion method, which is frequently used in the field of drug delivery. In brief, 10 mg of Lyz was dissolved in 500 μL deionized water, and then the solution was emulsified with 4 mL of 20% PLGA in DCM and acetone (3:1 by volume) by ultrasonication to form the W1/O primary emulsion. The primary emulsion was then poured into 25 mL of 1% PVA aqueous solution to produce the water-in-oil-in-water (W1/O/W2) secondary emulsion. Thereafter, the solution was magnetically stirred at room temperature until all the DCM and acetone evaporated completely. The produced microspheres were collected by centrifugation and washed twice with deionized water. Finally, the resultant microspheres were stored under vacuum.

**Characterization of the PLGA/CTS Microspheres.** Morphology of the above prepared microcapsules was observed by scanning electron microscopy (SEM; Hitachi TM-1000, Tokyo, Japan). To do this, microspheres were first suspended in alcohol solution, and then the dispersion was dropped onto aluminum foil and air-dried at ambient conditions. The sample was then placed on a metal stub and sputter coated with gold for better conductivity during SEM. PLGA microspheres with FITC-Lyz were suspended in alcohol solution and then placed on a slide glass for observation using a fluorescence microscope (Nikon Eclipse 80i, Japan).

To determine encapsulation efficiency (EE) of microspheres, 20 mg microspheres were dissolved in 1 mL methylene chloride, and 5 mL phosphate buffered saline (PBS) was added subsequently. This solution was stirred at 37 °C for 2 h. After centrifugation at 2000 rpm for 10 min, the aqueous supernatant was analyzed using calibration curves on a UV spectrophotometer (TU-1810, Purkinje General, China) at 220 nm according to the method described elsewhere.

EE was calculated as the percentage of actual amount of Lyz loaded in microspheres compared to the theoretical amount of payload loaded in microspheres.

The zeta potential measurement was used to determine the potential of Lyz-laden PLGA and PLGA/CTS microspheres, which was carried out on a Zetasizer Nano ZS series instrument (Zetasizer Nano ZS, Malvern Instruments, UK) in deionized water.

To analyze the surface chemistry of the composite microspheres, 10 mg microspheres were mixed with KBr, punched, and then their spectra were obtained using attenuated total reflectance fourier transform infrared spectroscopy (ATR-FTIR; Nicolet Instrument, Madison, USA) over the range of 1650–4000 cm⁻¹ at a scanning resolution of 2 cm⁻¹.

Thermogravimetric analysis (TGA) was conducted on a TA Instruments (204 F1 Netzsch, Germany) at a scan rate of 10 °C/min, up to 700 °C. Differential scanning calorimetry (DSC) was employed to measure the thermal properties of polymers on a TA Instruments (204 F1 Netzsch, Germany). Nitrogen was used as a purge gas with a flow rate of 20 mL/min. The Tg was taken at the midpoint of the stepwise specific heat increment.

**Fabrication of a Microspheres-Based Cylindrical Rod.** Three dimensional Lyz-loaded PLGA/CTS scaffolds were fabricated by loading the previously prepared microspheres into a cylindrical mold (diameter = 5 mm, length = 100 mm). The mold was heated to 60 °C (above the Ttrans, i.e., Tg in the current polymer system) for sintering at this temperature for 2 h to achieve bonding between adjacent microspheres. After the mold was cooled to the room temperature, the samples were removed from the mold.

**Modulation of Shape Memory and Payload Release by HIFU.** Lyz-loaded PLGA/CTS (2.5:1) scaffold with a permanent shape “I” was processed into the temporary shape of “V” (folded at T > Ttrans followed by cooling to T < Ttrans) and then immersed into 25 mL deionized water in a glass container (50 mL), which was placed in a water bath maintained at 37 °C. Driven by a function generator and a frequency amplifier (UP-400S, Scientz, China), HIFU transducer (Sonic Concepts, USA) was operated at a frequency of 1.1 MHz to focus the ultrasound waves onto the scaffold at a focal length of 60 mm. After a certain time of HIFU irradiation, surface temperature changes of the scaffold were measured by an infrared thermometer (RATEY MT4, USA). The released amount of Lyz was measured by UV spectrophotometry (TU-1810, Purkinje General, China).
Lyz in the release medium was determined at 220 nm by the UV spectrophotometer used above, as described in the literature. All HIFU-experiments were carried out on scaffolds in solution.

Figure 1 illustrates the overall experimental procedures used to fabricate the microspheres-based cylindrical rod for simultaneously modulating the shape recovery and drug release behaviors via using HIFU as an external trigger.

**Results and Discussion**

**Preparation of Microspheres and Cylindrical Rod.** PLGA copolymers have been used for making microspheres load a variety of biomolecules by encapsulation from using single or double emulsion methods. In this study, a water-in-oil-in-water double emulsion approach was employed for the preparation of drug-laden microspheres. As shown in Figure 2a, emission of green fluorescence indicates that the payload FITC-Lyz was encased in the PLGA/CTS microspheres. In SEM images, the monolithic PLGA microspheres were spherical and showed a smooth surface without pores (Figure 2b), but incorporation of CTS gave rise to increased surface roughness of the composite microspheres. Moreover, it seemed that diameters of composite microspheres increased with increasing the CTS to PLGA ratios from 1:4 to 1:1 (Figure 2c,d,e), likely due to the increased CTS adsorption during the emulsion process. After sintering treatment, microspheres in the fabricated cylindrical rod exhibited the phenomenon of bonding between the adjacent microspheres, but still maintained spherical morphology (Figure 2f). Formation of physical bonding between microspheres warrants structural and mechanical suitabilities for load-bearing applications of the microspheres-based three-dimensional (3-D) cylindrical structure.

**Compressive Properties of the Cylindrical Rod.**

Compressive strength and compressive modulus of the different cylindrical rods (5 × 15 mm, n = 6 for each group) before and after ultrasound irradiation were measured using a universal material testing machine (Instron 5969, USA). A crosshead speed of 5 mm/min was used at ambient temperature and humidity.

**Degradation Test.** Hydrolytic degradation of the microspheres-based scaffolds (0.5 g each) were performed by soaking samples in bottles filled with 25 mL PBS solution (pH 7.4) at 37 °C for up to 50 days. The sample weight and pH value of the medium were monitored every week. Mass remaining percentage was calculated using the following equation:

\[
\text{Mass remaining percentage} = \frac{M_d}{M_0} \times 100\%
\]

where \(M_d\) and \(M_0\) denote the dry and the original weight of the scaffolds, respectively.
In this study, CTS was used to functionalize PLGA by the adsorption method because of its cationic charge, improved drug release properties, biodegradability, and biocompatibility. Functionalization of the surfaces of PLGA microspheres by CTS was confirmed by the change in zeta potential in the deionized water. As shown in Figure 3a, the zeta potential of unmodified microspheres was initially negative because of the carboxyl end groups on PLGA, whereas the zeta potential changed to positive values when the PLGA microspheres were functionalized with different ratios of CTS. The positive zeta potential data of PLGA/CTS reveals the presence of CTS on the surface of the PLGA/CTS microspheres, which is consistent with earlier studies. Electrostatic attraction between positively charged CTS and negatively charged PLGA surface was likely to be the underlying mechanism for the formation of CTS coating. To further confirm the existences of the CTS on the PLGA/CTS microspheres, ATR-FTIR measurements (Figure 3c) of the composite microspheres were made, and the spectra exhibited characteristic peaks at ~3420 cm\(^{-1}\) and ~1570 cm\(^{-1}\), corresponding to the primary amide of CTS. This also suggests that CTS had been coated onto the PLGA microspheres. Figure 3b displays the Lyz EE of the composite microspheres with different PLGA to CTS ratios. As it shows, all the Lyz EEs are higher than 60%, but introduction of CTS to PLGA brought about slight decreases for the CTS-modified microspheres. This was likely because Lyz and CTS both have positive charges and are repulsive to each other during the emulsion process.

Thermal weight loss curves from TGA for the different microspheres are shown in Figure 4a. There are noted two main steps of weight loss: the first weight loss from 30 to 250 °C is associated with the water evaporation of the CTS; and the second one between 250 and 350 °C is attributed to the decomposition of PLGA. Clearly, incorporation of CTS led to enhanced thermal stability of the composite microspheres, in a positive correlation with the CTS contents incorporated. Thermally triggered SMPs usually make use of a thermal transition such as \(T_g\) or \(T_m\) for the recovery, thus it is necessary to further identify the transition temperature with the composite microspheres. DSC was performed to identify the characteristic temperature \(T_g\) of the above prepared microspheres. For the i-lactide-based copolymer, the \(T_{\text{train}}\) value is...
the same as the $T_g$. Being an amorphous polymer, pure PLGA usually has a $T_g$ in the range of 40–60 °C. From Figure 4b, it can be seen that the $T_g$ of PLGA microspheres, as the $T_{trans}$ for shape recovery, is determined to be $\sim 45$ °C; and increasing the CTS ratios from 4:1 to 1:1 in the PLGA/CTS microspheres gave rise to gradual shifts of $T_g$ to higher temperatures (up to $\sim 50$ °C). This suggests that the critical temperature $T_{trans}$ in an SMP system can be adjusted by varying the CTS content of the composite microspheres. In bone scaffolding applications, a slight increase of $T_g$ over the body temperature in the used polymer system is advantageous in retaining structural stability and integrity.

**Modulation of Shape Memory and Payload Release by HIFU.** PLGA had been previously reported with shape memory ability. With the incorporation of CTS into PLGA microspheres by surface physical adsorption, it is of interest to examine influences of the CTS modification on macroscopic shape recovery of the composite microspheres-based 3-D structure. A bending test was therefore performed (Figure 5a), which involved folding samples to 180° shape, and the focus of the HIFU at 300 W beam was then directed to the scaffold immersed in water to trigger the shape recovery process for $\sim 150$ s. The shape recovery ratio, $R$, calculated from using the following formula: $R = (180° - \theta)/180° \times 100\%$ ($\theta$ refers to the final angle), was used to quantitatively determine the shape memory capability. The $R$ parameter has been used to describe the ability of a material to memorize its permanent shape. It is noted that the shape recovery ratio reached the maximum of $\sim 97.6\%$ when the PLGA/CTS ratio was 2.5:1, whereas the PLGA counterpart on its own has a slightly lower $R$ value of $\sim 96\%$ (Figure 5b). However, when CTS/PLGA ratio increased to 1:1, the shape recovery ratio declined to $\sim 92\%

**Figure 5.** (a) Schematic illustration of shape recovery ratio test of cylindrical samples. (b) The effect of PLGA/CTS ratios on shape recovery ratios.
It is known that SMPs generally consist of two types of segments, i.e., (physical or chemical) cross-links determining the permanent shape and switching segments enabling to form the temporary shape at temperatures above \( T_{\text{trans}} \). Since CTS was anchored to the microsphere surface by adsorption forming physical cross-linking between CTS and PLGA macromolecular chains, it may acts as a stationary phase constraining random motion of molecular chain segment of PLGA. This led to increased shape recovery ability, equivalent to a situation of SMPs with more hard segments. However, it is still intriguing to figure out how the further increment in CTS content (e.g., for the case of PLGA/CTS = 1:1) brought about the decreased shape recovery ratio.

The 5 wt % Lyz-loaded PLGA/CTS (2.5:1) scaffold possessed with best shape recovery ability was subsequently used to study the HIFU-enabled spatial and temporal control of shape memory and drug release effects. To begin with, the HIFU-induced heating effect was first examined by irradiating the PLGA/CTS (2.5:1) scaffold for different periods of time at varied acoustic powers, in which the surface temperature changes of scaffold were monitored by infrared thermometer. It can be seen that the rate of temperature rise increased with the acoustic power applied (Figure 6a). For instance, when the HIFU output power was 300 W, the sample could be quickly heated above 50 °C within 100 s of HIFU irradiation and finally kept a steady state at nearly 65 °C, which is above the \( T_{\text{trans}} \) observed in Figure 4b.

Figure 6b shows the synchronized shape recovery and drug release of the Lyz-loaded PLGA/CTS (2.5:1) rod upon cyclic HIFU exposure. When HIFU at 300 W was turned on for 30 s, the shape recovery started from a deformed “V” shape, and the loaded drug was released simultaneously. Once HIFU was turned off, the shape recovery halted immediately retaining the intermediate shape, and the drug release fell down, showing typical pulsatile release profile. After four cycles of HIFU irradiation, the sample returned to the initial shape of a straight bar (Figure 6c). The simultaneous control of the shape recovery process and the drug release from the SMP by remote HIFU activation could lead to a variety of potential biomedical applications. For instance, it may reduce the risk of operation infection when an SMP device is implanted through minimally invasive surgery.

On the other hand, drug release amount and shape recovery rate can also be controlled by varying the output power of HIFU. As shown in Figure 7a, no recovery occurs in the absence of HIFU irradiation. At a power output of 300 W (or higher), the sample can rapidly recover to the permanent shape in 120 s, and the shape recovery ratio can reach over 95%. If lower HIFU power outputs (e.g., 60 W, 150 W) were applied, the shape recovery process could proceed as well but with...
lowered shape recovery ratios, which means taking longer time to achieve a full shape recovery. Likewise, the released dosage can also be regulated by varying the power of ultrasound delivered to the system (Figure 7b). HIFU can trigger the amount of Lyz release from the scaffold; when ultrasound is off, the released amount of drug will suddenly cut down to a negligible level. Although different methods (e.g., physical, chemical, and biological) can be employed to induce drug releases,42 the underlying mechanism relating to ultrasound as a physical stimulus is that ultrasonic irradiation raises the temperature of the scaffold to above the $T_g$, and thus enhances the diffusion coefficient of the SMP, resulting in rapid release of the entrapped drug molecules. Whereas the release is stopped when the polymer is cooled down to below $T_g$ once the ultrasound irradiation is turned off.16 Clearly, the ability to change the dose of administered HIFU energy offers the flexibility to make HIFU suitable for different clinical requirements. It should be noted that sample deforming for modulating shapes also affected the released amounts of Lyz to some extent if comparing the release behaviors of deformed and undeformed samples under the same sequence of HIFU steps (data not shown).

Finally, using the Lyz-loaded PLGA/CTS straight rod as the starting material, we were able to process it into other dissimilar shapes, and their ultrasound-triggered shape recovery processes were all complete within 120 s of HIFU exposure (Figure 8). This demonstration indicates that the biodegradable drug-loaded PLGA/CTS scaffold is capable of being transformed into many kinds of shapes and a number of temporary shapes can be memorized based on practical needs. Such a desirable shape recovery effect highlights its potential in biomedical applications, for instance, as resorbable screw-hole filler to reduce the likelihood of bone refracture after removal of repairing plates and screws.43 In this regard, incorporating some relevant inorganic particles (e.g., hydroxyapatite) into an SMP could enhance ultrasound absorption and shape change/ control.41,44

Mechanical and degradation properties of the cylindrical rod. Mechanical and biodegradation properties are the important concerns for SMPs used for load-bearing applications, e.g., as cellular scaffolds for bone repair and regeneration. Figure 9 shows the compressive strength and the compressive modulus of the microspheres-based scaffolds before and after ultrasound treatment at 60 W for 30 s. Compared with the PLGA counterpart, PLGA/CTS scaffolds show high compressive strength and compressive modulus. Although acoustic cavitation and streaming of ultrasound may distort the interaction between the bonded microspheres, likely leading to decreased mechanical properties of these microspheres-based scaffolds, this is not significant in our observation. There is no statistical difference in the moduli of the scaffolds with and without of ultrasound treatment. The cylindrical rod was found to have compressive moduli and compressive strengths in the range of the trabecular bone, as reported in literature.21,23,45 As microspheres were used for making the cylindrical rod, a further exploration on the micromechanical property of the microspheres (e.g., through AFM based mechanical property characterization) would throw a light on the correlation between micromechanical properties of the microspheres and their behavior in regulating drug release.

PLGA degrades by hydrolysis of its ester linkages in the presence of water to produce the original monomers, lactic acid, and glycolic acid. No significant difference was observed in...
between PLGA and PLGA/CTS scaffolds in weight loss, whereas compared with pure PLGA scaffold, introduction of 50% CTS into PLGA (i.e., PLGA/CTS = 1:1) increased the pH value of the soaking solution containing the rod sample (0.5 g) from 5.5 to 6.5 on day 50 (Figure 10). A retarded degradation was observed from the composite microspheres in contrast to the pristine PLGA due to the effective acid-neutralizing effect of CTS on acid metabolites of PLGA. It has been shown that PLGA generate acidic internal environment after gradual hydrolysis into lactic acid and glycolic acid, which is detrimental to biopolymer stability. Thus, an extra merit of introducing CTS into PLGA microspheres is its capability in neutralizing the acidic degradation products of the PLGA in the course of degradation.

### CONCLUSIONS

We have developed a novel PLGA/CTS microspheres-based biodegradable cylindrical rod integrated with functionalities of SME and controlled drug release. The concept of using HIFU as a remotely controllable external stimulus to achieve spatiotemporal modulation of drug delivery and synchronized shape recovery has also been demonstrated. The critical role of the CTS component in regulating the thermal, shape memory, mechanical, and degradation properties of the microsphere-based cylindrical rod was identified.

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**Notes**

The authors declare no competing financial interest.

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