Supporting Information

1. HIFU Experiment Setup

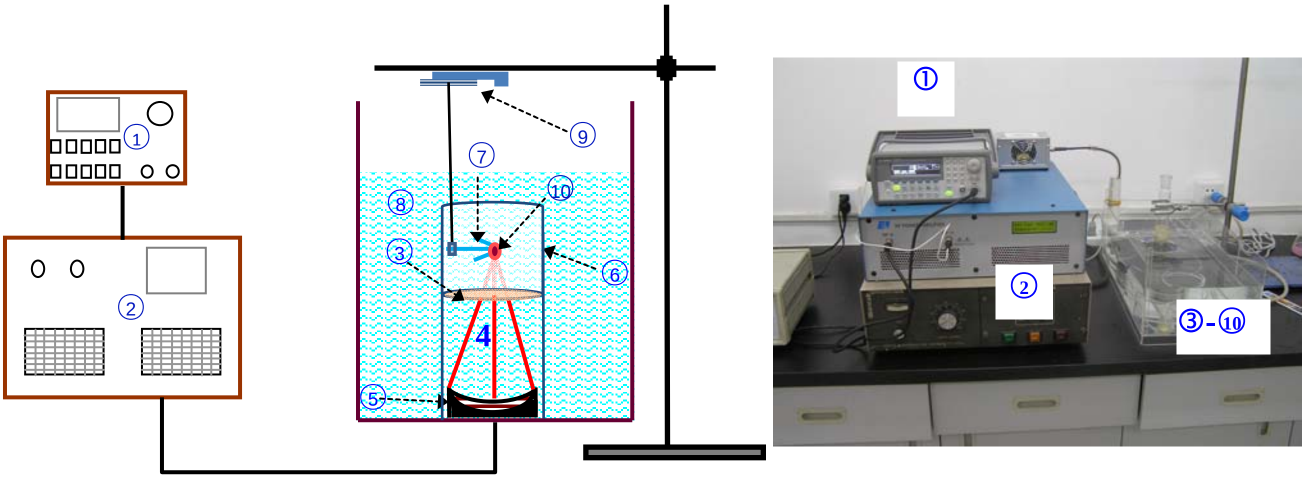

Figure S1. Schematic illustration of the experimental setup (left) and photo of the high intensity focused ultrasound (HIFU) apparatus (right). 1: Arbitrary waveform generator, 2: RF power amplifier, 3: Latex membrane, 4: Ultrasound beams, 5: Acoustic lens transducer, 6: Glass container, 7: Drug-loaded polymer, 8: Water bath 9: Translation stages, 10: HIFU focal spot.

2. Synthesis and Sample Preparations

Chemicals: Methyl methacrylate (MMA) and butyl acrylate (BA) (both from Chengdu Kelong Chemical Reagent Factory) were distilled in vacuum prior to use. Copper sulfate (Chengdu Kelong Chemical Reagent Factory), Sulphur Hexafluoride Microbubbles (SF6 microbubble, Shanghai Bracco Sine Pharmaceutical Corp. Ltd.) and Ethylene dimethacrylate (EGDMA, ACROS Organic, Vlaanderen, Belgium) were used as received. 2,2'-Azobis(isobutyronitrile) (AIBN, Shanghai Chemical Reagent) was used after recrystallization.

Synthesis of cross-linked P(MMA-BA). Cross-linked P(MMA-BA) copolymers were prepared by using free radical polymerization. Briefly, monomers MMA and BA with a certain mole ratio were mixed with EGDMA (varying amounts for various cross-linking densties) and AIBN (0.56 wt% of the reaction mixture). Subsequently, the mixture was transferred into a glass mold (100 mm in length, 100 mm in width and 2 mm in height) sealed with silicon rubber and polymerized at 60 ^{o}C for 24 hour. The resulting polymer was then taken out from the glass mold and vacuum dried at 80 ^{o}C for 3 h to remove unreacted monomers.

Preparation of P(MMA-BA) containing copper sulfate. Copper sulfate particles were first milled and sieved with a 500 mesh (pore size is ~28 μm) decimate sift; then a certain amount of copper sulfate was added into the MMA/BA monomer mixture and the suspension was filled into the glass mold. Subsequently, the glass mold was placed in ultrasonic cleaner (KQ-250DE, Kun Shan Ultrasonic Instruments Co., ltd) and the polymerization proceeded at 60 ^{o}C for 24 hour under ultrasound vibration. Afterward, the resulting sample was taken out from the glass mold and vacuum dried at 80 ℃ for 3 h to remove unreacted monomers. For thermometric probe-embedded polymer samples, a thermometric probe was placed in the glass mold before the reaction mixture was poured into it, and during the polymerization the probe was fixed inside the polymer.

3. Characterization of Polymer Samples Using Dynamic Mechanical Analyzer

The dynamical mechanical tests were performed on a Q-800 instrument (TA Instruments, USA) with dual cantilever mode. The storage modulus (E') and loss factor (tan δ) were measured in the temperature range of 0-180 ℃ at a heating rate of 3 ℃/min. The strain amplitude used was 50 μm and the test frequency was 1 Hz. The results summarized in Figure S2 and Table S1 show the effect of the molar ratio of MMA and BA on the T_{trans} of the resulting crosslinked P(MMA-BA) copolymers.

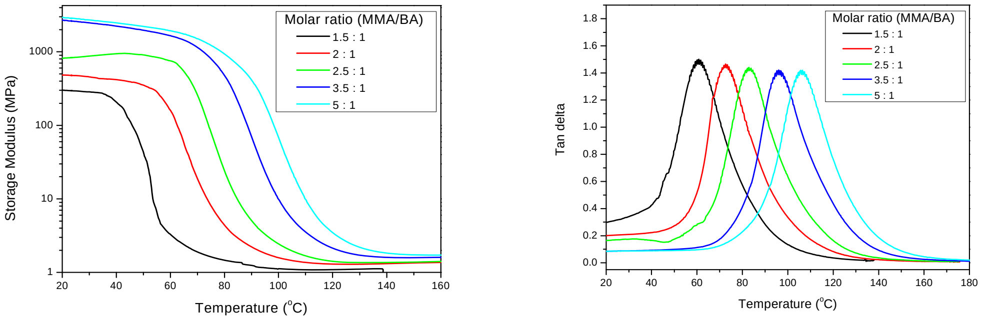

Figure S2. Storage modulus and Tan delta of crosslinked P(MMA-BA) copolymers with different monomer ratio (MMA: BA).

Table S1. T_{trans} of crosslinked P(MMA-BA) copolymers with different monomer ratios

Molar ratio (MMA/BA)	MMA content (wt %)	T_{trans} * (℃)
1.5 : 1	53.95	-7.9
2 : 1	60.97	17.5
2.5 : 1	66.13	46.5
3.5 : 1	73.2	52.3
5 : 1	80.67	59.5

*: T_{trans} is defined as the onset temperature of the glass transition the from DMA test.

The results summarized in Figure S3 and Table S2 show the small effect of loaded copper sulfate of varying amounts on the T_{trans} and mechanical properties of cross-linked P(MMA-BA) copolymers.

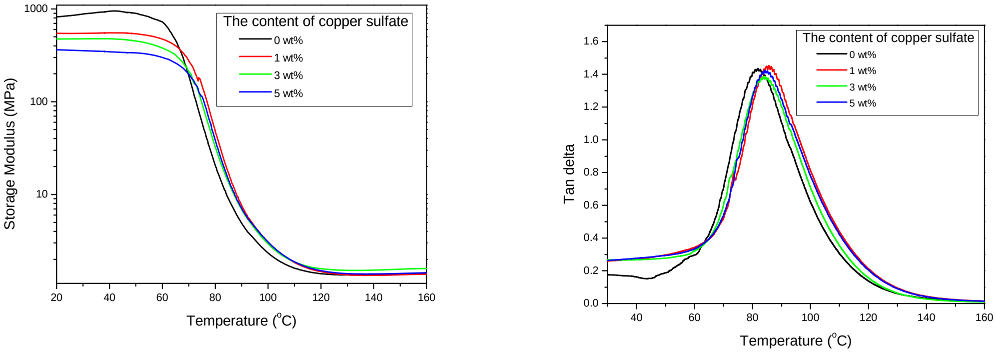

Figure S3. Storage modulus and Tan delta of a crosslinked P(MMA-BA) copolymer loaded with different amounts of copper sulphate.

Table S2. T_{trans} of a crosslinked P(MMA-BA) copolymer with different copper sulphate contents

Molar ratio (MMA : BA)	MMA content (wt %)	Copper sulfate content (wt %)	T_{trans} (℃)
2.5 : 1	66.13	0	46.5
2.5 : 1	66.13	1	45.8
2.5 : 1	66.13	3	46.5
2.5 : 1	66.13	5	46.7

Four cycles of the thermomechanical tests were performed with the sample containing 5wt% of copper sulfate. The results in Figure S4 show that very similar results can be obtained indicating no deterioration of the shape memory properties.

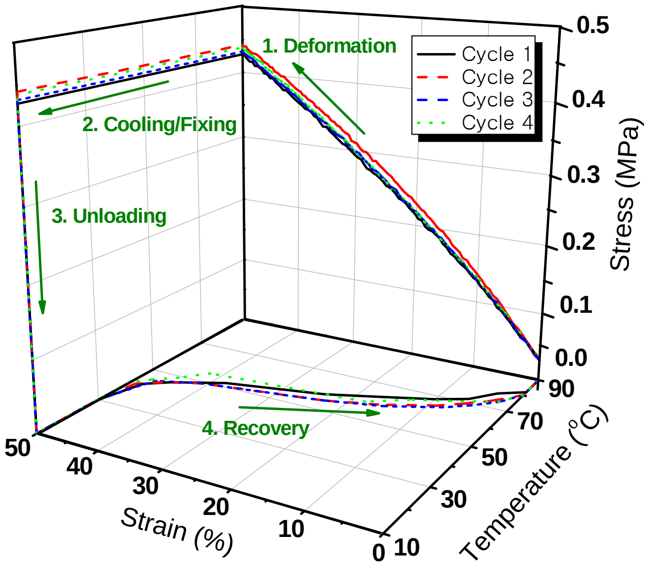

Figure S4. Repeated shape-memory thermomechanical cyclic tests for crosslinked P(MMA-BA) containing 5 wt% copper sulfate.

4. HIFU Experiments

HIFU-Induced Heating. In addition to the date in Figure 2a obtained under 25 W UIFU exposure, the temperature change profiles for the surface of the polymer, the interior of the polymer and the water surrounding the polymer in the reactor were also recorded with 50 W HIFU upon periodic ultrasound-on and off. The results are shown in Figure S5. As expected, higher temperature increases can be obtained.

Tests of HIFU controlled shape recovery. Using the setup in Figure S1, the spatial and temporal control of the shape recovery process by HIFU was investigated by programming the samples to a temporary shape and then monitoring the recovery to the original shape under different power outputs of HIFU. Generally, the samples were processed into straight strips as their permanent shape, after heating the samples to $T>T_{trans}$, an external deformation was applied to obtain the right-angle shape (temporary shape), which was subsequently fixed by reducing the temperature to $T<T_{trans}$. For the shape recovery, the samples were immersed in the water bath and subjected to HIFU beam exposure at different power outputs (0-30 W). During the recovery process, the angle of the deformed part was recorded by a goniasmometer after every 10 seconds.

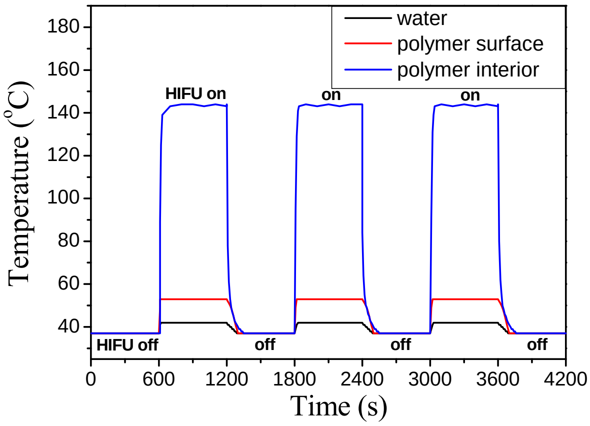

Figure S5. Temperature change upon cyclic HIFU exposure and removal for water in the reactor, polymer surface and polymer interior, the ultrasound power being 50 W.

Tests of HIFU controlled drug release. The drug release behavior of copper sulfate-loaded samples under HIFU was investigated by exposing the samples to HIFU beams using the setup in Figure S1. The samples were programmed into straight strips and weighed before being placed in the container, then 200 mL PBS buffer was filled in and the container was sealed with latex membrane. The HIFU power output was set at 0-50 W and an on-off HIFU exposure cycle was applied. The cycle was repeated for 7 times and the environmental water bath temperature was kept constant at 37 °C. The amount of released copper sulfate was measured by SpectrAA 220FS Atomic Absorption Spectroscopy.

Tests of synchronized shape recovery and drug release. A copper sulfate-loaded sample was processed into a T-shape (permanent shape) and then deformed into a temporary shape after heating it to $T>T_{trans}$; the sample was then cooled to 10 °C, below T_{trans}, to fix the temporary shape. Subsequently the sample was placed in the container mentioned above, then 200 mL PBS buffer was filled in and the container was sealed with latex membrane. An on-off cycle for HIFU exposure was applied to trigger or stop the shape recovery process and to control the drug release. The step-wise shape recovery process was recorded by using a digital camera (E350, Olympus), while the amount of released copper sulfate was measured by SpectrAA 220FS Atomic Absorption Spectroscopy.

5. Swelling Behavior of Crosslinked P(MMA-BA) with or without Loaded Copper Sulfate

Several experiments were carried out to examine the swelling behaviors of cross-linked P(MMA-BA) copolymer. In the first experiment, dried samples (sample weight: W_0) were immersed and swelled in 200 mL PBS buffer (0.01M, pH=7) at different temperatures (between about 33 °C and 90 °C). The weight change of each sample was recorded at regular time intervals (24 h) until the sample weight (W_t) remained constant (reaching the swelling equilibrium). Changes in the swelling ratio (defined as below) at equilibrium as a function of solution temperature are shown in Figure S4. It is no surprise to observe an increased swelling with increasing the temperature.

$$Swelling\ ratio(\%) = \frac{W_t - W_0}{W_0} \times 100$$

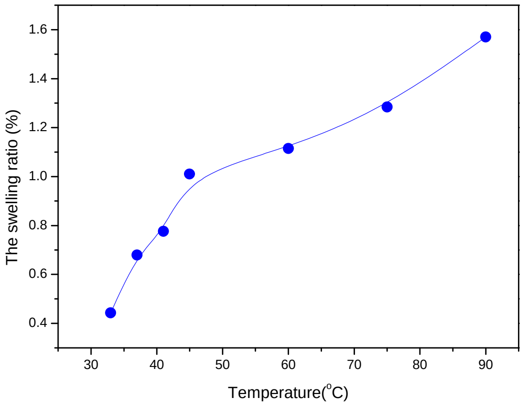

Figure S6. Plot of the equilibrium swelling ratio vs. solution temperature for cross-linked P(MMA-BA) copolymer.

In the second set of experiments, the swelling behaviors of cross-linked P(MMA-BA) samples with or without loaded copper sulfate at a constant solution temperature of 37 °C (in 200 mL PBS buffer, 0.01M, pH=7) were investigated. And in each case, the measurements were made both in the absence and in the presence of HIFU exposure (25 W). The results are shown in Figure S5. In both cases (with and without copper sulfate), the polymer swelling is greater under HIFU exposure. The difference is much more prominent for the drug-loaded polymer. In the absence of HIFU, the loading of copper sulfate appears to increase significantly the swelling of the polymer matrix, which is likely due to a greater porosity caused by the insertion of copper sulfate.

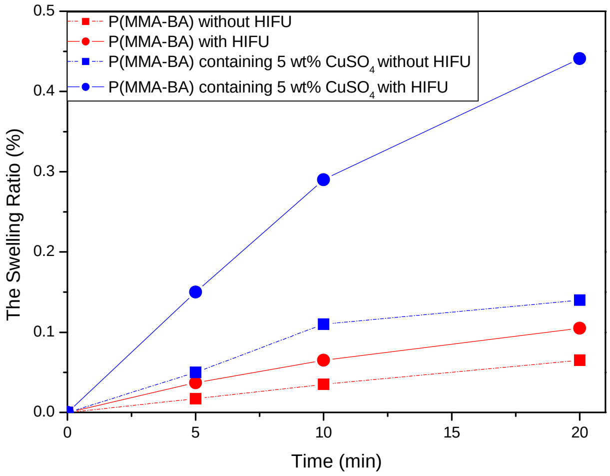

Figure S7. The swelling behaviors of cross-linked P(MMA-BA) samples with or without loaded copper sulfate (5 wt%) in 37℃ water, both in the absence and presence of HIFU exposure (25 W).

6. Control Tests of Drug Release

We also performed a number of drug release control tests. On the one hand, thermally activated release of copper sulfate from cross-linked P(MMA-BA) was investigated. In this experiment, a drug-loaded sample was immersed in 20 mL PBS buffer at 37 ^{o}C (below T_{trans}) and 80 ^{o}C water both (above T_{trans}) respectively. 5 mL PBS solution was taken out at a certain time interval (24 h) to measure the released copper sulfate while 5 mL of fresh PBS buffer was added in the flask to maintain a constant solution volume. The concentration of released copper sulfate was measured by SpectrAA 220FS Atomic Absorption Spectroscopy. Actually, almost no release was observed at 37 ^{o}C after 30 days. This result supports the hypothesis that the polymer heating to $T>T_{trans}$ induced by HIFU should be responsible for the HIFU triggered drug release from polymer matrix. Figure S7 shows SEM images of the drug-loaded polymer surface before and after 30 days in solution at 80 ^{o}C (recorded on a JSM-5900LV SEM with an acceleration volt 15 kV). The high porosity should be caused by the polymer swelling at this temperature.

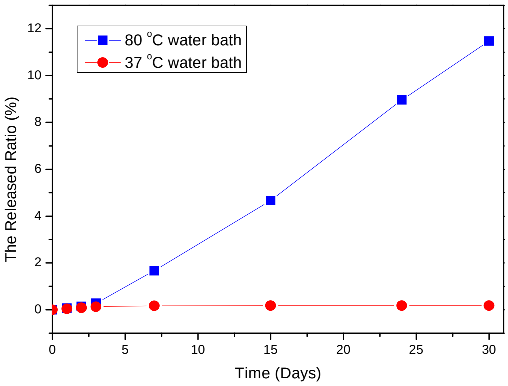

Figure S8. The release behavior of cross-linked P(MMA-BA) copolymer containing 5 wt% copper sulfate immersed in PBS buffer solution at 37 and 80 ^{o}C, respectively. The released ratio is defined as the amount of released copper sulphate compared to the original loaded amount.

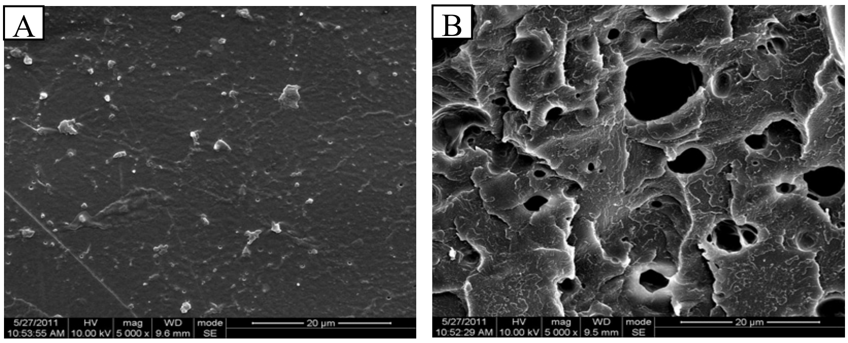

Figure S9. SEM images of cross-linked P(MMA-BA) containing 5 wt% copper sulfate before （A） and after (B) swelling for one month in water bath at 80 ^{o}C. The scale bar in both images is 20 um.

On the other hand, the HIFU induced release of copper sulfate in different cavitation environments was also investigated. In this case, the samples were cut into straight strips and placed in the container, then 200 mL degassed water or SF6 microbubble solution was filled in and the container was sealed with a latex membrane. Setting the HIFU power output at 25

W, after every 10 min 5 mL the samples of the solution in the container was taken out for measuring the amount of released copper sulfate, while 5 mL of fresh water or SF6 microbubble solution was added in the container to keep the solution volume constant. The results in Figure S8 show that the HIFU induced drug release is related to the cavitation effect.

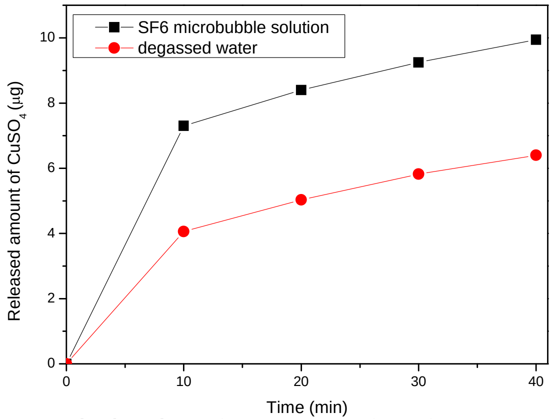

Figure S10. The release behavior of copper sulfate from cross-linked P(MMA-BA) in degassed water and in SF6 microbubble solution at 37 °C at a HIFU power output of 25W.