Supporting Information

Ultrasonic de-crosslinking of pH- and magneto-responsive PHEMA/PMMA microgel to Janus nanoparticle: a new synthesis based on "grafting from"/"grafting to" polymerization

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S1. Experimental Procedures

S1.1 Synthesis of 2-bromo-N-(2-hydroxyethyl)-2-methylpropanamide (EA-IBB) (ATRP initiator)

Anhydrous DCM (10 mL), ethanolamine (0.25 gr, 4.1 mmol) and TEA (0.43 gr, 4.2 mmol) were introduced into a 100 mL three necked flask. After cooling down to 4 ℃, a solution of 0.94 g BIBB (4.1 mmol) in 5 mL anhydrous DCM was added dropwise during 2 h. The mixture was stirred for 4 h at room temperature. Triethylammonium bromide as a white precipitate was filtered off and other impurities were extracted using water saturated with Na_2CO_3. The organic phase was dried with anhydrous magnesium sulfate, and DCM was evaporated under reduced pressure. Finally, EA-IBB was obtained as viscose oil (70% yield).

S1.2. Synthesis of *Nα,Nα′*-di-Boc-L-cystine (Boc-Cys-OH)$_2$ as crosslinker

(Boc-Cys-OH)$_2$ was prepared according to our previousely reported procedure [S1]. Briefly, Di-*tert*-butyl dicarbonate (Boc_2O) (1 g, 4.6 mmol) and cystine (0.5 g, 2.1 mmol) were dissolved in THF/water (1:1, total volume of solution is 20 mL). After cooling down to about 0°C, Na_2CO_3 (0.5 g) was added to the mixture and stirred for 30 min in this temperature and an overnight at room temperature. Then, the solution was extracted twice with diethyl ether. The THF/water solution was placed in ice bath and semi-saturated citric acid added to adjust the pH of mixture to 4-5. Then, the acidic solution was extracted with DCM (three times). The organic phases were collected, dehydrated by sulfuric acid and concentrated through evaporation of DCM under reduced pressure to give a yellow oily product, which finally changed to a white precipitate as time passed.

S1.3. Synthesis of magnetite nanoparticles (SPION)

Magnetite nanoparticles were synthesized *via* co-precipitation method under nitrogen atmosphere [S2]. Briefly, $FeCl_3.6H_2O$ (0.65 g 2.4 mmol) and $FeCl_2.4H_2O$ (0.25, 1.2 mmol) were dissolved in 20 mL deionized water and the solution heated to 70 ℃ under nitrogen gas. Then, 10 mL ammonia solution (25%) was added dropwise into stirred reaction mixture. After 2h the obtained magnetic nanoparticles were separated by external magnetic field and washed with deionized water (3* 25 mL) and ethanol (2×30 ml) and then dried under vacuum for 12 h.

S1.4. Synthesis of amino-Functionalized magnetic nanoparticles with APTES (mSPION)

Amine modified magnetic nanoparticles were synthesized through reacting APTES with hydroxyl groups of iron oxide NPs [S2]. Briefly, the magnetic nanoparticles (0.2 g) were dispersed in ethanol (60 mL) under sonication for 5 min. Then, 5 mL of APTES and deionized water (2 mL) were added into dispersed NPs and stirred for 7 h under N_2 atmosphere. The resulting NPs were separated by external magnetic field and washed four times with ethanol and then dried under vacuum for 24h to yield amine decorated SPION with 88% yield.

S2. Additional Data

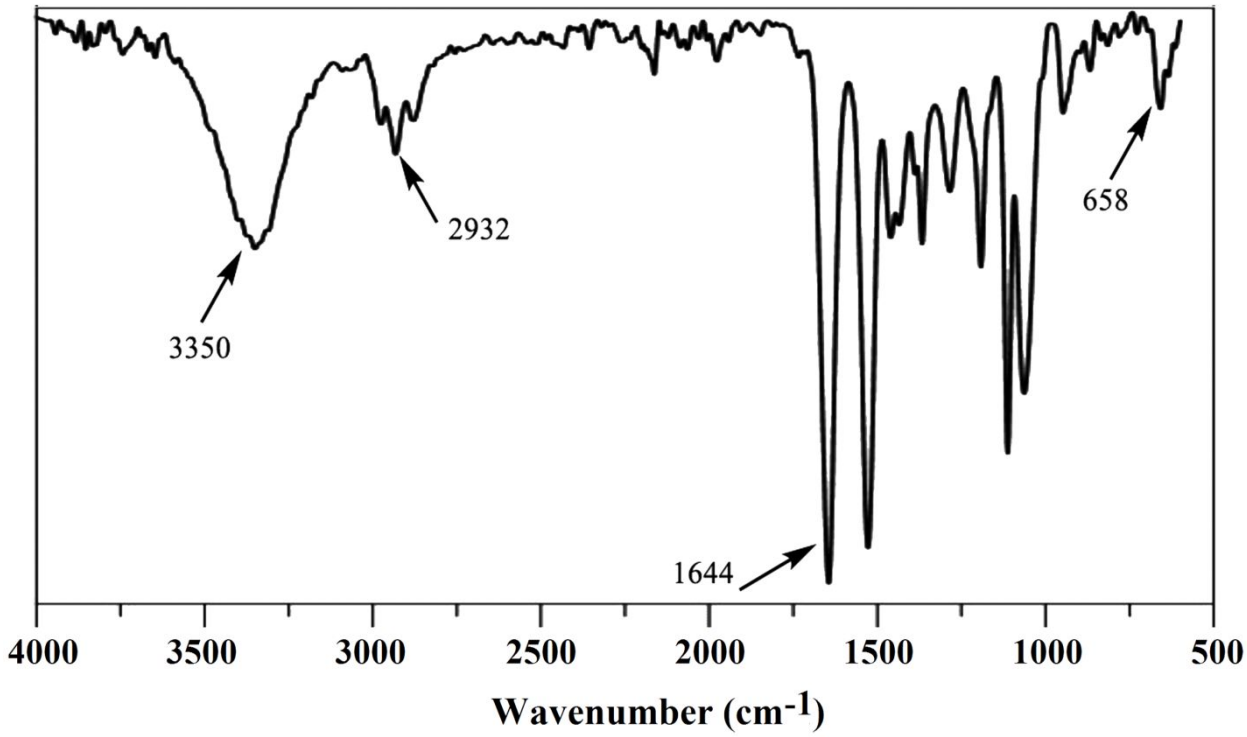


Figure S1. FT-IR spectrum of EA-IBB initiator

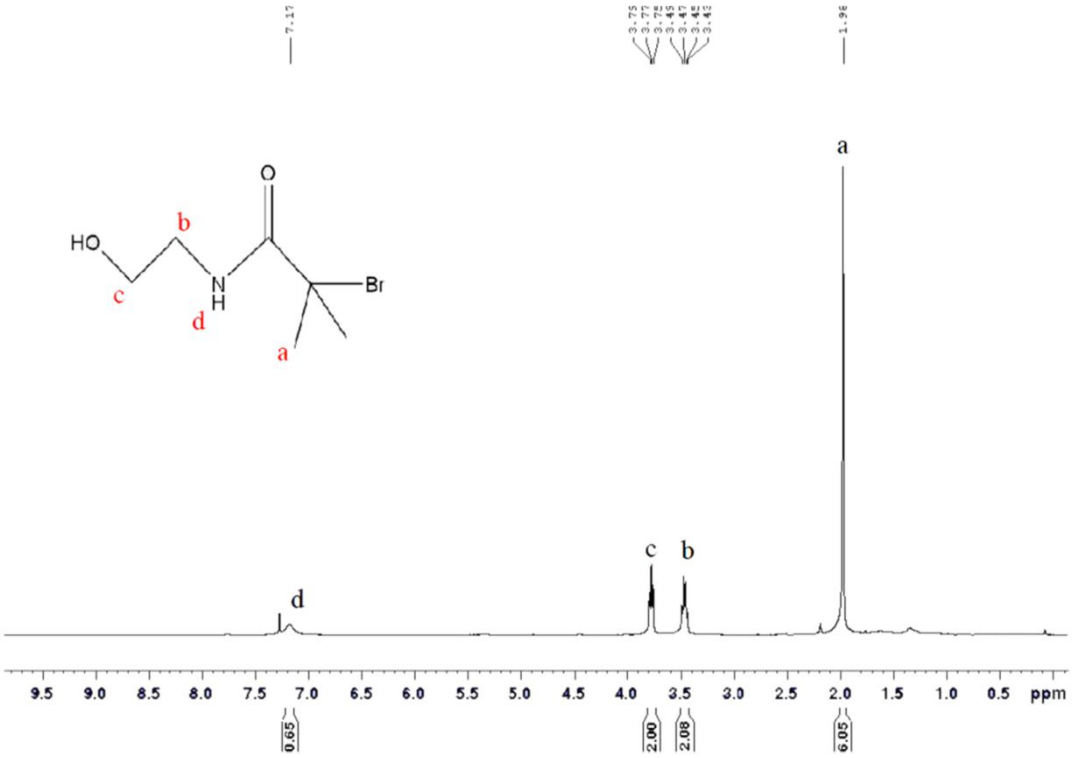


Figure S2. 1H-NMR spectrum of EA-IBB initiator

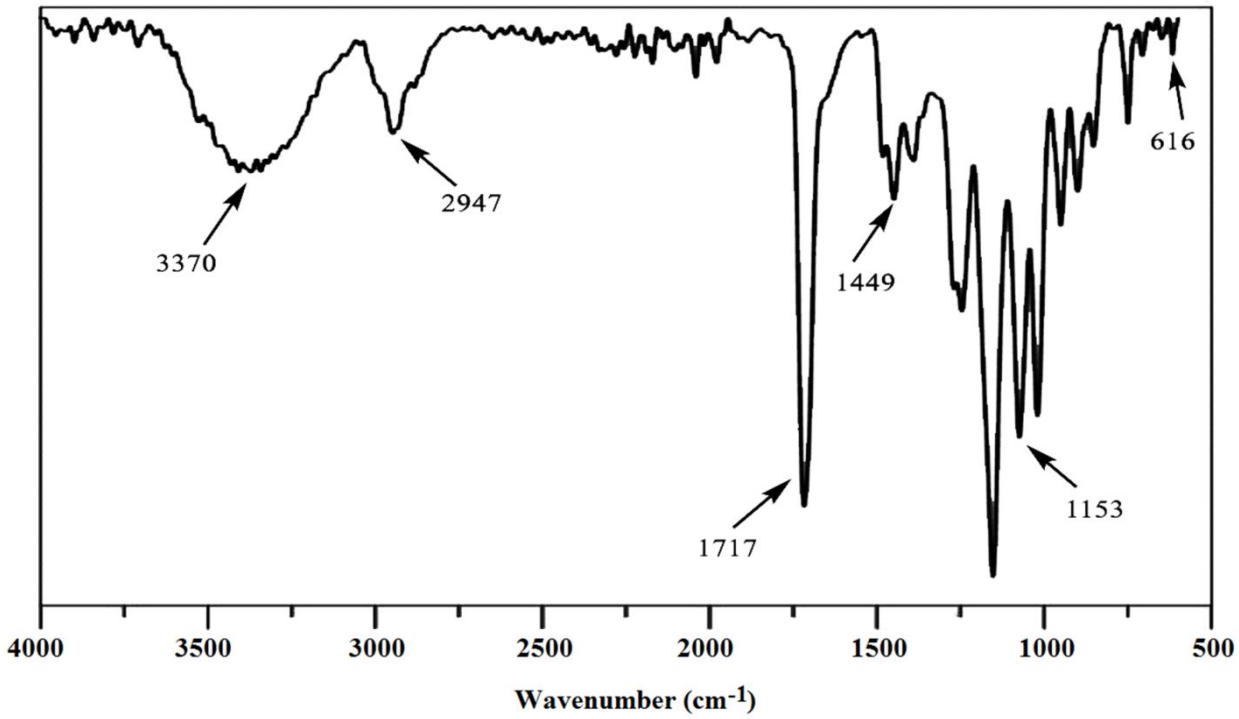


Figure S3. FT-IR spectra of PHEMA

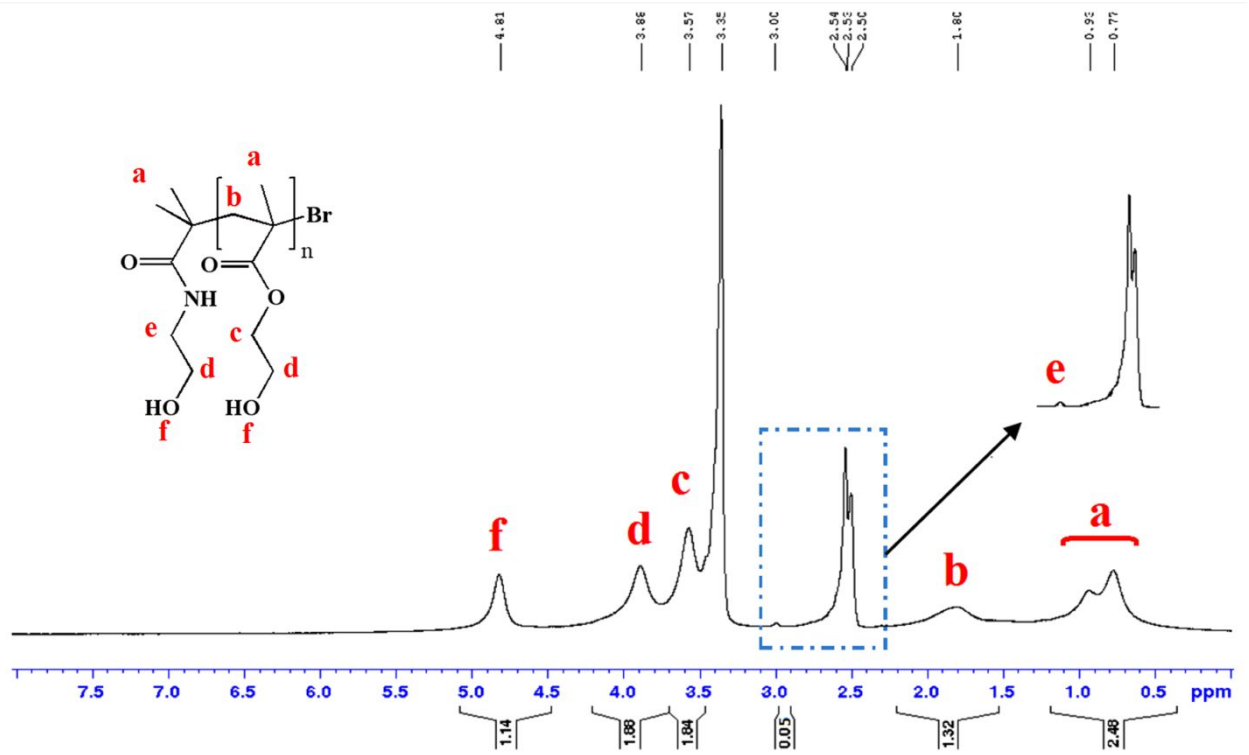


Figure S4. 1H-NMR spectrum of PHEMA

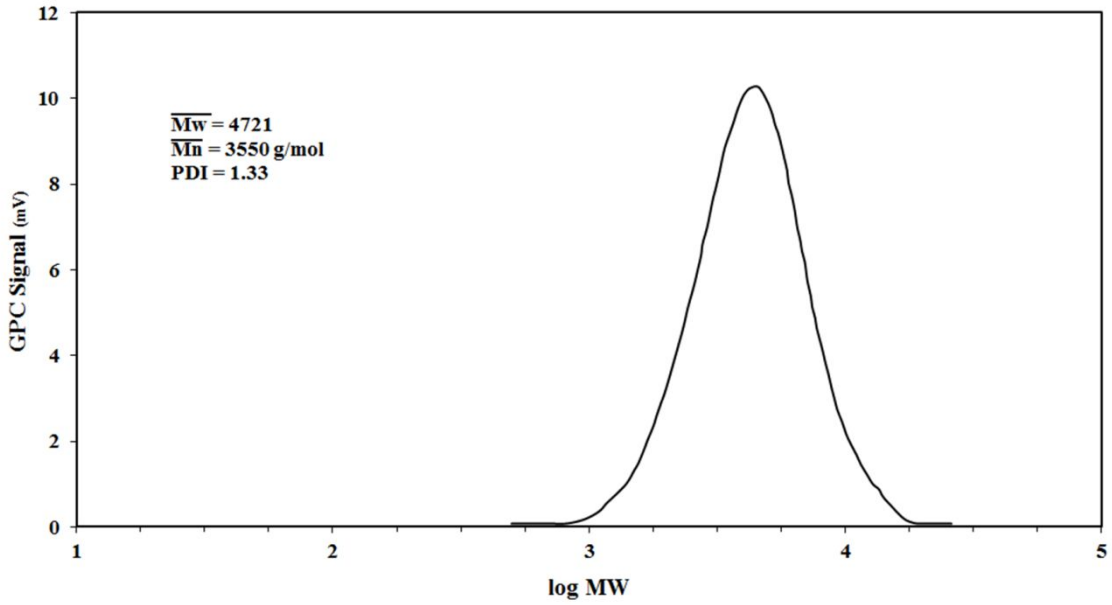
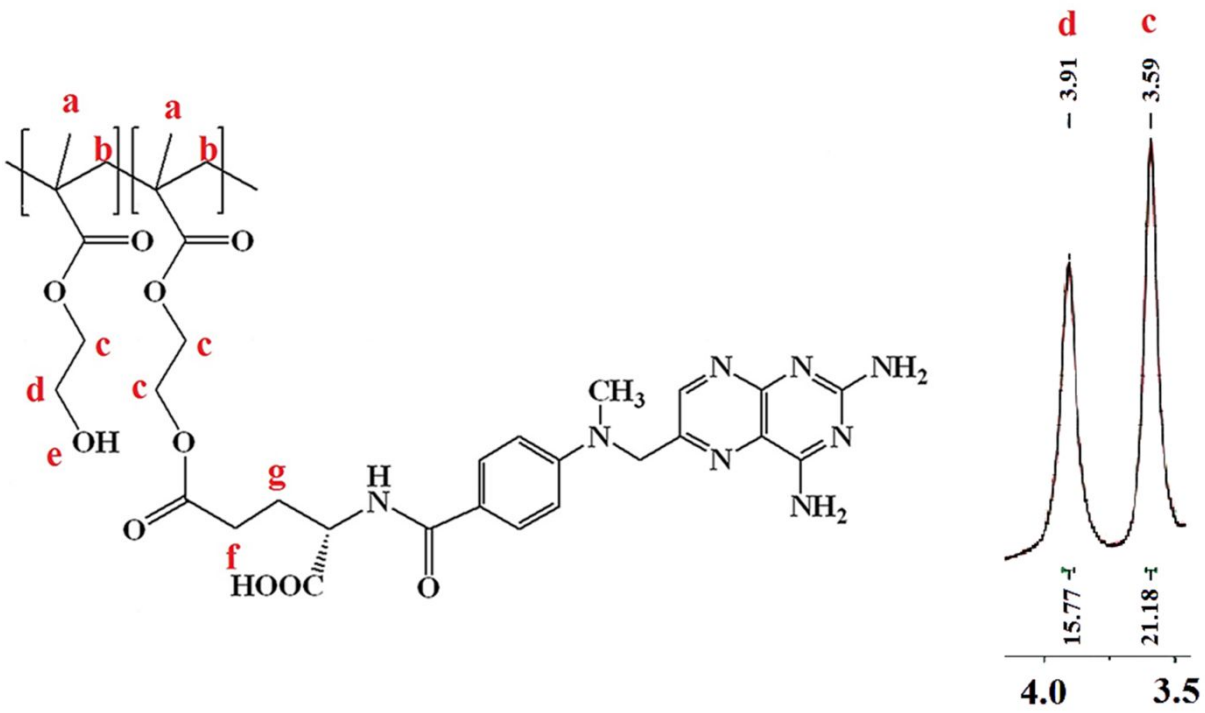


Figure S5. GPC chromatogram for PHEMA made by ATRP



Peak area of MTX: $\frac{21.18 - 15.77}{2} = 2.705$

Amount of MTX/polymer ratio: $\frac{2.705}{2.705 + 15.77} = 0.146$

Number of drug-conjugated repeating units to all the repeating units: $0.146 = \frac{1}{x} \Rightarrow x = 6.85$

MW of HEMA=130.14 g/mol and MW of MTX= 454.44g/mol

Drug to polymer ratio: $\frac{454.44}{6.85 \times 130.14 + 454.44} \times 100 = 33.76\ \%$

Figure S6. The MTX/polymer ratio calculated by integrating the methylene protons **(c, d)** in the PHEMA

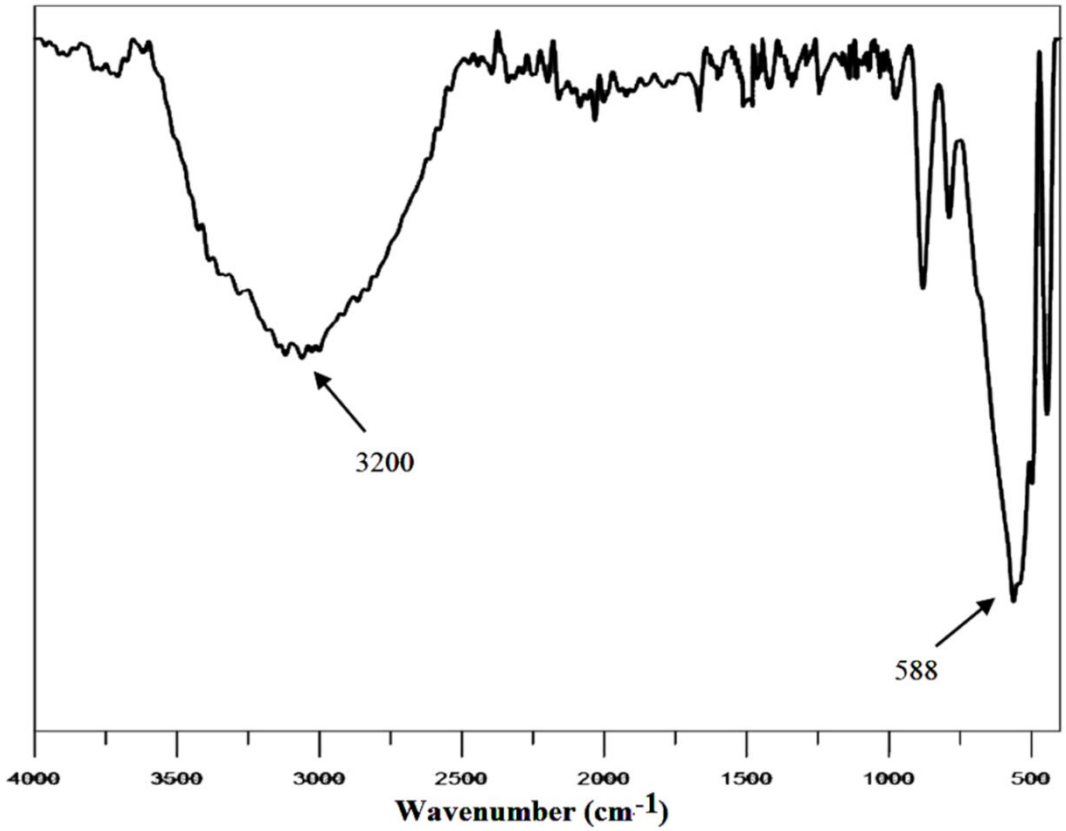


Figure S7. FT-IR spectra of SPION

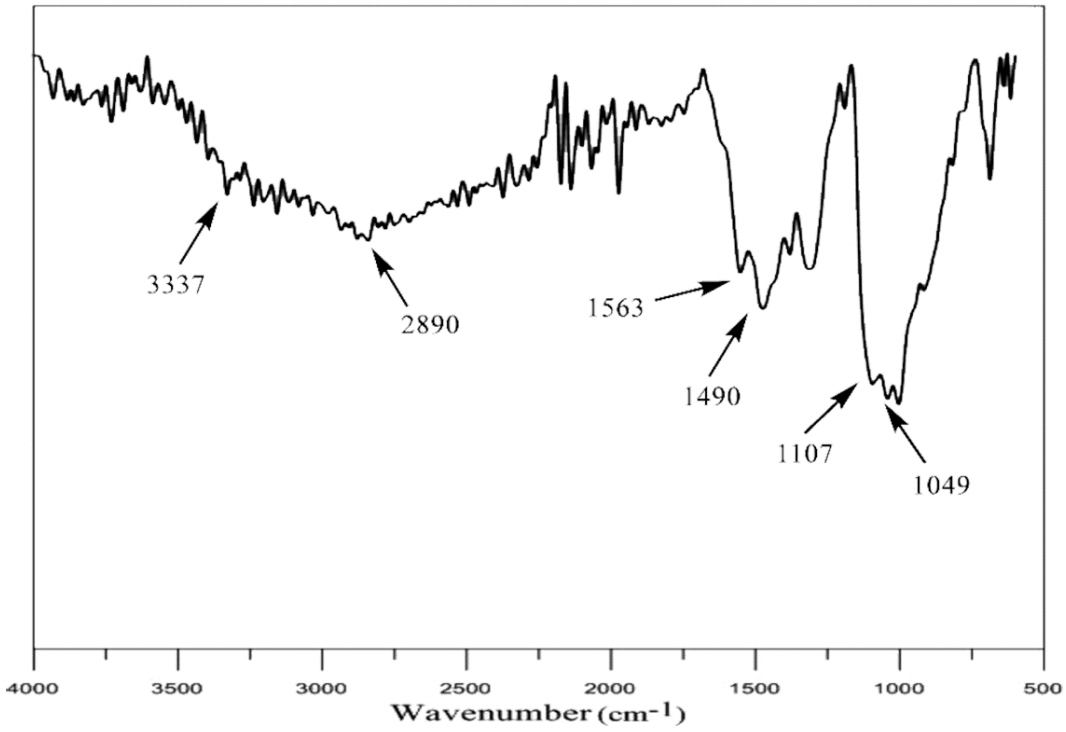


Figure S8. FT-IR spectra of mSPION

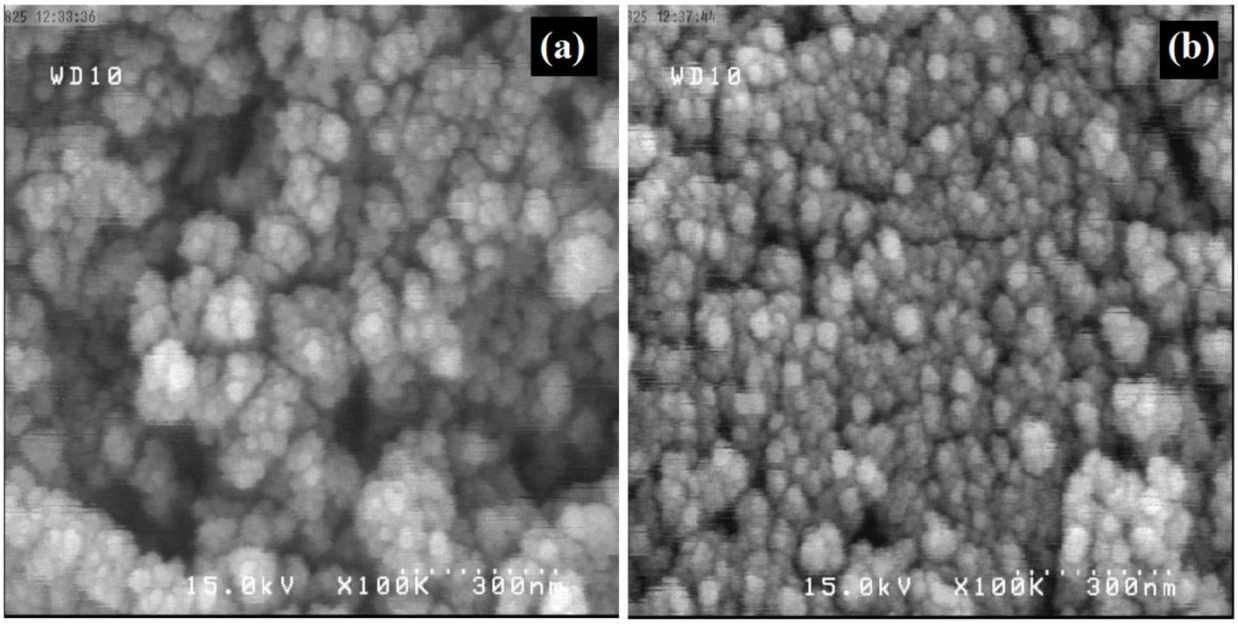


Figure S9. SEM images of SPION (a) and mSPION (b)

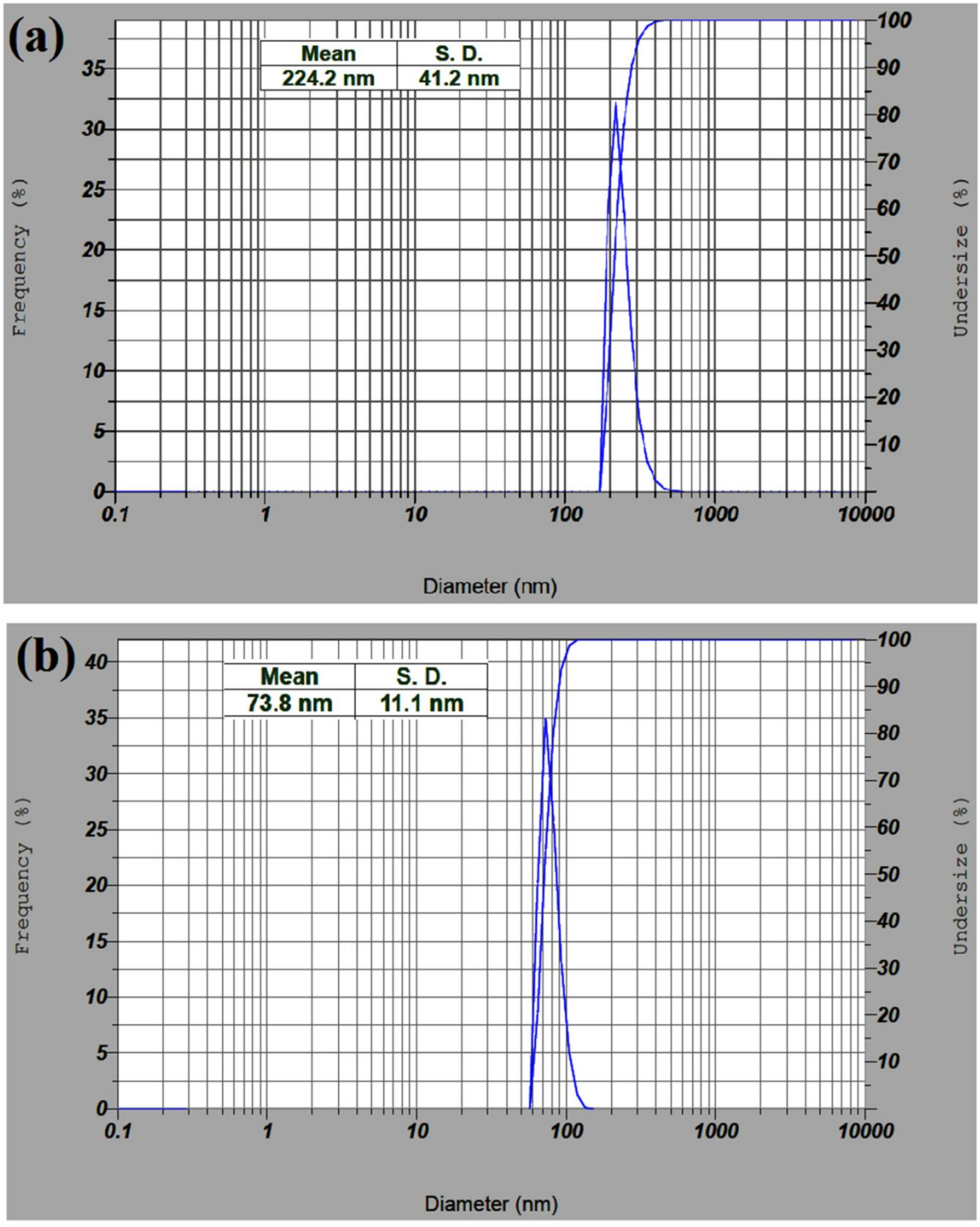


Figure S10. Particle size of SPION (a) and mSPION (b) obtained from DLS analysis at pH=7

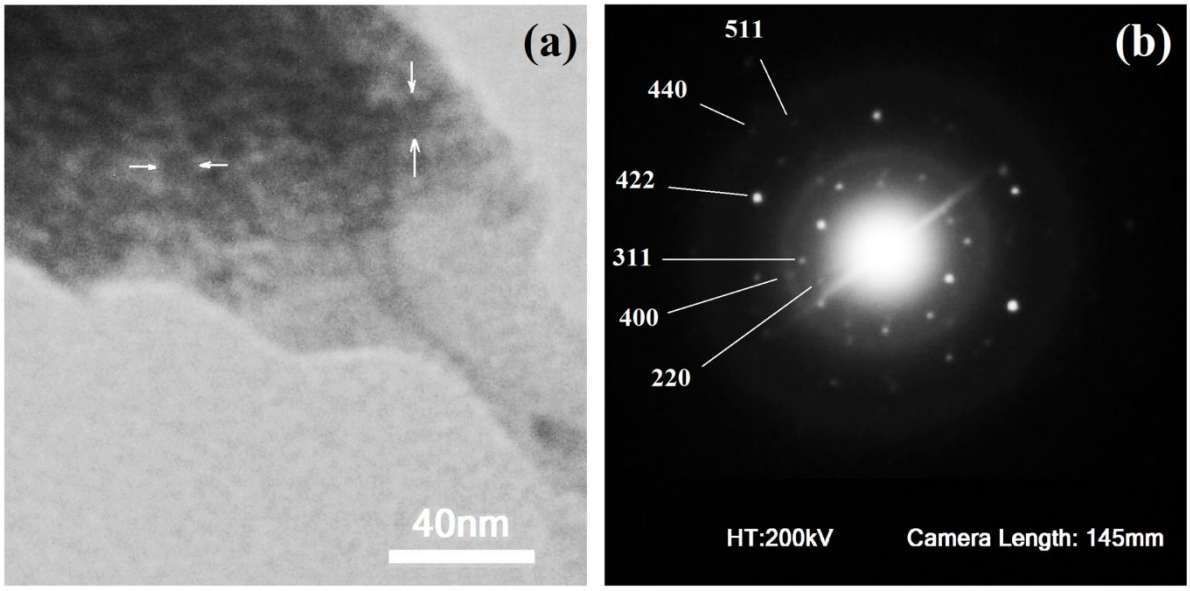


Figure S11. TEM image of mSPION-coated CPM-COOH microparticles with higher magnification (a) and SAED pattern of mSPION-coated CPM-COOH microparticles (b)

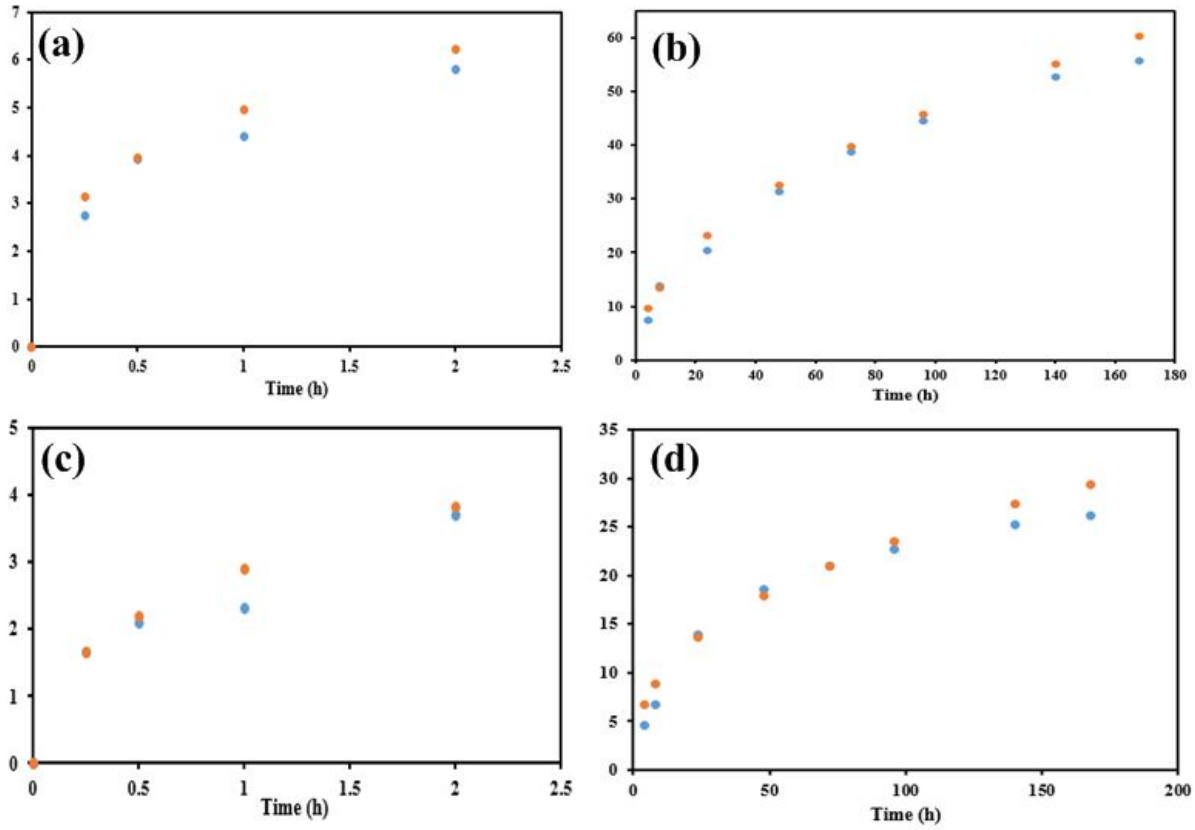
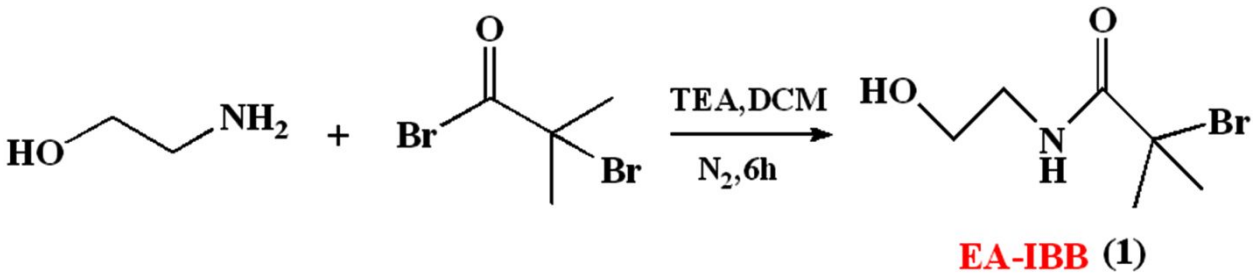
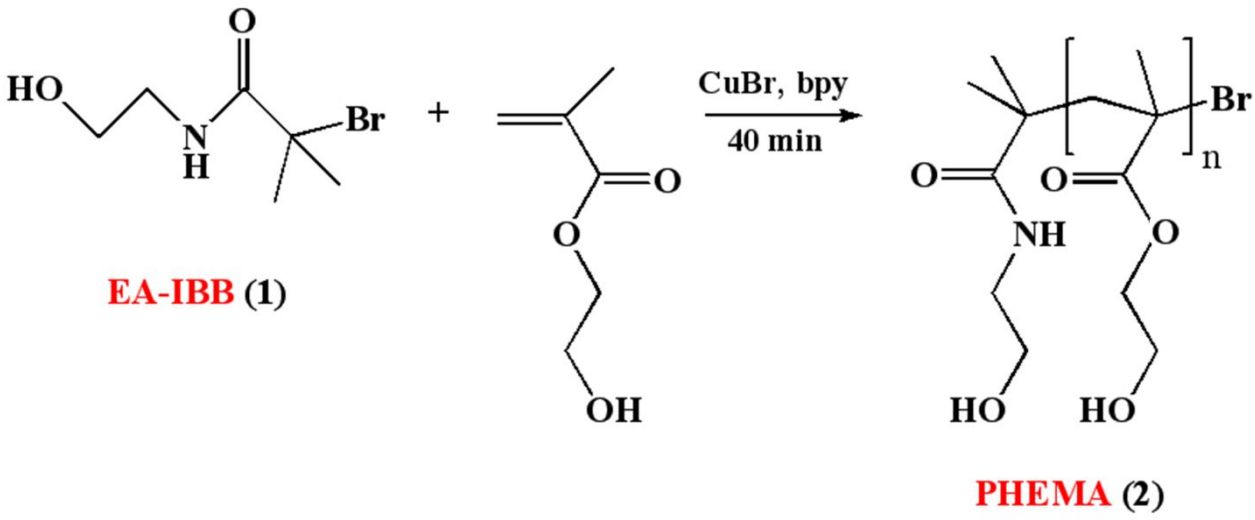


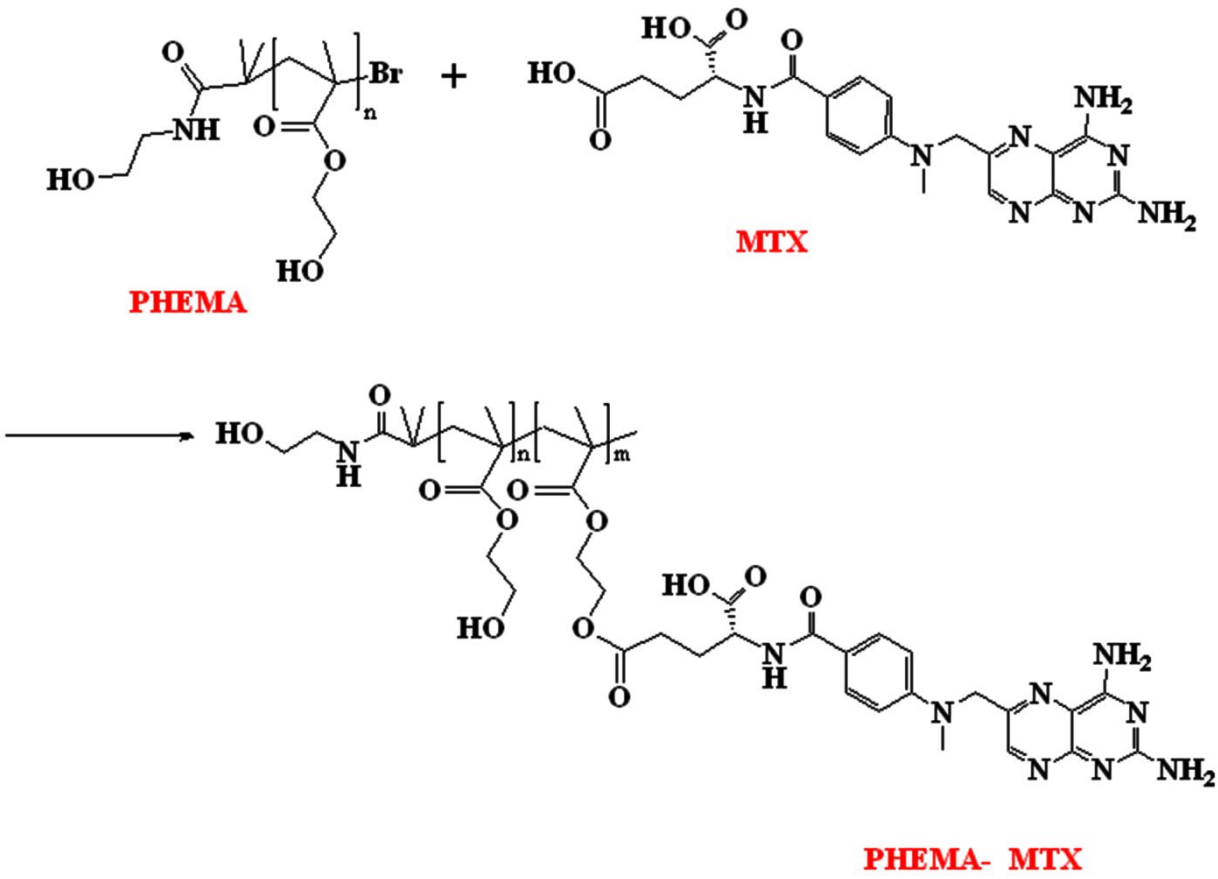
Figure S12. Korsmeyer-Peppas diagrams of MTX release from PMMA-Fe3O4-PHEMA Janus NP at stage 1, pH 5.8 (a) and stage 2, pH 5.8 (b) and stage 1, pH 7.4 (c) and stage 2, pH 7.4 (d)



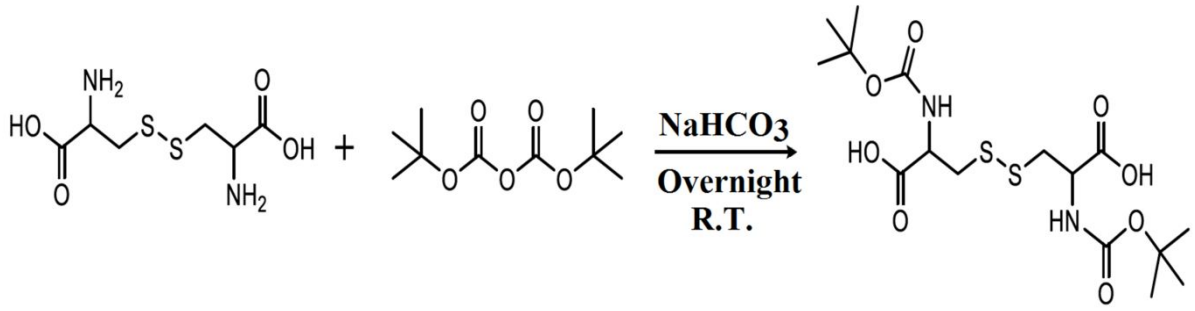
Scheme S1. Synthesis of EA-IBB



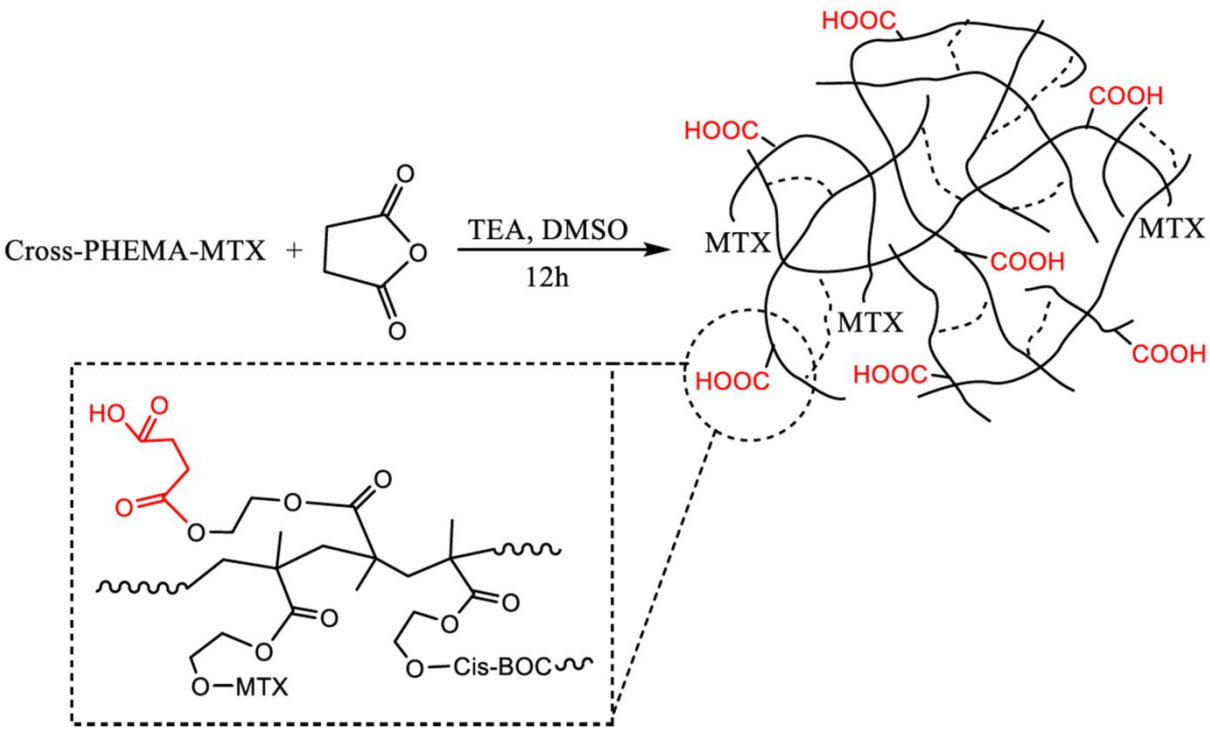
Scheme S2. Synthesis of PHEMA



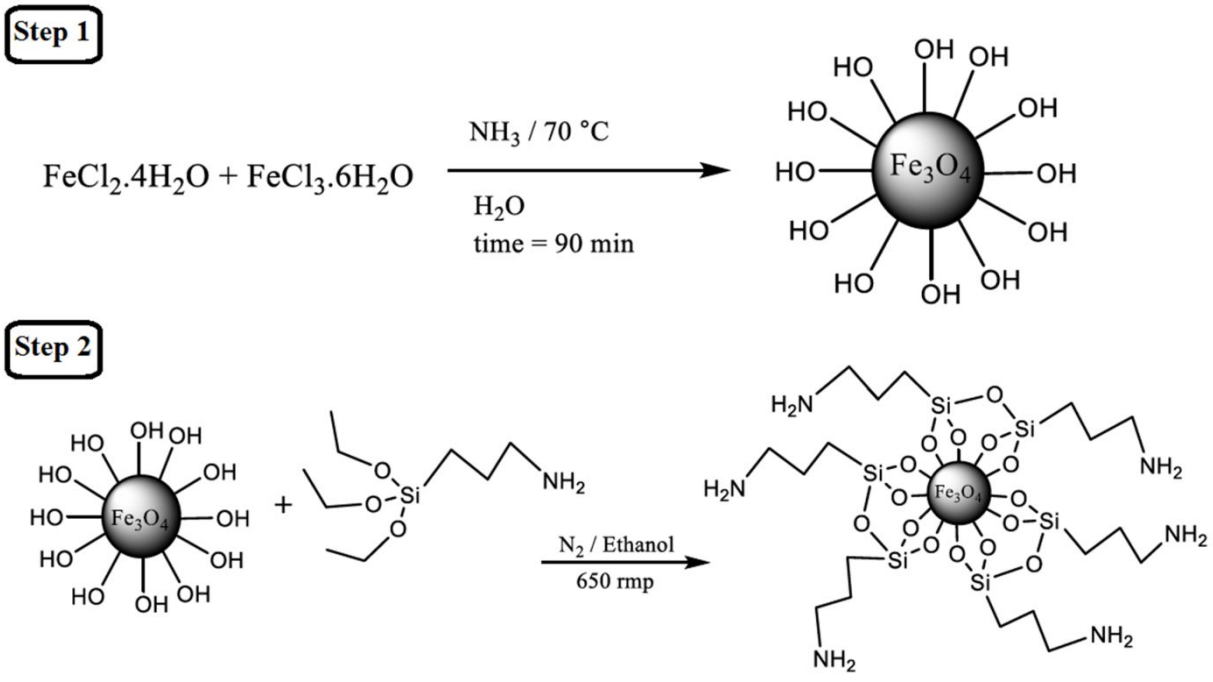
Scheme S3. Synthesis of PHEMA –MTX



Scheme S4. Synthesis of (Boc-Cys-OH)$_2$ as the crosslinker



Scheme S5. . Synthetic procedure of CPM-COOH



Scheme S6. Synthesis of SPION (Step 1) and mSPION (Step 2)

References

(S1) Khoee, S.; Yousefalizadeh, G.; Kavand, A. Preparation of Dual-Targeted Redox-Responsive Nanogels Based on Pegylated Sorbitan for Targeted and Antitumor Drug Delivery. *Eur. Polym. J.* **2017**, *95*, 448–461.

(S2) Khoee, S.; Mansouri Bakvand, P. Synthesis of Dual-Responsive Janus Nanovehicle via PNIPAm Modified SPIONs Deposition on Crosslinked Chitosan Microparticles and Decrosslinking Process in the Core. *Eur. Polym. J.* **2019**, *114* (March), 411–425.