Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supporting Information

of

Opposite swelling characteristics through changing the connectivity in a biopolymeric hydrogel based on glycogen and glycine

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Experimental section

Chemicals.

Glycogen (Loba Chemie Pvt. Ltd., Mumbai, India), methacrylic anhydride (Alfa Aeser, USA), Glycine (SRL. Pvt. Ltd., India), Boc-Glycine (SRL. Pvt. Ltd., India), 2-hydroxyethyl methacrylate (HEMA, TCI Pvt. Ltd., Tokyo, Japan), dried dimethyl sulfoxide (DMSO) (SRL. Pvt. Ltd., India), acetone (E-Merck (I) Pvt. Ltd., Mumbai, India) were used as received. Milli Q water was used for all the experiments.

Synthesis

Synthesis of glycine methacrylamide (GM): Glycine based monomer, glycine methacrylamide (GM) was synthesized by reaction between glycine and methacrylic anhydride (Scheme S1). The synthetic details of GM are as follows:

Glycine (1.33×10^{-2} mol) was dissolved in MilliQ water (30 mL) in a 100 mL RB flask. Then aqueous solution of NaOH (3.25×10^{-2} mol) was added to it. Subsequently the RB was transferred to an ice bath equipped with magnetic stirrer. Then methacrylic anhydride (1.62×10^{-2} mol) was added drop by drop to the reaction mixture with continuous stirring. The reaction was continued for next 6 h. After that, the reaction mixture was acidified to pH 2 with addition of 1 (N) HCl. Subsequently, the product was extracted from the aqueous reaction media by solvent extraction using ethyl acetate for several times (7-8 times) and dried over anhydrous Na_2SO_4. Then the solvent was removed in a rotary evaporator. Finally, the product (white solid) was extracted by column chromatography and dried by rotary evaporator (Eluent: DCM/methanol; 9:1; R_f: 0.5, Yield: 85%).

[^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.80 (H_e, -COOH), 8.20 (H_c, N-H), 5.69 (H_{a1}), 5.35 (H_{a2}), 3.74 (H_d, methylene proton), 1.84 (H_b, -CH_3)

^{13}C NMR (400 MHz, DMSO-d_6): δ (ppm) = 171.8 (C_f), 168.1 (C_d), 139.8 (C_b), 120.2 (C_a), 41.4 (C_e), 18.9 (C_c)]

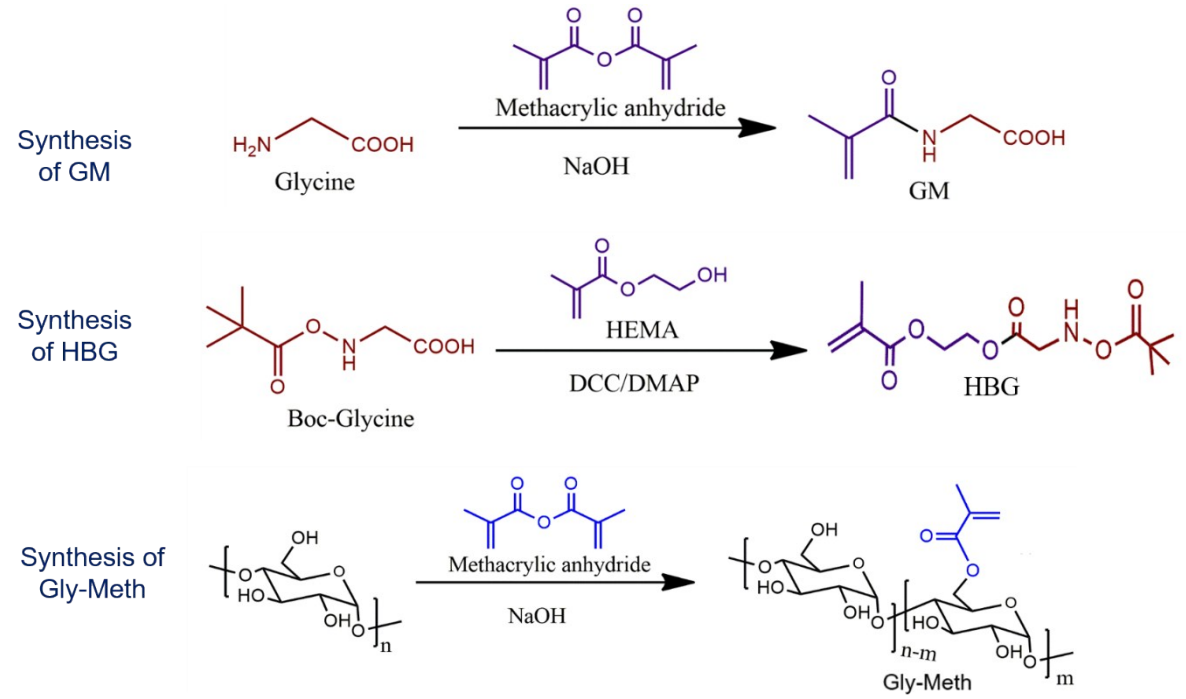
Synthesis of HEMA(Boc-glycinate) (HBG): Glycine based another monomer HEMA-Boc-glycinate (HBG) has been synthesized by esterification reaction between Boc-glycine and HEMA (Scheme S1).[1,2] The typical experimental procedure is as follows: Boc-glycine (5.7×10^{-3} mol) was dissolved in anhydrous DCM (50 mL) in a 100 mL RB. Then DCC (1.14×10^{-2} mol) was added with continuous stirring. After 5 min, the RB was transferred to an ice bath and HEMA (5.4×10^{-3} mol) was added to it followed by the addition of DMAP (5.4×10^{-3} mol). Then the reaction was continued for 12 h. After that, the reaction mixture was filtered to separate white insoluble by-product *N, N'*-dicyclohexylurea. Then the reaction mixture was washed with brine solution and dried using anhydrous Na_2SO_4. Finally, the product i.e. HEMA(Boc-glycinate) (HBG) was isolated by column chromatography (Eluent: Pet-ether/Ethyl acetate; 4:1; R_f: 0.5). The product was appeared as blackish yellow oily liquid (Yield: 88%).

[^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.03 (H_{f1}, vinylic proton), 5.51 (H_{f2}, vinylic proton), 5.20 (H_j, N-H), 4.28 (H_h, methylene), 3.83 (H_i, methylene), 1.85 (H_g, -CH_3), 1.35 (H_k, -CH_3 of Boc)

^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) = 170.2 (C_m), 167.0 (C_j), 155.7 (C_o), 135.8 (C_h), 126.1 (C_g), 79.8 (C_p), 62.8 (C_k), 62.1 (C_l), 42.2 (C_n), 28.2 (C_q), 18.1 (C_i)]

Synthesis of glycogen methacrylate (Gly-Meth): Aqueous solution of glycogen (500 mg in 30 mL MilliQ water) was taken in a RB flask. The RB was transferred to an ice-bath to maintain the reaction temperature at ~ 4 °C. Then methacrylic anhydride (6×10^{-4} mol) was added to it drop by drop.[3, 4] The pH of the reaction was maintained in the range of 8-9 with frequent addition of 0.1 (N) aqueous NaOH solution (Scheme S1). The reaction was continued for 4 h. Afterward, the reaction mixture was transferred to a dialysis tube (12 KDa Mol. Wt. cut off) and dialysis was performed in MilliQ water for 48 h. The water was changed after each 6 h interval. Finally, the dried product was obtained by lyophilisation.

[^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 6.04 and 5.67 (H_{8a} and H_{8b}, vinylic protons), 5.46 (H_1, glycogen), 5.08-4.89 (OH at C_3, C_4 and C_6), 4.56 (OH at C_2), 3.62-3.05 (H_{2-6}), 1.87 (H_7) ^{13}C NMR (400 MHz, Solid State): δ (ppm) = 168.8 (C_7), 137.3 and 135.2 (C_8 and C_9), 102.8 (C_1), 82.2 (C_5), 72.7 (C_{2-4}), 61.1 (C_6), 18.4 (C_{10})]



Scheme S1. Synthetic steps of GM, HBG and Gly-Meth

Synthesis of crosslinked hydrogel-1 (Gly-Meth-cl-GM): Aqueous solution of Gly-Meth (250 mg in 12 mL MilliQ water) was prepared at room temperature in a two-necked RB equipped with magnetic stirrer, oil-bath with coil heater. Then aqueous solution of monomer (GM, 2 g in 2 mL MilliQ water) and initiator (KPS, 0.1 g in 1 mL MilliQ water) were added subsequently. After that, 10 cycles of gas-degas with N_2 and vacuum were performed to create inert atmosphere. Afterward, the reaction temperature was raised to 75 °C and reaction was continued with stirring. Subsequently, aqueous solution of crosslinker (MBA, 0.05 g in 1 mL MilliQ water) was injected to the reaction mixture after 30 min. Then the reaction was continued for next 3 h. Finally, the reaction mixture was introduced to open atmosphere and

allowed to cool at ambient temperature. The gel like mass was then soaked in excess amount of acetone for overnight and dried under vacuum. The dried polymer product (Gly-Meth-*cl*-GM) was used further.

Here GM was grafted on Gly-Meth by free radical polymerization between GM and the methacrylate group of Gly-Meth under inert atmosphere in presence of free radical initiator (KPS). The grafted polymeric network was further crosslinked in presence of MBA to form the crosslinked graft copolymer Gly-Meth-*cl*-GM (Scheme 1).

[^{13}C NMR (400 MHz, Solid State): δ (ppm) = 178.9 (C_f), 173.6 (C_{7+d+i}), 102.6 (C_1), 83.1 (C_5), 72.1 (C_{2-4}), 55.1 (C_{8+b+h}), 45.3 (C_{9+a+g}). 42.1 (C_e), 17.0 (C_{10+c})]

Synthesis of crosslinked hydrogel-II (Gly-Meth-cl-HG): Gly-Meth (250 mg) was dissolved in DMSO (7 mL) in a two-necked RB at room temperature. Then 2 mL of monomer (HBG) was added to it followed by addition of initiator solution (0.01 g AIBN in 1 mL DMSO). Inert atmosphere was created by 10 cycles of gas-degassing using N_2 gas and vacuum. Afterward, the RB was transferred to a hot oil-bath (80 °C) equipped with coil-heater and magnetic stirrer. The reaction was continued under inert atmosphere with continuous stirring. After 30 min, MBA solution (0.05 g in 1 mL DMSO) was injected to the reaction mixture. The reaction was continued for next 3 h. After completion of reaction, the reaction mixture was allowed to cool at ambient temperature and introduced to open atmosphere. Finally, the reaction mixture was slowly poured to cold water for precipitation and left for 24 h for complete removal of DMSO. Then the obtained white coloured mass (Gly-Meth-*cl*-HBG) was dried under vacuum.

[^{13}C NMR (400 MHz, Solid State): δ (ppm) = 177.7 (C_m), 170.9 (C_{7+j+t}), 156.7 (C_o), 103.2 (C_1), 79.8 (C_{5+p}), 72.5 (C_{2-4}), 63.2 (C_{6+k+l}), 55.5 (C_{8+h+s}), 45.1 (C_{9+g+r}). 42.7 (C_n), 28.8 (C_q), 16.9 (C_{10+i})]

The dried product was soaked in TFA for 12 h for Boc deprotection. Then the pH of obtained gel like mass was neutralized with addition of 0.1 (N) NaOH solution. After that, the

neutralized gel like mass was dialyzed under cold water using a dialysis tube (12 KDa. Mol. Wt. cut off) for 48 h. Finally, the gel was dried under reduced pressure. The dried product is abbreviated as Gly-Meth-*cl*-HG.

Here, crosslinked graft copolymer (Gly-Meth-*cl*-HBG) was developed by grafting of PolyHBG on Gly-Meth by free radical polymerization between HBG and the methacrylate group of Gly-Meth in presence of initiator AIBN and crosslinker MBA. The Boc-deprotection was performed by TFA (Scheme 1). Finally, the ammonium salt formed due to the use of excess TFA was neutralized to free amine group by NaOH, leading to the formation of Gly-Meth-*cl*-HG.

[^{13}C NMR (400 MHz, Solid State): δ (ppm) = 178.5 (C_m), 168.5 (C_{7+j+t}), 103.1 (C_1), 82.5 (C_5), 72.7 (C_{2-4}), 67.2 (C_k), 63.5 (C_l), 60.2 (C_6), 55.0 (C_{8+h+s}), 45.0 (C_{9+g+r}). 40.9 (C_n), 16.8 (C_{10+i})]

Characterization:

^{1}H NMR analysis

The ^{1}H NMR spectral analysis of GM (solvent: DMSO-d_6), HBG (solvent: $CDCl_3$) and Gly-Meth (solvent: DMSO-d_6) were performed in a 400 MHz NMR instrument (Model: Ascend^{TM} 400, from Bruker, USA).

Fig. S1 demonstrates the ^{1}H NMR spectrum of GM. Chemical shifts appeared at 5.69 and 5.35 ppm are corresponding to two vinylic protons (H_{a1} and H_{a2}). The signals at 8.20, 3.74 and 1.84 ppm are responsible for N-H proton (H_c), methylene protons (H_d) and methyl protons (H_b). The labile proton of carboxylic acid (H_e) demonstrates chemical shift at 11.80 ppm.

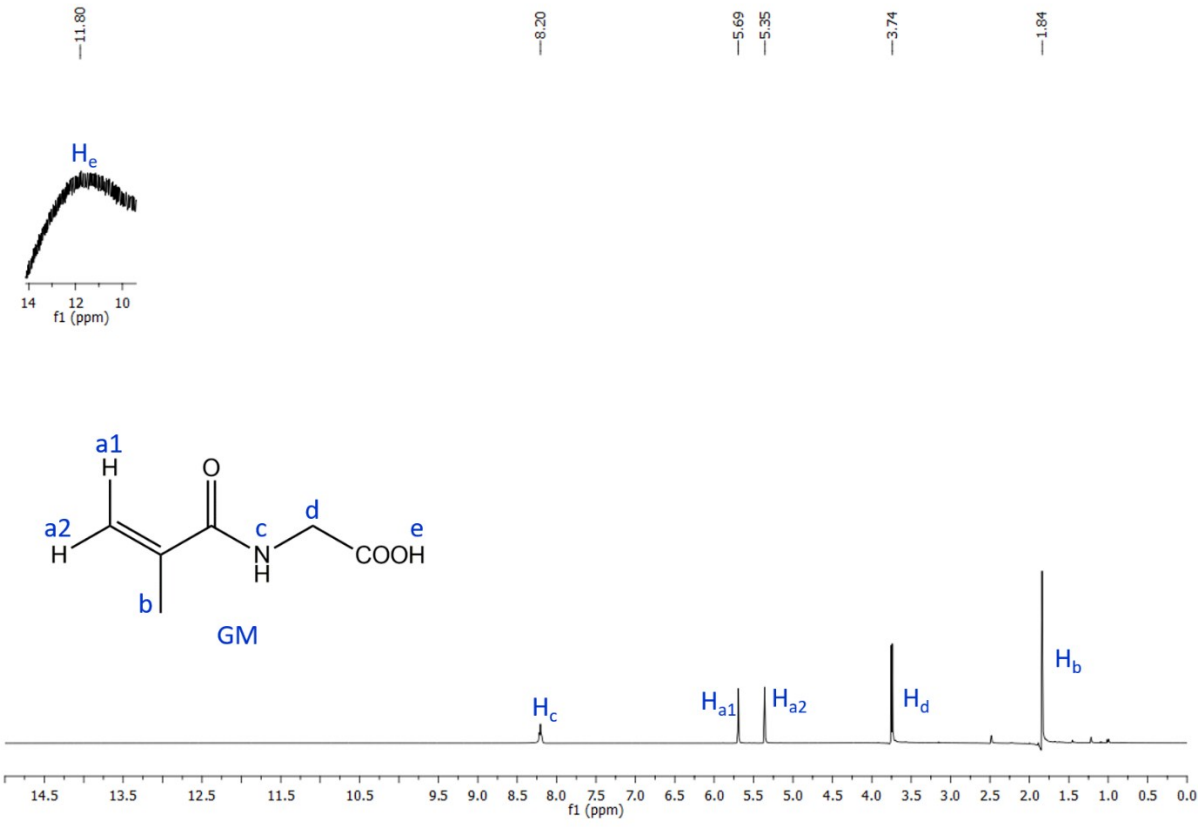


Fig. S1. ^{1}H NMR spectrum of GM.

Fig. S2 demonstrates the ^{1}H NMR spectrum of HBG. Two vinylic protons (H_{f1} and H_{f2}) demonstrate chemical shifts at 6.03 and 5.51 ppm, respectively. The methylene protons (H_h and H_i) demonstrate chemical shifts at 4.28 and 3.83 ppm, respectively. The methyl protons of Boc moiety (H_k) and HEMA moiety (H_g) exhibit chemical shifts at 1.35 and 1.85 ppm, respectively. The N-H proton (H_j) shows chemical shift at 5.20 ppm.

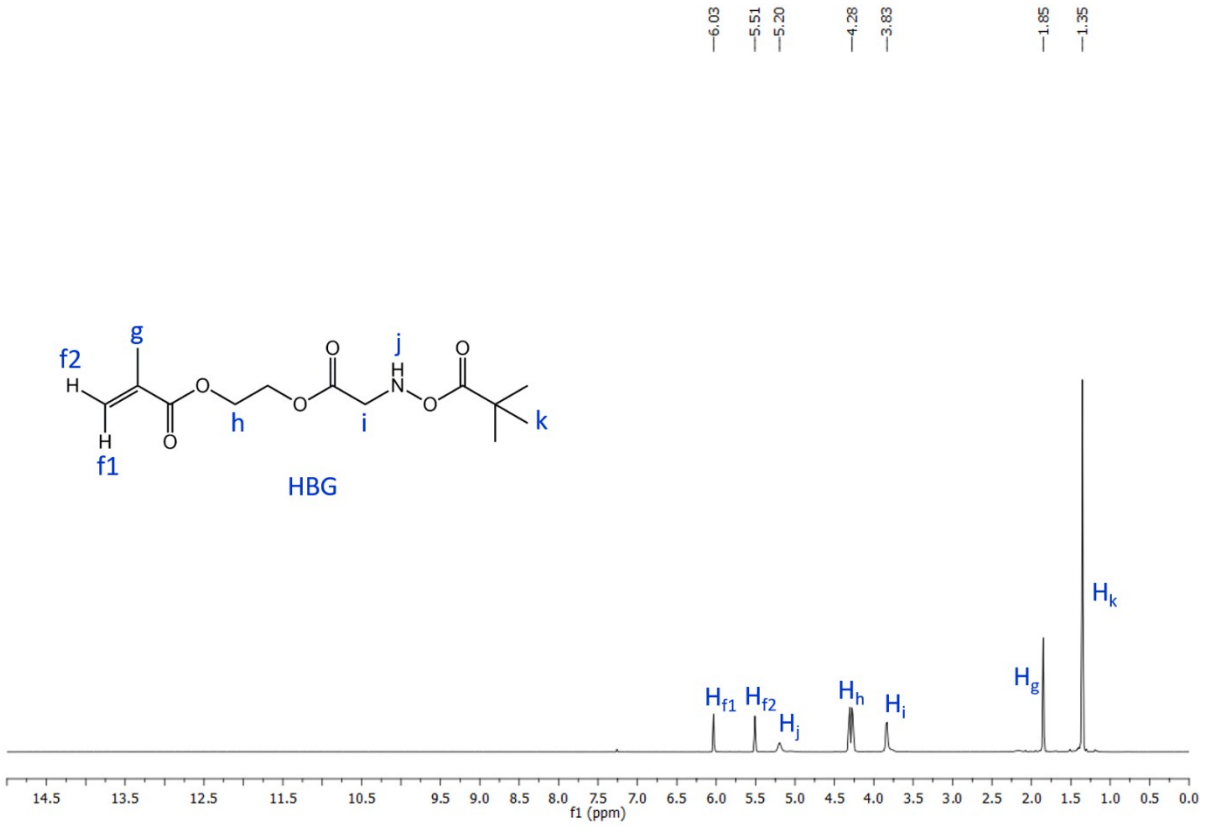


Fig. S2. ^{1}H NMR spectrum of HBG.

The ^{1}H NMR spectrum of Gly-Meth is shown in Fig. S3. The chemical shift appeared at 5.46 ppm is responsible for anomeric proton (H_1). The chemical shifts appeared at 4.89-5.08 ppm are corresponding to –OH proton at 3, 4 and 6 positions. The –OH proton attached with C2 exhibits chemical shift at 4.56 ppm. The ring protons ($H_{2\text{-}6}$) demonstrate chemical shift at 3.62-3.06 ppm. The vinylic protons (H_{8a} and H_{8b}) of attached methacrylate group causes chemical shift at 5.67 and 6.04 ppm, respectively. The protons of methyl group of methacrylate (H_7) reveal chemical shift at 1.87 ppm. The appearance of new protons (H_7, H_{8a} and H_{8b}) of methacrylate groups confirm the incorporation of methacrylate group onto the glycogen network.

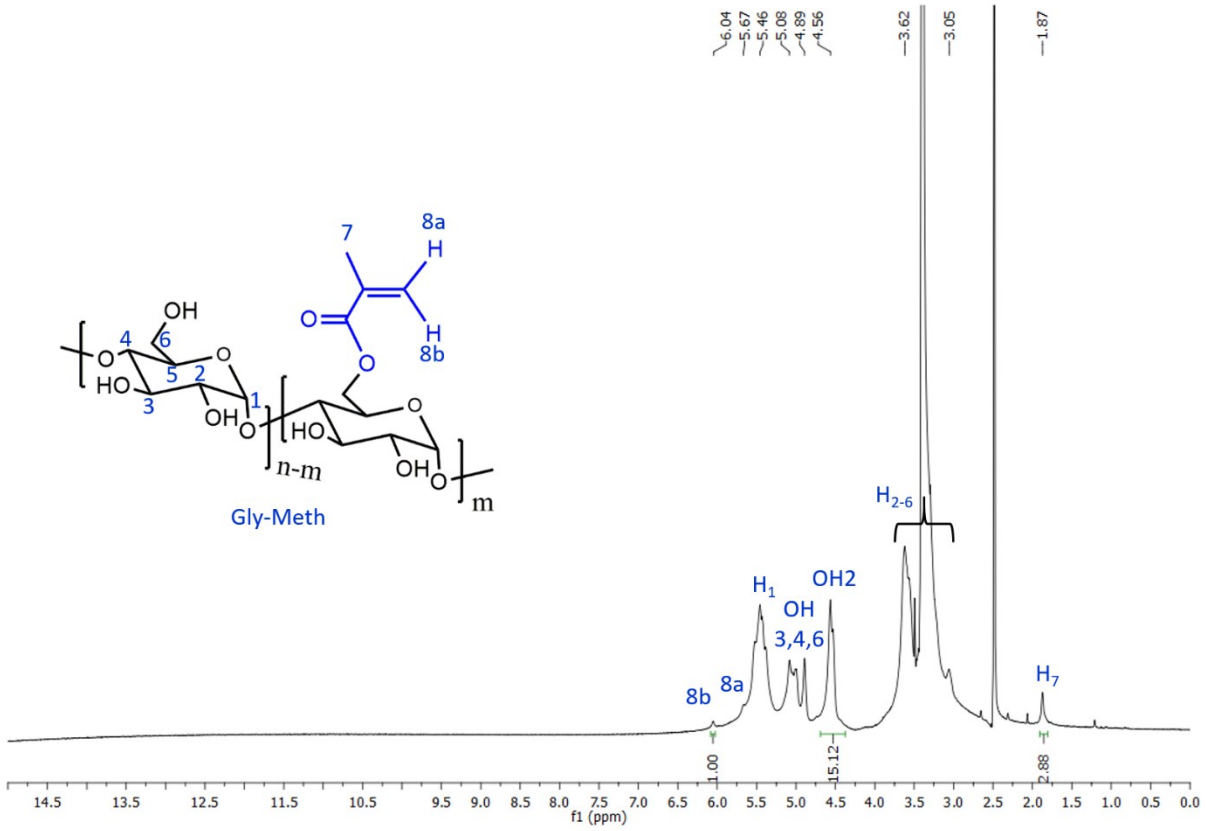


Fig. S3. ^{1}H NMR spectrum of Gly-Meth.

^{13}C NMR analysis:

The ^{13}C NMR spectra of GM (solvent: DMSO-d_6) and HBG (solvent: $CDCl_3$) were recorded using same 400 MHz NMR instrument. The solid state ^{13}C NMR analyses of Gly-Meth, Gly-Meth-*cl*-HBG, Gly-Meth-*cl*-HG and Gly-Meth-*cl*-GM were performed in a 400 MHz NMR instrument (Model: ECX400, Jeol, Japan).

^{13}C NMR spectrum of GM is represented in Fig. S4. The vinylic carbons (C_a and C_b) show chemical shifts at 120.2 and 139.8 ppm, respectively. The carbonyl carbons (C_d and C_f) demonstrate chemical shifts at 168.1 and 171.8 ppm, respectively. The methyl carbon (C_c) and methylene carbon (C_e) show chemical shifts at 18.9 and 41.4 ppm.

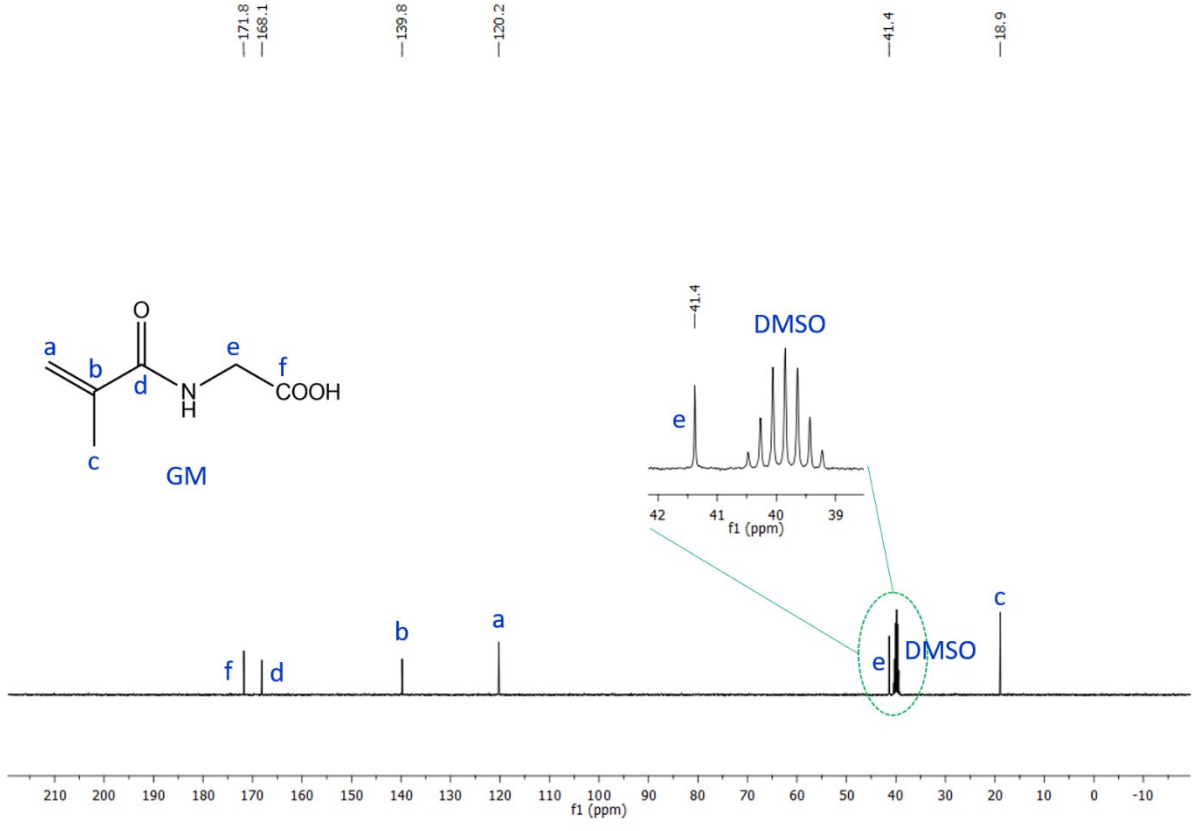


Fig. S4. ^{13}C NMR spectrum of GM.

^{13}C NMR spectrum of HBG is shown in Fig. S5. The vinylic carbons (C_h and C_g) demonstrate chemical shifts at 135.8 and 126.1 ppm. The carbonyl carbons (C_m, C_j and C_o) reveal chemical shifts at 170.2, 167.0 and 155.7 ppm. The chemical shifts of methylene carbons (C_k, C_l and C_n) were appeared at 62.8, 62.1 and 42.2 ppm. The tertiary carbon (C_p) and methyl carbon (C_q) of Boc moiety exhibit chemical shifts at 79.8 and 28.2 ppm, respectively. The methyl carbon (C_i) of HEMA moiety displays chemical shift at 18.1 ppm.

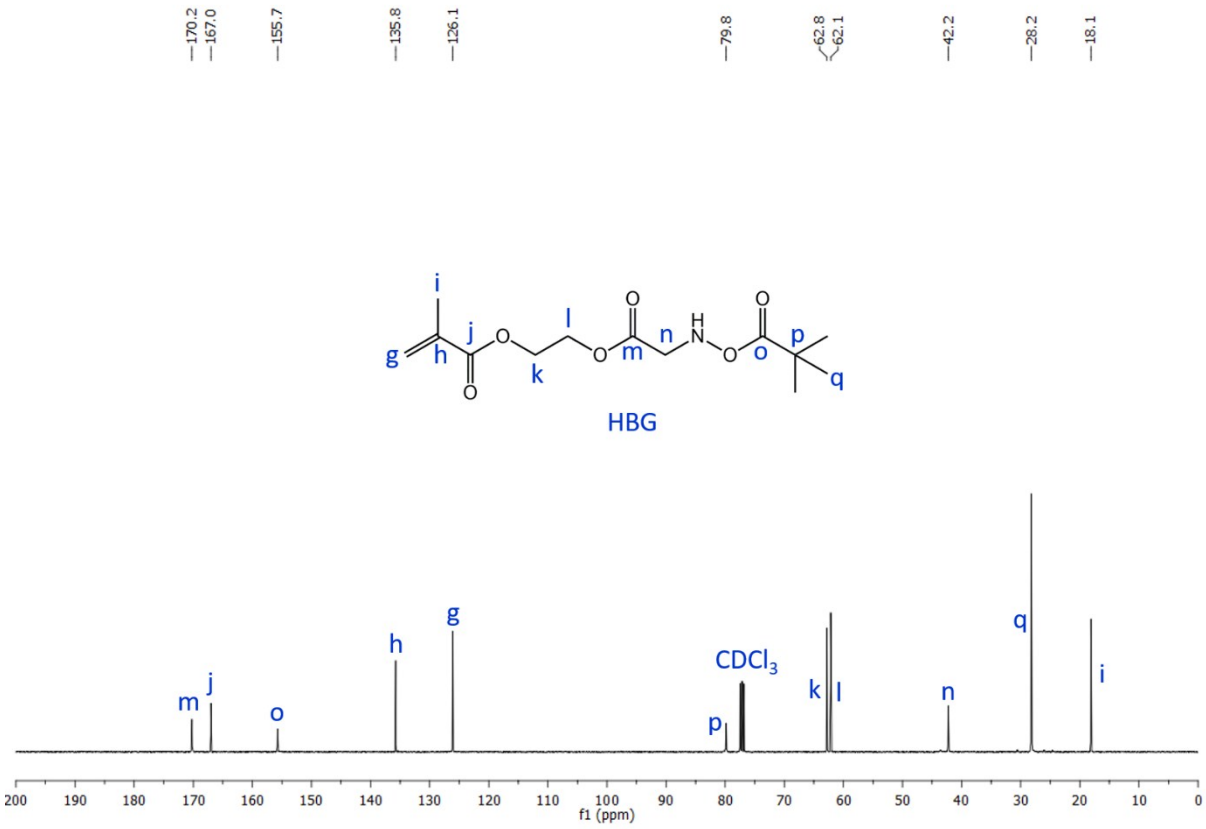


Fig. S5. ^{13}C NMR spectrum of HBG.

Fig. S6 represents solid state ^{13}C NMR spectrum of Gly-Meth. The chemical shifts appeared at 102.8, 8.2, 72.7 and 61.1 ppm are corresponding to carbons of glycogen moiety (C_1, C_5, $C_{2\text{-}4}$ and C_6, respectively). The small peaks appeared at 168.8, 137.3 and 135.2 ppm are responsible for the carbonyl carbon (C_7) and two vinylic carbons (C_8 and C_9) of attached methacrylate group. The methyl carbon (C_{10}) of methacrylate group demonstrates chemical shift at 18.4 ppm. Therefore, the chemical shifts correspond to the methacrylate group suggest the formation of Gly-Meth.

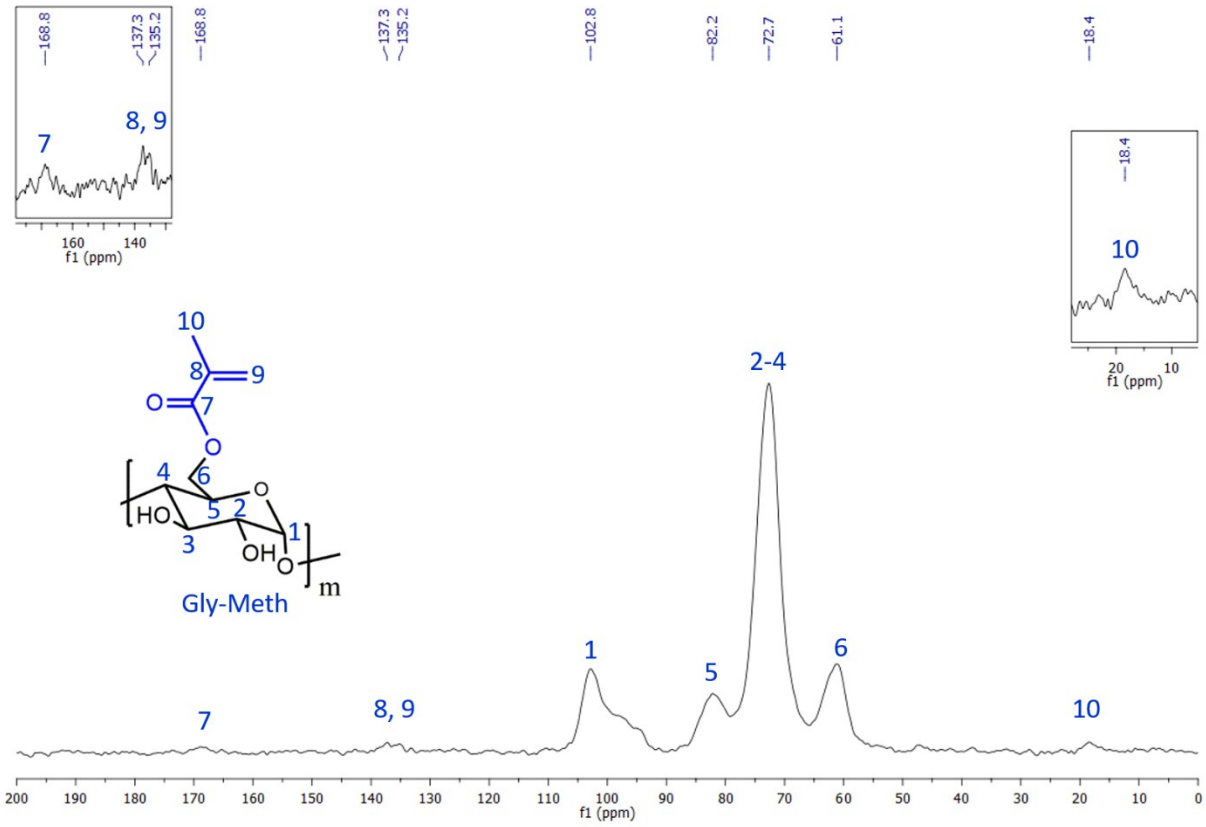


Fig. S6. Solid state ^{13}C NMR spectrum of Gly-Meth.

Fig. S7 demonstrates the solid state ^{13}C NMR spectrum of Gly-Meth-*cl*-GM. The characteristic chemical shifts for glycogen moiety has been found at 102.6, 83.1 and 72.1 ppm (for C_1, C_5 and $C_{2\text{-}4}$), confirming the presence of Gly-Meth moiety in the copolymeric network. The carbon of –COOH group (C_f) of GM moiety demonstrates chemical shift at 178.9 ppm. The amide carbonyl (C_d) of GM, the carbonyl carbon of Gly-Meth (C_7) and the carbonyl carbon of MBA moiety (C_i) exhibit chemical shift at 173.6 ppm. The methylene carbon of GM moiety (C_e) demonstrates chemical shift at 42.1 ppm. The methyl carbon of Gly-Meth (C_{10}) and GM (C_c) exhibit chemical shift at 17.0 ppm. The sp^3 carbons appeared due to the polymerization of vinylic group of Gly-meth, GM and MBA show chemical shifts at 55.1 ppm (corresponds to C_8, C_b and C_h) and 45.3 ppm (corresponds to C_9, C_a and C_g). Moreover, the absence of any peak in the range of 120 to 140 ppm (for vinylic carbon) and the newly appeared sp^3 carbon suggest the successful polymerization between Gly-Meth, GM and MBA.

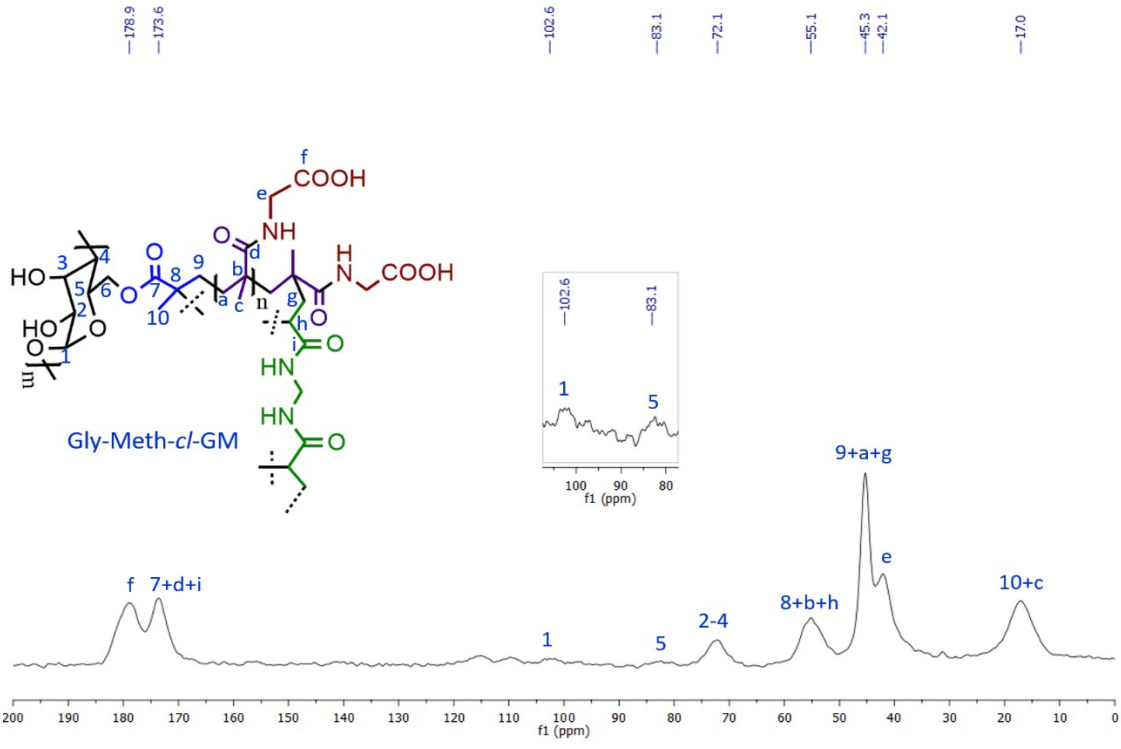


Fig. S7. Solid state ^{13}C NMR spectrum of Gly-Meth-*cl*-GM.

Fig. S8 represents the solid state ^{13}C NMR spectrum of Gly-Meth-*cl*-HBG. The chemical shift appeared at 177.7 and 156.7 ppm represent the carbonyl carbons (C_m and C_o respectively) of HBG moiety. The other carbonyl carbons of Gly-Meth, HBG and MBA (C_7, C_j and C_t) exhibit chemical shift at 170.9 ppm. The carbons of glycogen (C_1 and $C_{2\text{-}4}$) demonstrate chemical shifts at 103.2 and 72.5 ppm. The carbon at 5 position of Gly-Meth (C_5) and the tertiary carbon of HBG moiety (C_p) reveal a broad chemical shift at 79.8 ppm. The broad signal at 63.2 ppm is responsible for C_6 carbon of Gly-Meth, and two methylene carbons (C_k and C_l) of HBG. Another methylene carbon of HBG (C_n) demonstrates chemical shift at 42.7 ppm. The methyl carbons of BOC group (C_q) show chemical shift at 28.8 ppm. The other methyl carbons of Gly-Meth (C_{10}) and HBG (C_i) exhibit chemical shift at 16.9 ppm. The sp^3 carbons formed owing to the polymerization of vinylic groups of Gly-Meth, HBG and MBA show chemical shifts at 55.5 ppm (responsible for C_8, C_h and C_s) and 45.1 ppm (responsible for C_9, C_g and C_r). The absence of chemical shifts at the range of 120 to 140 ppm (vinylic region) and the newly observed chemical shifts for sp^3 carbon supports successful polymerization process.

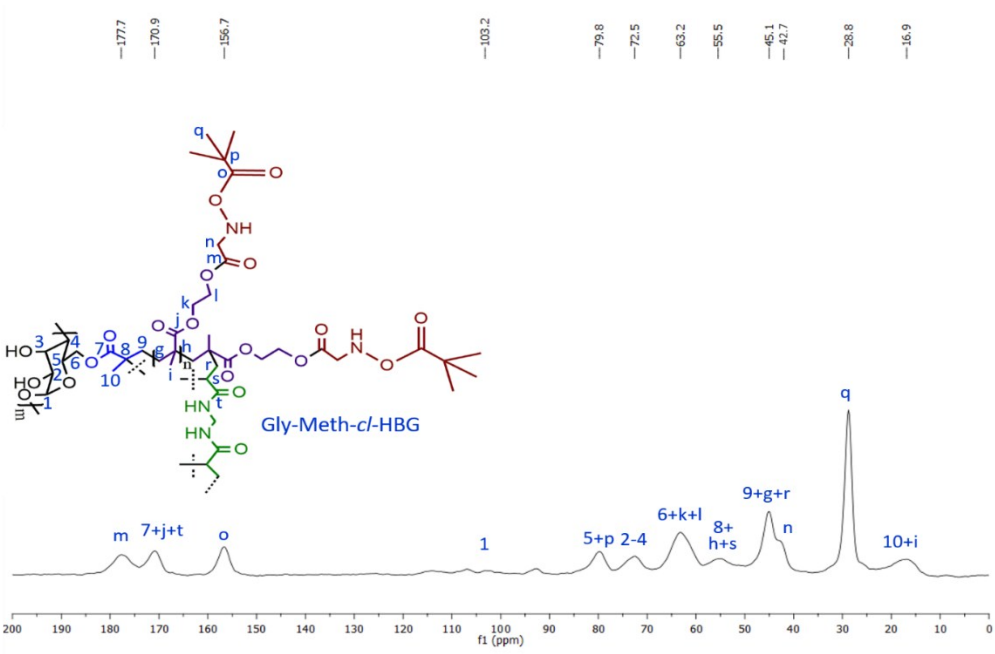


Fig. S8. Solid state ^{13}C NMR spectrum of Gly-Meth-*cl*-HBG.

Boc-deprotection of Gly-Meth-*cl*-HBG by TFA leads to the formation of Gly-Meth-*cl*-HG. Fig. S9 represents the solid state ^{13}C NMR spectrum of Gly-Meth-*cl*-HG. The Chemical shifts at 103.1, 82.5, 72.7 and 60.2 ppm are characteristic signals of Gly-Meth (responsible for C_1, C_5, $C_{2\text{-}4}$ and C_6). The chemical shift at 178.5 ppm is responsible for one carbonyl carbon (C_m) of Boc-deprotected HBG (HG) moiety. The other carbonyl carbons of Gly-Meth, HG and MBA (C_7, C_j and C_t) exhibit chemical shift at 168.5 ppm. The chemical shifts at 67.2, 63.5 and 40.9 ppm are corresponding to the methylene carbons of HG moiety (C_k, C_l and C_n). The methyl carbons of Gly-Meth (C_{10}) and HG (C_i) demonstrate chemical shift at 16.6 ppm. The sp^3 carbons formed due to the polymerization of vinylic groups of Gly-Meth, HBG and MBA show chemical shifts at 55.0 ppm (responsible for C_8, C_h and C_s) and 45.0 ppm (responsible for C_9, C_g and C_r). Two additional signals at 162.3 and 116.0 ppm are responsible for the carbons (of –COOH and $–CF_3$ groups, respectively) of unseparated TFA molecules. The absence of the chemical shifts responsible for Boc group at 156.7, 79.8 and 28.8 ppm indicate removal of Boc-protection, keeping the amine group free.

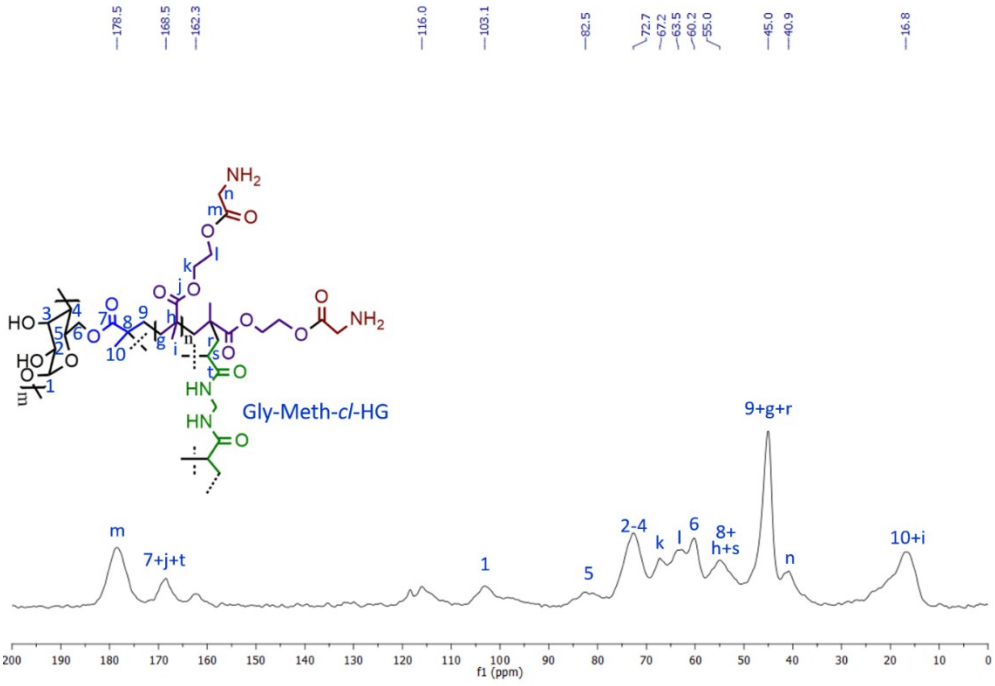


Fig. S9. Solid state ^{13}C NMR spectrum of Gly-Meth-*cl*-HG.

Swelling Experiment:

Pre-weighted dried hydrogels (Gly-Meth-*cl*-GM and Gly-Meth-*cl*-HG) were soaked in aqueous buffer solution of pH 1.2, 3, 5, 7, 9 and 12. The swelled hydrogels were withdrawn from the aqueous media and were wiped with tissue paper to remove the water present at the surface and measured the weight with a regular time interval. Then the swelled hydrogel was returned back to the aqueous media for further swelling. % of swelling was calculated using eq. S1.

$$\%\, Swelling = \frac{S_t - S_0}{S_0} \times 100 \qquad (eq.\, S1)$$

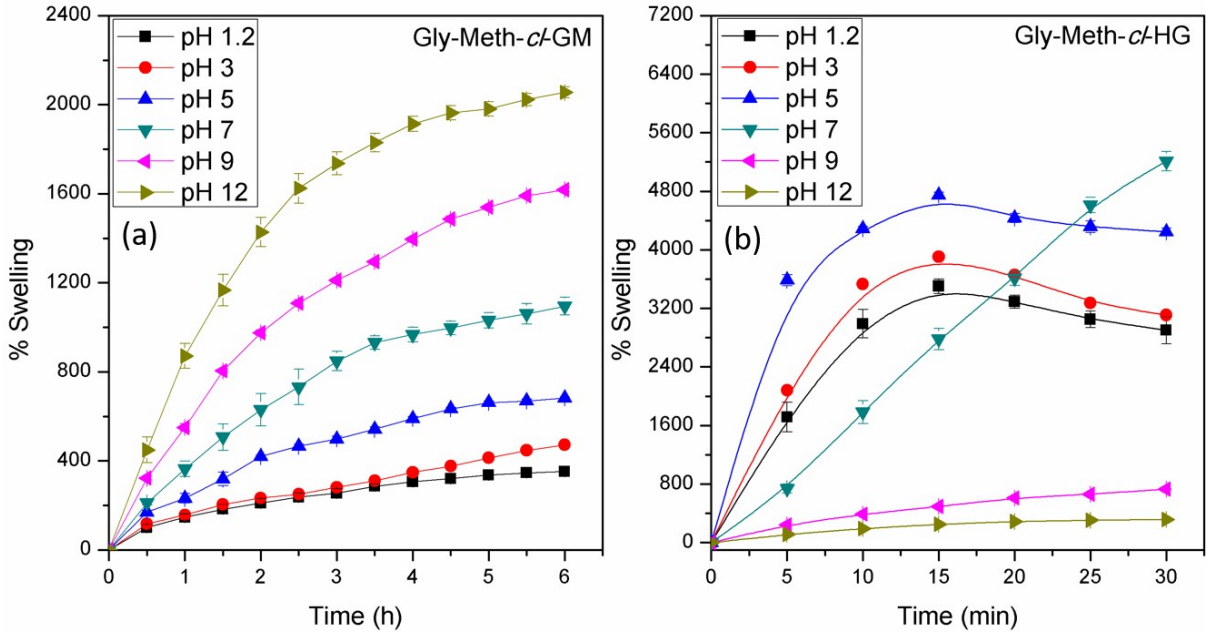


Fig. S10. pH sensitive swelling behaviour of (a) Gly-Meth-*cl*-GM and (b) Gly-Meth-*cl*-HG.

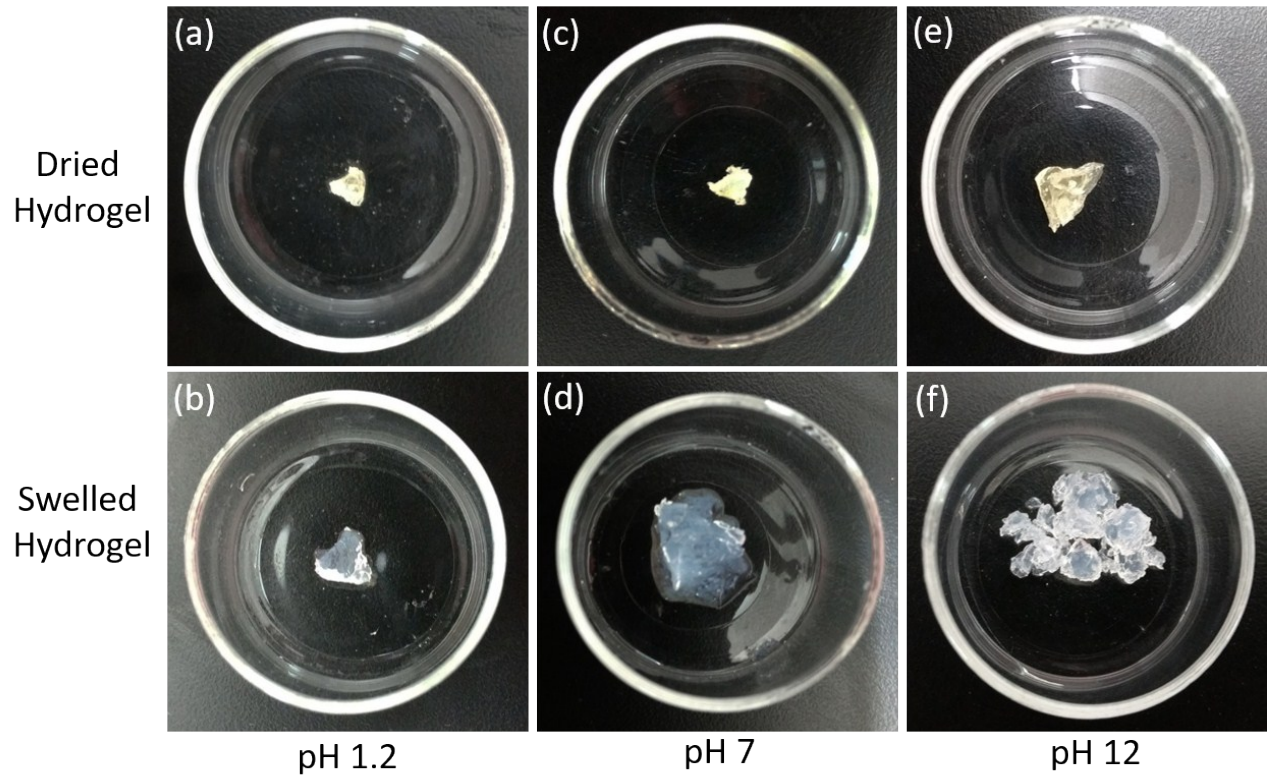


Fig. S11. Digital images of dried and corresponding swelled hydrogels (Gly-Meth-*cl*-GM) at different pH media.

From the images, it is obvious that Gly-Meth-*cl*-GM demonstrates highest swelling at pH 12, intermediate swelling at pH 7 and lowest swelling at pH 1.2.

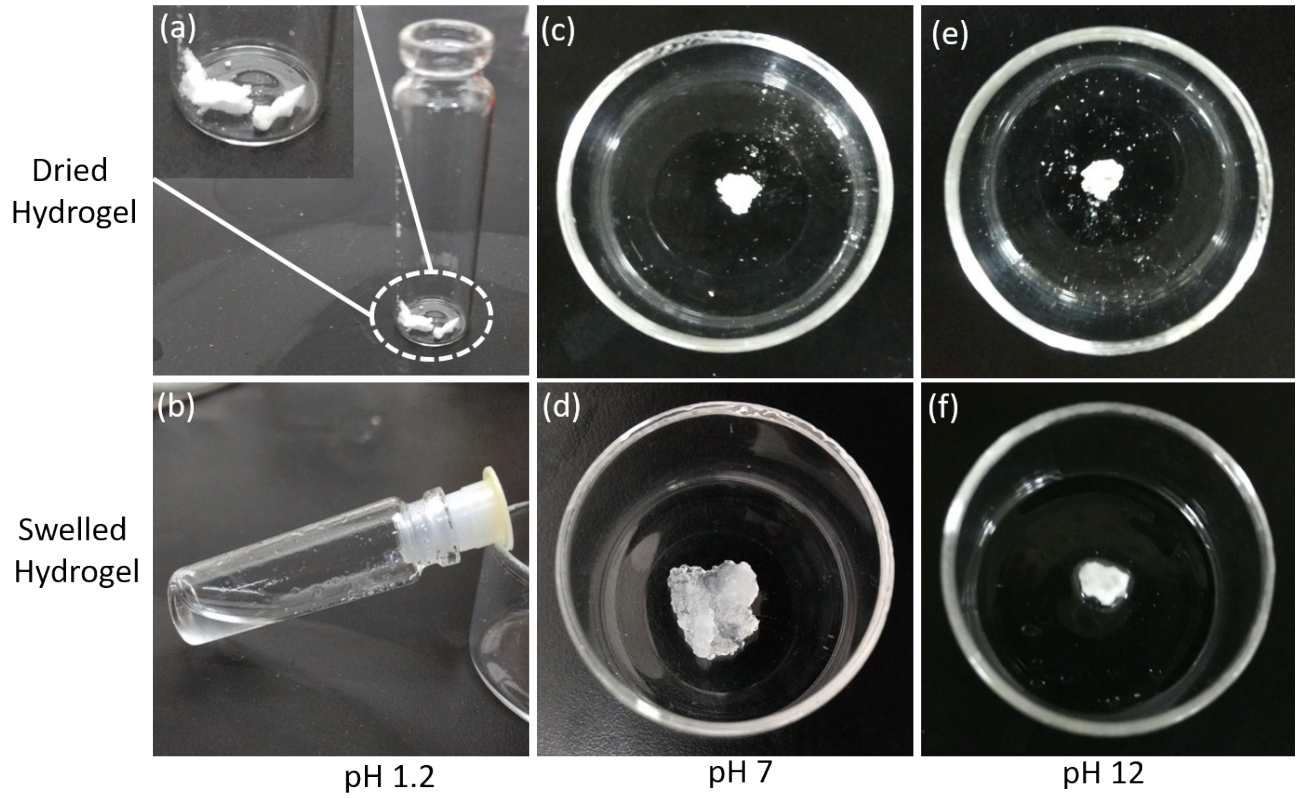


Fig. S12. Digital images of dried and corresponding swelled hydrogels (Gly-Meth-*cl*-HG) at different pH media.

From the images, it is obvious that Gly-Meth-*cl*-GM get soluble at pH 1.2, higher swelling at pH 7 and lowest swelling at pH 12.

Lyophilisation followed by FESEM analysis:

The hydrogels (Gly-Meth-*cl*-GM and Gly-Meth-*cl*-HG) swelled at pH 1.2, 7 and 12 were lyophilized by freeze-drier (Model: ScanVac CoolSafe, from LaboGene, Denmark). Then the dried spongy hydrogel scaffolds were cut into pieces by sharp blade and the FESEM (Model: Supra 55, Zeiss, Germany) morphologies of cross-sectional portions were assessed to compare the porosity.

Rheological study:

The gel properties of swelled hydrogels from all the pH media (Gly-Meth-*cl*-HG and Gly-Meth-*cl*-GM) were investigated by rheological analysis using a rheometer (Bohlin Gemini-2, Malvern, UK). Dynamic amplitude sweep and viscosity sweep measurements were performed for each swelled hydrogel.

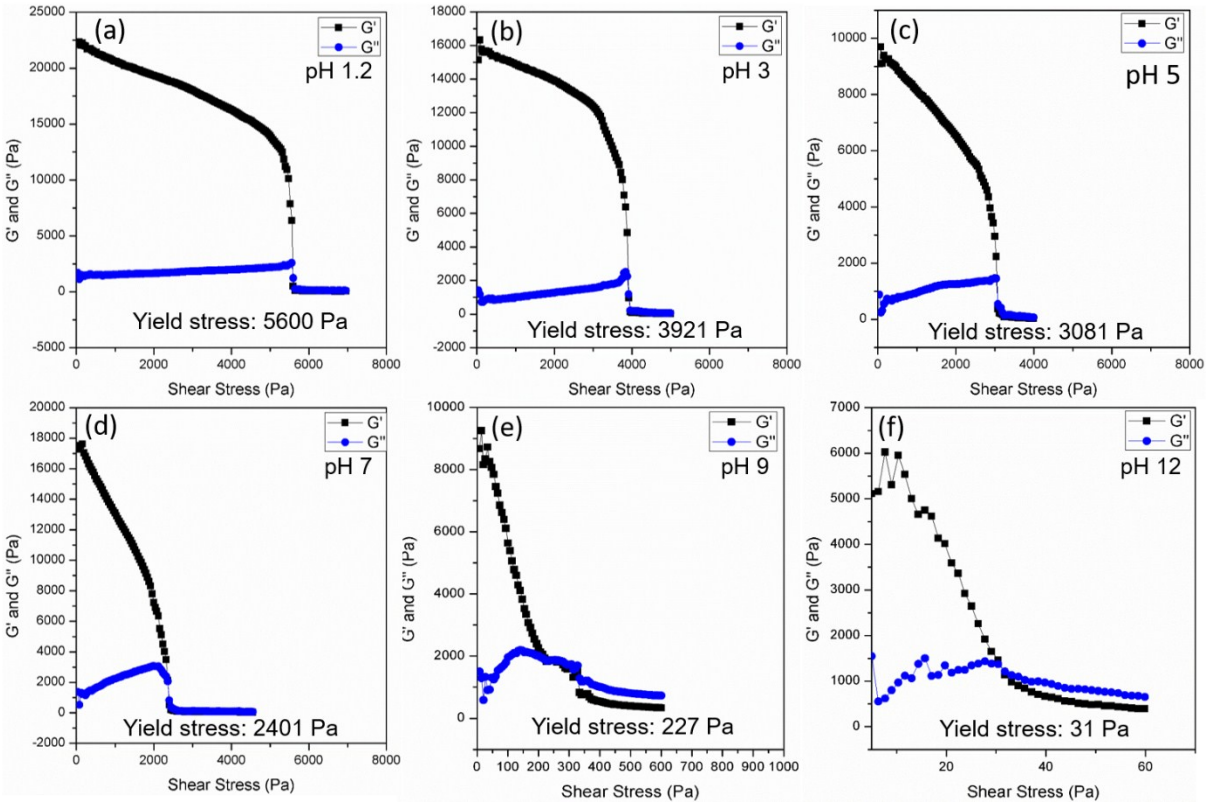


Fig. S13. Amplitude sweep plots of Gly-Meth-*cl*-GM at (a) pH 1.2, (b) pH 3, (c) pH 5, (d) pH 7, (e) pH 9 and (f) pH 12.

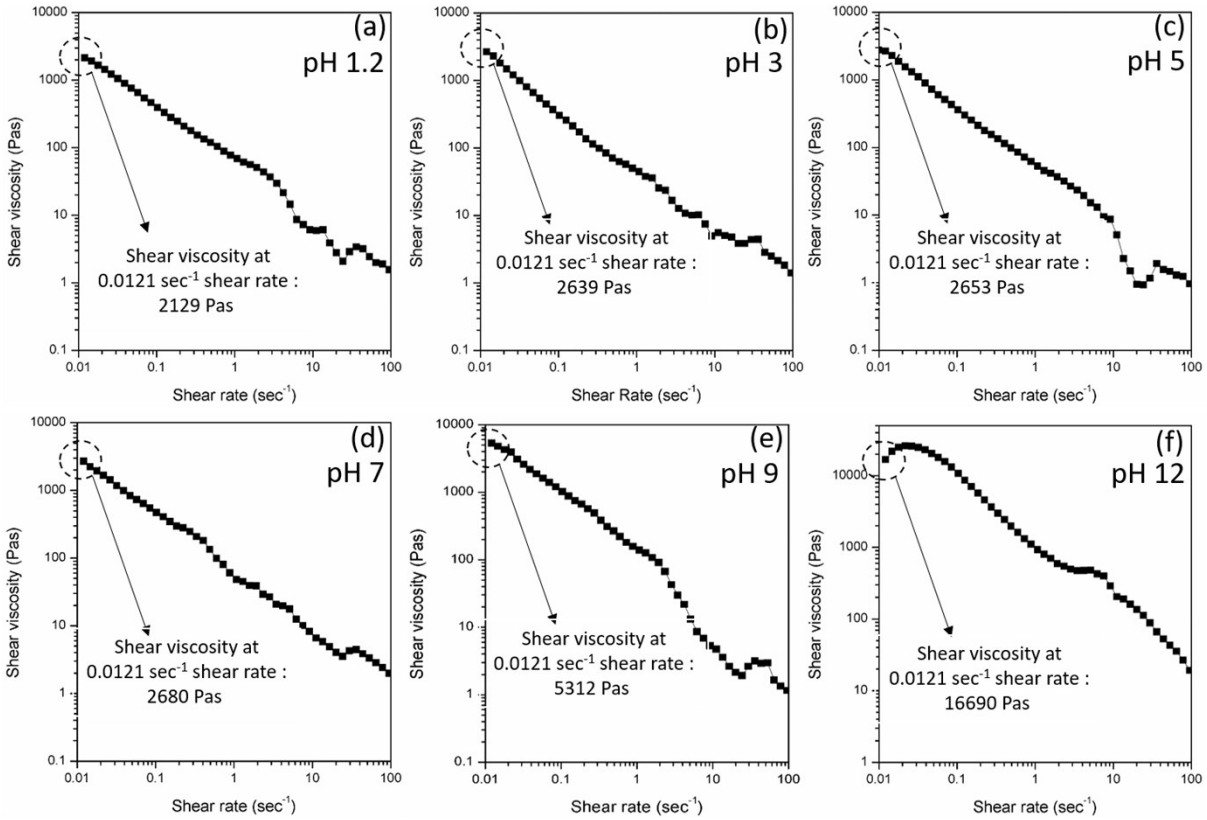


Fig. S14. Viscosity sweep plots of Gly-Meth-*cl*-HG at (a) pH 1.2, (b) pH 3, (c) pH 5, (d) pH 7, (e) pH 9 and (f) pH 12.

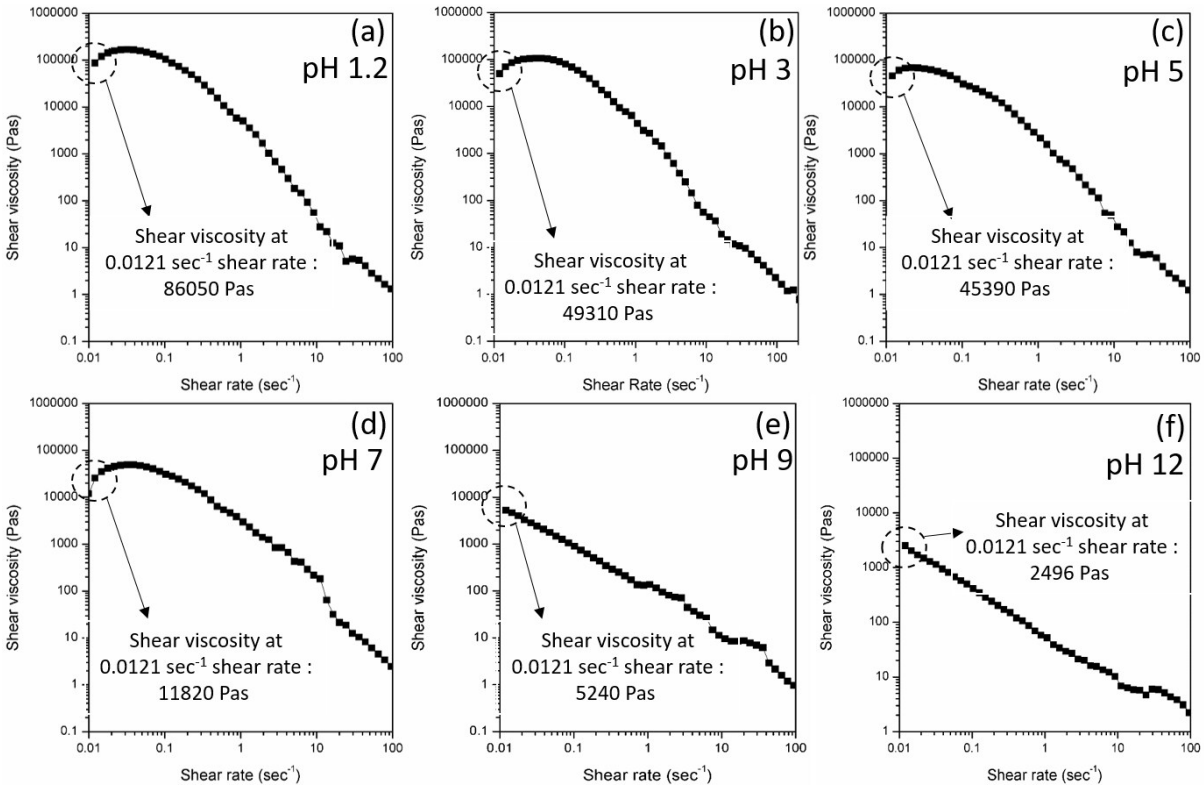


Fig. S15. Viscosity sweep plots of Gly-Meth-*cl*-GM at (a) pH 1.2, (b) pH 3, (c) pH 5, (d) pH 7, (e) pH 9 and (f) pH 12.

Molecular Modelling:

Geometry Optimization and Ab-initio Molecular Dynamics:

Avogadro software (version 1.1.1) has been used to obtain the initial coordinates of polymers (Gly-Meth-*cl*-GM and Gly-Meth-*cl*-HG). These coordinates were used for the input for the *Geometry Optimization in gas phase. The minimization was performed at B3LYP/6-31gs level. DFTD-d3 was also used to include the dispersion correction. After the optimization, the optimized coordinates were used for ab-initio* molecular dynamics (AIMD) simulations calculation in gas phase. AIMD simulations were performed using GPU-based TeraChem (version 1.93) software package[5] at RHF/3-21g level.

QM/MM Molecular Dynamics:

Initial coordinates of the polymers were generated from the equilibrated trajectories of the gas phase calculations. Then the polymers were solvated in water using VMD software package (version 1.9.2) and inhouse codes were used to make it a spherical shape. QM/MM MD simulations were carried out using GPU-based TeraChem (version 1.93) software package. For a particular system, polymer was treated quantum mechanically whereas water molecules were treated with TIP3 force field. All the QM/MM simulations were carried out at RHF/3-21g level. Langevin thermostat was used with a collision frequency of 1.0 ps^{-1} and the temperature was set to 300 K. DFTD-d3 was used to include the dispersion correction. 1 fs was used for the time step. Spherical boundary conditions were applied during the QM/MD simulations (TeraChem only supports spherical boundary conditions). After running approximately 10000 steps (~10 ps), we observed that the systems were in equilibrium. Then, we carried out the simulations for another ~10 ps for production run. Two set of systems, one basic and another acidic medium, were used for the QM/MM simulations. In basic medium, we have removed all the acidic hydrogen atoms from the Gly-Meth-*cl*-GM polymers, whereas in acidic medium no hydrogen atoms were removed. For Gly-Meth-*cl*-HG polymers, we have added one H atom

with each amine group in acidic medium (to form $–NH_3^+$ by protonation), while in basic medium no hydrogen atom was removed. Finally, the swelling behaviour of polymers were investigated by determining the surface water molecules (SWMs) which were 3 Å from their surface. The averaging of SWMs was done by taking 100 frames from the production trajectory. All figures are made by VMD software package (version 1.9.2).[6] The lower level theory/basis were chosen as the system sizes were very large as well as hardware limitation. However, one can expect the results should follow same tend for high level theory/basis calculations.

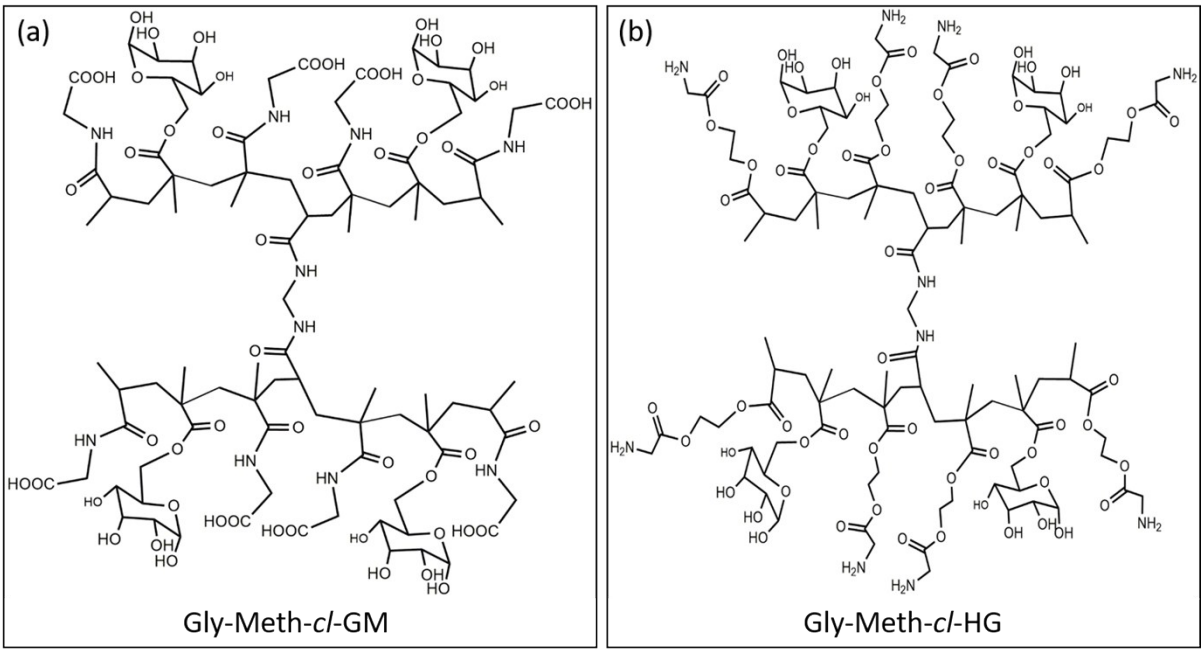


Fig. S16. Simplified molecular structure of simulated (a) Gly-Meth-*cl*-GM and (b) Gly-Meth-*cl*-HG.

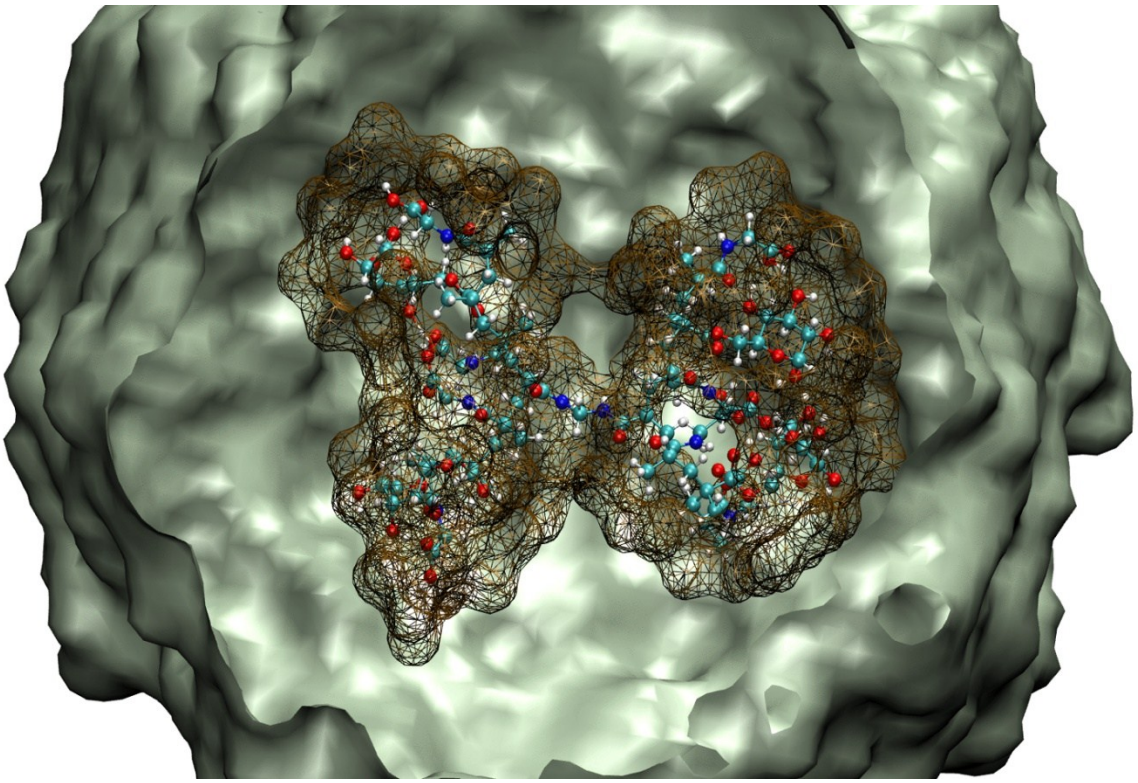


Fig. S17. Simulated hydrated polymer (Gly-Meth-*cl*-GM in acidic medium). Colour Code: Cyan - Carbon atom; Red - Oxygen atom; Blue - Nitrogen atom; White - Hydrogen atom; Dark yellow frame work – SWMs; and Gray - water molecules.

***In vitro* drug delivery study:**

The developed hydrogels have been used as drugs carrier, where Gly-Meth-*cl*-GM is used as carrier of naproxen sodium and Gly-Meth-*cl*-HG used as carrier of ciprofloxacin hydrochloride (tablet formulation). The *in vitro* release study has been performed using a drug dissolution apparatus (Lab India, DS 8000). The experimental conditions were maintained as per the recommendation of USFDA[7]. In brief, for naproxen sodium dissolution media: 900 mL phosphate buffer (mild basic, pH 7.5); fixed RPM: 50; recommended sampling time: 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 14 h were used (as per USFDA)[7]. For ciprofloxacin hydrochloride, dissolution media: 0.1 N HCl (acidic); fixed RPM: 100; recommended sampling time: 1, 2, 4 and 7 h (as per USFDA)[7]. The temperature was maintained at 37 ºC for both the cases. Here the drugs were released in both the dissolution media (0.1 N HCl and phosphate buffer pH 7.5) to assess the pH responsive release behaviour of both the hydrogels.

Fig. S18 demonstrates the pH sensitive *in vitro* drug release profile. From Fig. S18a it is obvious that the release of naproxen sodium from Gly-Meth-*cl*-GM is faster at pH 7.5 (~88 % release in 14 h) compare to the acidic media (0.1 N HCl; ~22 % release in 14 h). This observation can be explained by considering the higher swelling of Gly-Meth-*cl*-GM at basic media compare to the acidic media (Fig. S10a). Higher swelling at basic media results greater hydration of gel network, which is accomplished with higher diffusion of the entrapped drug molecule. On the other hand, the release of ciprofloxacin hydrochloride from Gly-Meth-*cl*-HG is found to be faster (Fig. S18b) at acidic media (0.1 N HCl; ~60 % release at 7 h) as compared to the basic media (pH 7.5; ~20 % release at 7 h). This pH sensitive release behaviour is also the consequence of higher swelling of Gly-Meth-*cl*-HG at acidic media compare to the basic environment (Fig. S10b).

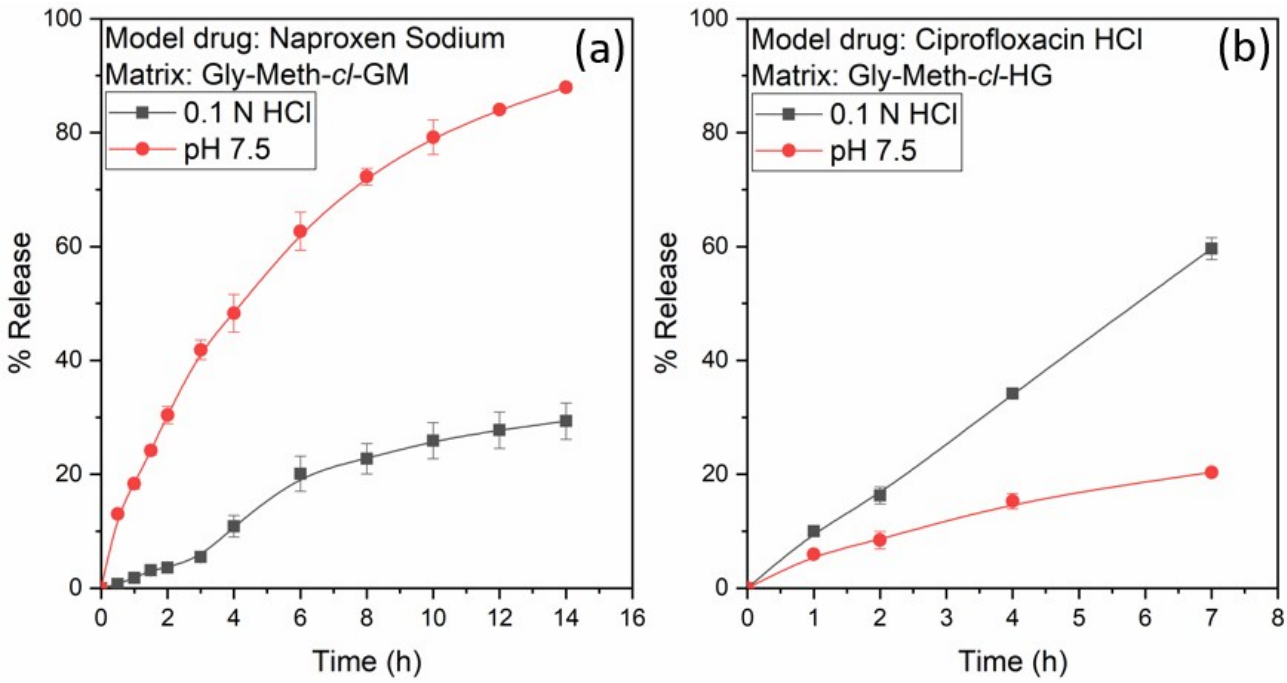


Fig. S18. pH sensitive *in vitro* release study of (a) naproxen sodium from Gly-Meth-*cl*-GM and (b) ciprofloxacin hydrochloride from Gly-Meth-*cl*-HG.

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