Electronic Supplementary Information (ESI)

for

β- Cyclodextrin based pH and thermo-responsive biopolymeric hydrogel as dual drugs carrier

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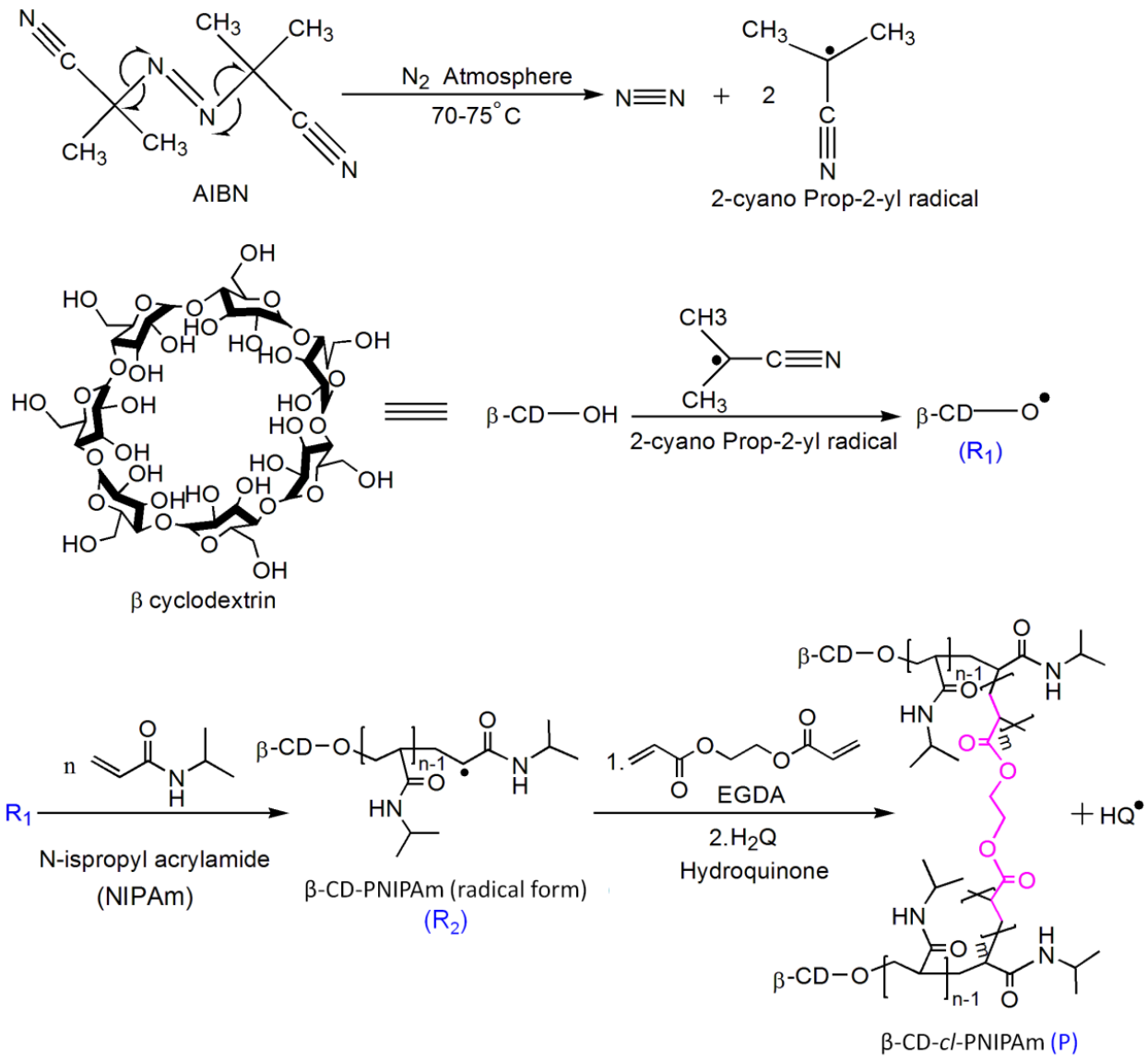
Synthesis of β-CD-*cl*-PNIPAm Hydrogelator.

8.8107×10^{-4} moles of β-CD was dissolved in 30 mL double distilled water in a double necked round bottom (RB) flask, at room temperature. Then the reaction mixture was maintained at 70-75 °C temperature and continuous stirring at a speed of 300 rpm. To generate an inert atmosphere inside the RB flask, N_2 gas was purged. Then required amount of AIBN (Table S1) was dissolved in 2 mL DMSO and poured to the prior solution after 10 min. After 10 min, monomer (NIPAm) (Table S1) was added with the reaction mixture. Then 6.42×10^{-4} moles of EGDA was added to the react, when the reaction solution was turned milky white and the reaction was continued at a temperature of 70-75 °C with constant rotation for another 4 h. The polymerization reaction was terminated using 5 mL (0.1 v/w %) saturated solution of hydroquinol. The product obtained from the reaction was allowed to cool down to room temperature, and then immersed in acetone and left overnight for complete removal of homopolymers and other impurities. Lastly, the product was separated from acetone and the obtained gel like mass (i.e. β-CD-*cl*-PNIPAm hydrogel) was dried in a vacuum oven at 60 °C till constant weight. The possible synthetic outline for the formation of β-CD-*cl*-PNIPAm hydrogelator is depicted in Scheme S1.

Table S1. Synthesis details, % Crosslinking and % ESR of various β-CD-*cl*-PNIPAm hydrogelators.

Amount of β-cyclodextrin = 8.8107×10^{-4} mole Crosslinker concentration = 6.42×10^{-4} mole				
Hydrogelator	Initiator Conc. (mol × 10^{-4})	Monomer Conc. (mol × 10^{-2})	% Crosslinking	% ESR (pH 7.4), 37 °C
β-CD-*cl*-PNIPAm 1	0.60	2.65	60.8	236.9±7
β-CD-*cl*-PNIPAm 2	0.91	2.65	75.6	210.5±6
β-CD-*cl*-PNIPAm 3	1.21	2.65	67.3	222.6±6
β-CD-*cl*-PNIPAm 4	**0.91**	**3.53**	**97.3**	**178.0±5**
β-CD-*cl*-PNIPAm 5	0.91	4.41	80.1	199.6±5

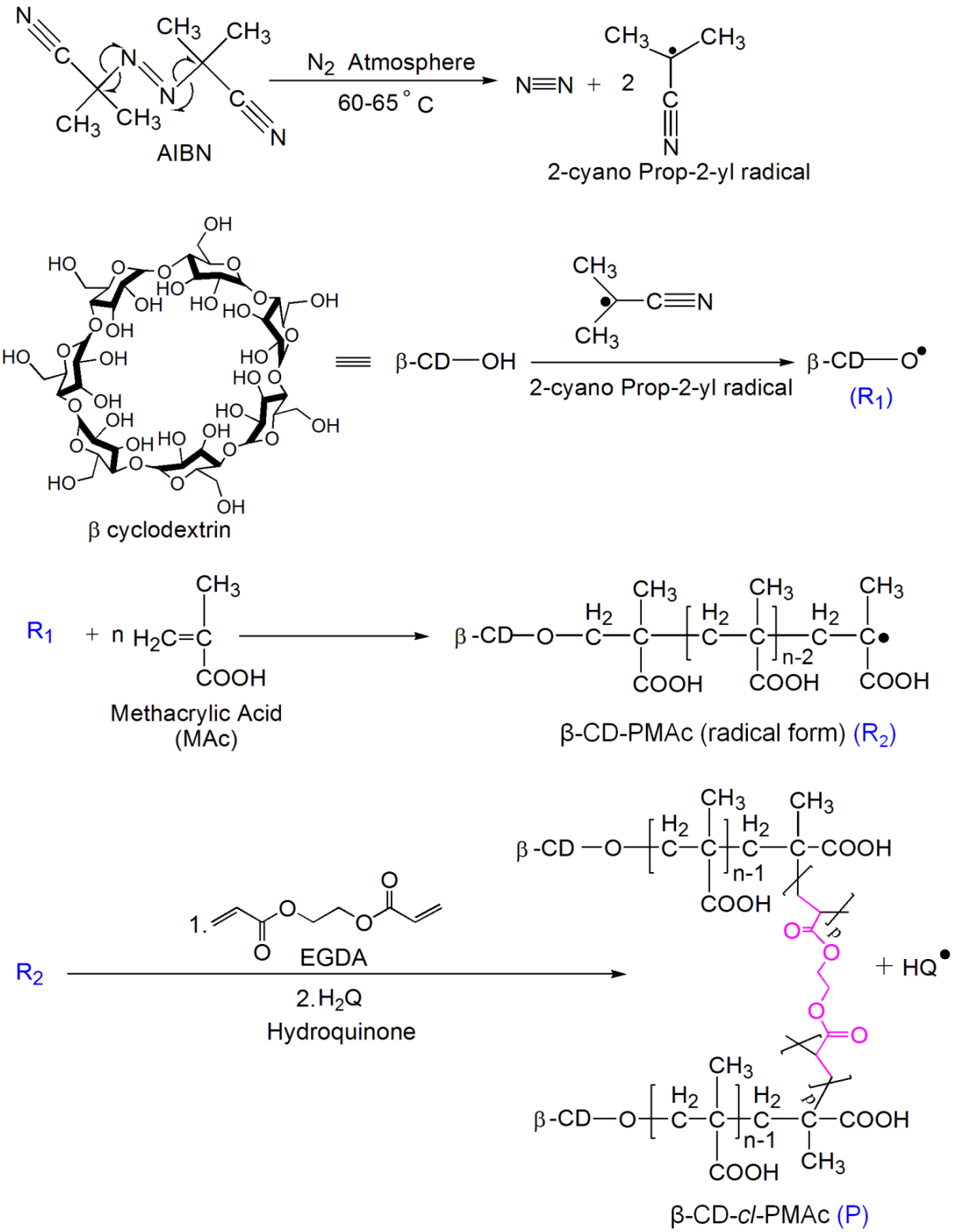


Scheme S1. Probable polymerization reaction scheme for the synthesis of β-CD-*cl*-PNIPAm hydrogelator.

Synthesis of β-CD-*cl*-PMAc Hydrogelator. 8.8107× 10^{-4} moles of β CD was dissolved in 50 mL double distilled water in a double necked round bottom (RB) flask at room temperature. Then the solution temperature was increased to 60-65 °C. N_2 gas was purged inside the RB flask to create an inert atmosphere. Requisite amount of AIBN (Table S2) dissolved in 2 mL DMSO was poured to the prior solution after 10 min. Then after 10 min, required amount of monomer (MAc) (Table S2) was added with the reaction mixture. When the solution became viscous, 6.42 × 10^{-4} moles of EGDA was added to the reaction mixture and stirring was continued at the same conditions for another 4 h. The polymerization reaction was stopped using 5 mL (0.1 v/w %) saturated solution of hydroquinol. The product obtained from the reaction was allowed to cool down to room temperature, soaked in methanol-water mixture (70:30 v/v) for 3 h followed by acetone and then left overnight for complete removal of homopolymers and other impurities. Lastly, the product was separated from acetone and the obtained gel like mass (i.e. β-CD-*cl*-PMAc hydrogel) was dried in a vacuum oven at 60 °C till constant weight was achieved. The probable synthesis outline for the generation of β-CD-*cl*-PMAc hydrogelator is depicted in Scheme S2.

Table S2. Synthesis details, % Crosslinking and % ESR of various β-CD-*cl*-PMAc hydrogelators

Amount of β-cyclodextrin = 8.8107× 10^{-4} mole Crosslinker concentration = 6.42 × 10^{-4} mole				
Hydrogelator	Initiator Conc. (mol × 10^{-4})	Monomer Conc. (mol × 10^{-2})	% Crosslinking	% ESR (pH 7.4), 37 ºC
β-CD-*cl*-PMAc 1	0.60	2.36	69.3	957.8±28
β-CD-*cl*-PMAc 2	0.91	2.36	82.0	840.2±25
β-CD-*cl*-PMAc 3	1.21	2.36	76.1	907.4±27
β-CD-*cl*-PMAc 4	0.91	3.55	84.2	742.5±22
β-CD-*cl*-PMAc 5	**0.91**	**4.73**	**95.2**	**661.7±19**
β-CD-*cl*-PMAc 6	0.91	5.92	92.9	731.7±21



Scheme S2. Probable polymerization reaction scheme for the synthesis of β-CD-*cl*-PMAc hydrogelator.

Characterization techniques.

FTIR Spectroscopy. The FTIR analysis of β-CD-*cl*-(PNIPAm-co-PMAc), Metronidazole, Ofloxacin and swollen tablet were recorded with the help of a FTIR spectrophotometer (Model IR-Perkin Elmer, Spectrum 2000). The scan range was 4000-500 cm^{-1}.

^{1}H-nuclear magnetic resonance (NMR) spectroscopy. The ^{1}H-NMR spectra of β-CD-*cl*-PNIPAm 4 hydrogelator, β-CD-*cl*-PMAc 5 hydrogelator and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator were studied using 400 MHz spectrophotometer (Zeol, Japan), where DMSO d_6 was used solvent.

^{13}C-nuclear magnetic resonance (NMR) spectroscopy. Solid state ^{13}C nuclear magnetic resonance (NMR) spectra of β-CD-*cl*-PNIPAm 4 hydrogelator, β-CD-*cl*-PMAc 5 hydrogelator and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator were recorded at 400 MHz on a JEOL solid state NMR spectrometer (model: ECX400).

CHN analysis. The CHN analysis of synthesised β-CD-*cl*-PNIPAm 4 hydrogelator, β-CD-*cl*-PMAc 5 hydrogelator and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator have been investigated using an Elemental Analyser (vario EL CHNS analyser).

FESEM analysis. The surface morphology of β-CD-*cl*-PNIPAm 4 hydrogelator, β-CD-*cl*-PMAc 5 hydrogelator and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator were investigated using field emission scanning electron microscopy (FESEM Supra 55, Make – Zeiss, Germany).

Dynamic light scattering (DLS) analysis. DLS study of β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator was performed at pH 1.2 and 7.4 at 37 °C and at pH 7.4 at 25 °C using particle size analyser (Model: SZ-100, Make: Horiba Scientific, Japan).

Swelling, deswelling and reswelling studies.

Swelling: Preweighed amount (~1 g) of various grades of β-CD-*cl*-PNIPAm hydrogel and β-CD-*cl*-PMAc hydrogel were taken in a tea bag and immersed in buffers (pH 1.2 and pH 7.4) at 37 °C. Swelling study of β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel was assessed in acidic (pH

1.2) and alkaline (pH 7.4) media at 25 °C and 37 °C. Synthesized β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel was allowed to swell for 24 h. The swollen hydrogel was withdrawn after every 1 h and the excess water at the surface of the gel was blotted off carefully using tissue paper and then reweighed. The equilibrium swelling was attained at ~14 h. The % equilibrium swelling ratio (% ESR) was calculated using eq. (S1).[1]

$$\%ESR = \frac{W_f - W_i}{W_i} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(S1)}$$

Deswelling: To determine the reversible nature of the β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel, deswelling study was executed using preweighed amount of the fully swollen hydrogel at 37 °C with 100 mL of 7.4 buffer solution on a constant temperature oven. At every 1h of time interval, the gels were drawn from oven and weight was taken until a constant weight was attained. The % deswelling ratio (% DSR) has been calculated using eq. (S2).[1]

$$\%DSR = \frac{W_f - W_t}{W_f} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(S2)}$$

Where, W_f and W_t are weights of the hydrogel at equilibrium and after time t, respectively.

Reswelling: Reswelling study was carried out by taking preweighed fully deswelled β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel and % ERSR was calculated using eq. (S3)

$$\%ERSR = \frac{W_f - W_i}{W_i} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots \text{(S3)}$$

Where, W_f is the weight of hydrogel in reswelling equilibrium and W_i is the weight of deswelled hydrogelator.

Compressive Test. β-CD-*cl*-PNIPAm hydrogel, β-CD-*cl*-PMAc hydrogel and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel were swollen to equilibrium at pH 7.4 before testing. The samples were prepared in the form of cylinders having diameter of 14 mm and height of 14 mm. The compressive stress was estimated using the following mathematical expression.

$$Compressive\ Stress = \frac{F}{A} \ldots\ldots\ldots\ldots\ldots \text{(S4)}$$

Where, F is the force acting on the section of the sample and A is the cross sectional area of the hydrogel sample.

Cell Viability Study and Morphological assessment. Swollen cl-(PNIPAm-co-PMAc) hydrogel, β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel were sterilized by using 70% alcohol and UV followed by repeated PBS (pH=7.4) washing. The study was done on MG-63 cell line obtained from NCCS Pune, cultured in high glucose of DMEM (Himedia) media with 10% FBS and 1% antibiotic solution in 5% CO_2 atmosphere at 37 ^oC (Heracell 150i, Thermo, USA). After 3 days culture, cells were harvested from tissue culture flasks using 0.25% trypsin in 1 mM EDTA (Himedia) and plated onto pellets. Cell density was counted and plated equal volume on samples and tissue culture plate (TCP) as a control in 24 well plate. [2]

MTT assay of the MG-63 cells on the samples and control were examined after 1, 3 and 5 days of experiment. The culture medium was discarded from 24 well plate followed by washing with PBS and incubated with 5 mg mL^{-1} MTT solution (that was obtained from Sigma Aldrich, USA) at 37 ^oC for 4 hours. DMSO (100 μL) was added to each well to dissolve the insoluble purple formazan crystals formed by the reduction of MTT by the mitochondrial dehydrogenase enzyme that present in active cells. The culture plate was placed on a horizontal shaker and swirled for 30 min. Absorbance was recorded with the help of a microplate reader (Bio-RAD 680, USA) at 570 nm.

After 1, 3, and 5 days, cell morphological assessment was evaluated by rhodamine-phalloidin (Life Technologies, Invitrogen) and DAPI (4′, 6-diamidino-2-phenylindole, (Life Technologies, Invitrogen) as of manufacturer's statement. Briefly, cells were fixed in 4% paraformaldehyde, permeabilized using Trition-X100 followed by blocking the nonspecific sites using 1% BSA (Sigma). Rhodamine–phalloidin (for cytoskeleton staining) dye was added to β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator sample and incubated for 15 min followed by three times PBS washing. DAPI dye (nucleus staining) was also applied for 5 min and rinsed

with PBS followed by imaging under fluorescent microscope (Carl Zeiss, Germany) using ZEN software.

Live Dead assay. Preweighed samples of β-CD, cl-(PNIPAm-co-PMAc) hydrogel, β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator based tablets were taken of 1, 3, and 5 days post culture.

The cell–sample construct was at first washed with PBS and then incubated for 30 min at room temperature in a solution having 2 mM calcein acetomethoxy (AM) and 4 mM ethidium homodimer. After 30 min of incubation at normal temperature, the cell–sample assembly was experimented using a fluorescent microscope (Oberkochen, Carl Zeiss, Germany) with excitation filters of 450–490 nm for green (Calcein AM) and 510–560 nm for red (ETD-1) using ZEN software.

***In vitro* metronidazole and Ofloxacin (in combination) release study.**

Preparation of tablets: β-CD and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator (100 mg) were used to prepare 200 mg tablet of combined drugs (metronidazole and Ofloxacin). The gel (100 mg) was allowed to swell with small amount of warm water to form dough like mass, to which binder poly (vinyl pyrollidone) (10 mg), metronidazole (50 mg) and Ofloxacin (40 mg) were mixed to create a grain like mass. Then the grain was fully dried at 40 °C. Afterward, magnesium tri silicate (1 mg) and talc (1 mg) were added to the tablet to lubricate it. Finally, with the help of a tablet-making machine, the prepared tablets were compressed at a typical weight of 200 mg using 2–3 t/cm^2 pressure.

Drug release kinetics and mechanism models. The zero order kinetic model [eq. (S5)] is mainly employed for transdermal, and tablet based drug delivery systems.[3]

$$C_t = C_0 + K_0 t \quad \text{(S5)}$$

Where C_0 and C_t are the amount of initial drug release and drug release after time t. K_0 (unit concentration/time) is the rate constant of drug release kinetics.

The first order kinetic model (eq. S6) implies the drug release from porous matrix, holding the water soluble drugs .[4]

$$log\ C_t = log\ C_0 - \frac{K_1 t}{2.303} \quad \ldots\ldots\ldots\ldots\ldots \quad \text{eq. (S6)}$$

Where, C_t and C_0 are amount of drug released at time t and amount of drug present in the hydrogel initially. K_1 is the rate constant.

The Korsemeyer-Peppas model (eq. S7) is given below: [5]

$$\frac{M_t}{M_\infty} = Kt^n \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{eq. (S7)}$$

Where, M_t/M_∞ is the portion of drug release in time 't', 'K' is a constant and that depends on the characteristic of the drug–hydrogel device system, and 'n' is diffusion exponent. The 'n' value suggests different manners of release mechanisms. When n<0.45, it supports Fickian diffusion. In this case, diffusion process controls the release of drug from the matrix. If the value of 'n' is in the range of 0.45 and 0.89, then it recommends non-Fickian diffusion mechanism, where the release of drug depends on both diffusion as well as erosion of the matrix at the same time. If the value of n>0.89, the main approach towards drug delivery is Super Case II mechanism, where erosion of matrix device is the key factor for the release of drug from the matrix.[6]

***In vivo* release study**:

Healthy albino Rabbits were obtained from registered breeder and were acclimatize for 10 days. Each animal were fur marked for identification and allocated in separate cages with sufficient food and water at 20−25 °C and 40−70% relative humidity in a 12 h light−dark cycle. A zero hour fasting blood sample was withdrawn early in the morning. After administration of two different formulation of FDC tablet Metronidazole and Ofloxacin at a dose level of 50 mg and 40 mg respectively, Blood Samples (0.5 mL) were withdrawn from the marginal ear vein

at predetermined time intervals of 0.5, 1, 2, 3, 4, 8, 12 and 24 hours using a disposable syringe. The blood samples were collected in the RIA vials containing an anticoagulant and centrifuged at 4000 rpm for 5 minutes to separate the plasma.

150µL subjects plasma, 50µL of IS were transferred into 1.5 mL polypropylene micro-centrifuge tubes. Samples were deproteinized by addition of 300µL of ACN, vortexed for 5 minutes and then centrifuged at 12000 rpm for 5 minutes. ~20 µL of the clean upper layer was injected directly into the chromatographic system.

The drug plasma concentration was measured by HPLC (Shimadzu Corp, SPD-M20A 230V). Hydrochlorothiazide was used as an internal standard. Analysis was performed by a Thermo 250-4, 5µm C18 column using an isocratic elution mode with a mobile phase of 5 mM Phosphate buffer (pH 5): ACN (50:50) (83:17 v/v) at a flow rate of 1 mL/min at using a PDA detector.

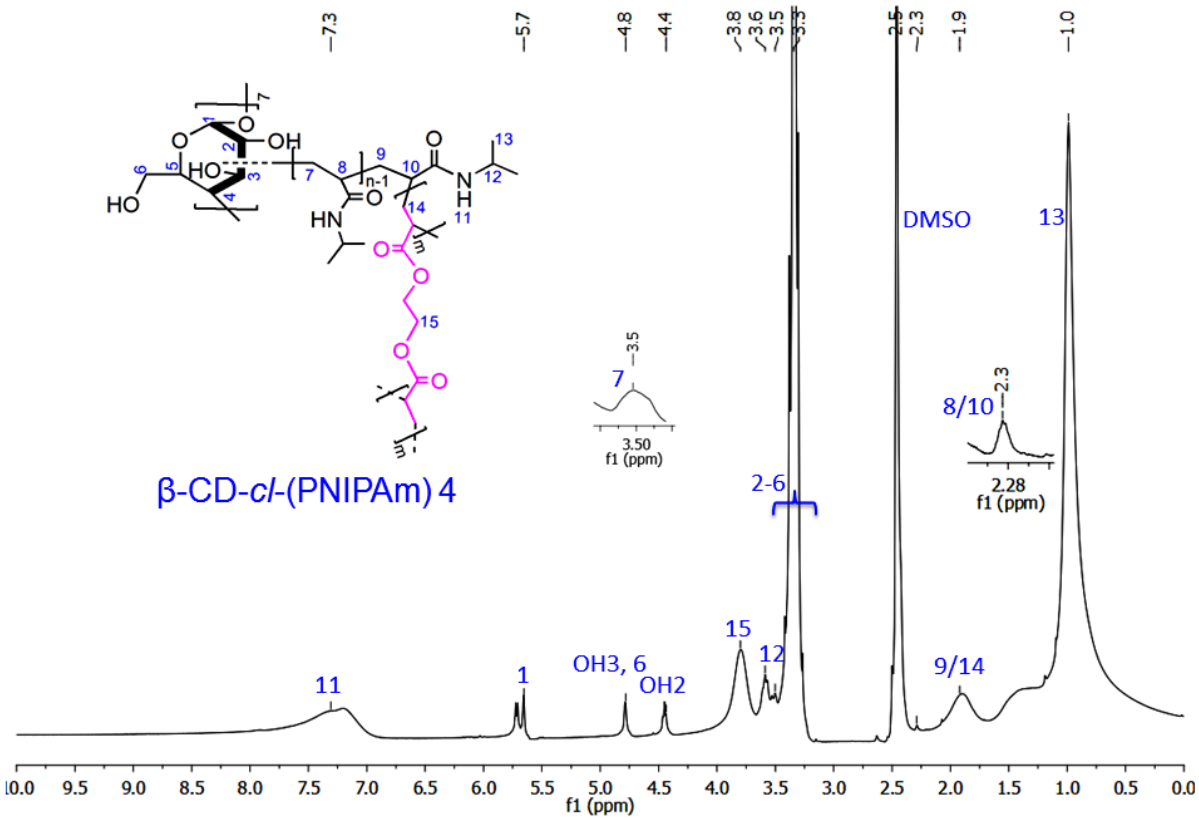


Figure S1. ^{1}H NMR spectrum of β CD-*cl*-PNIPAm 4 hydrogelator in DMSO-d6.

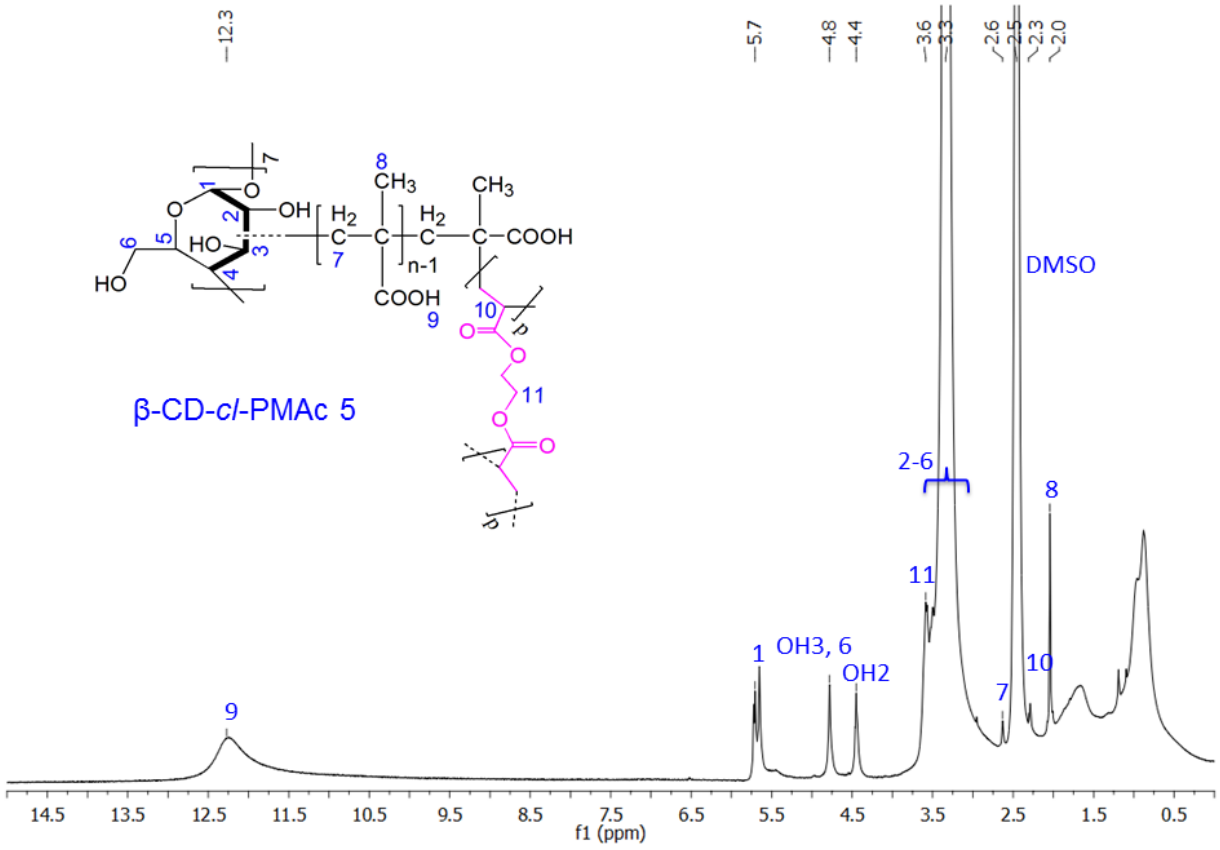


Figure S2. ^{1}H NMR spectrum of β-CD-*cl*-PMAc 5 hydrogelator in DMSO-d6.

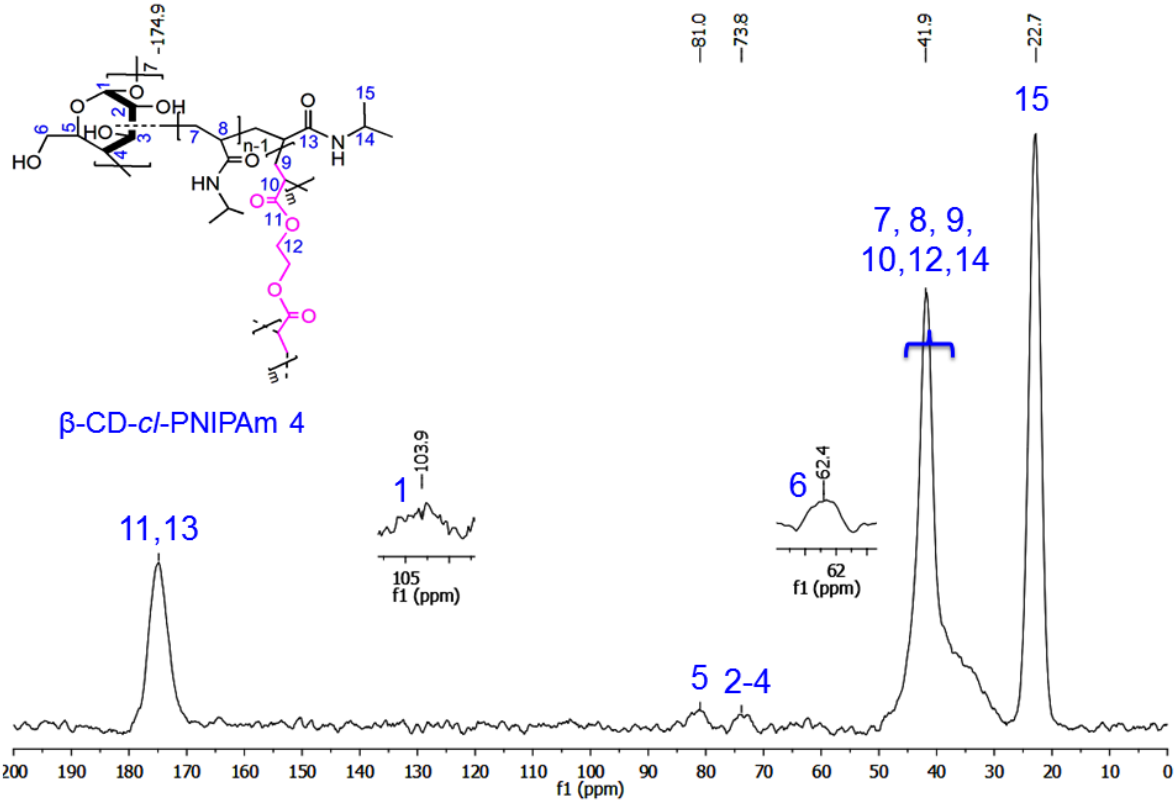


Figure S3. Solid state ^{13}C NMR spectrum of β-CD-*cl*-PNIPAm 4 hydrogelator.

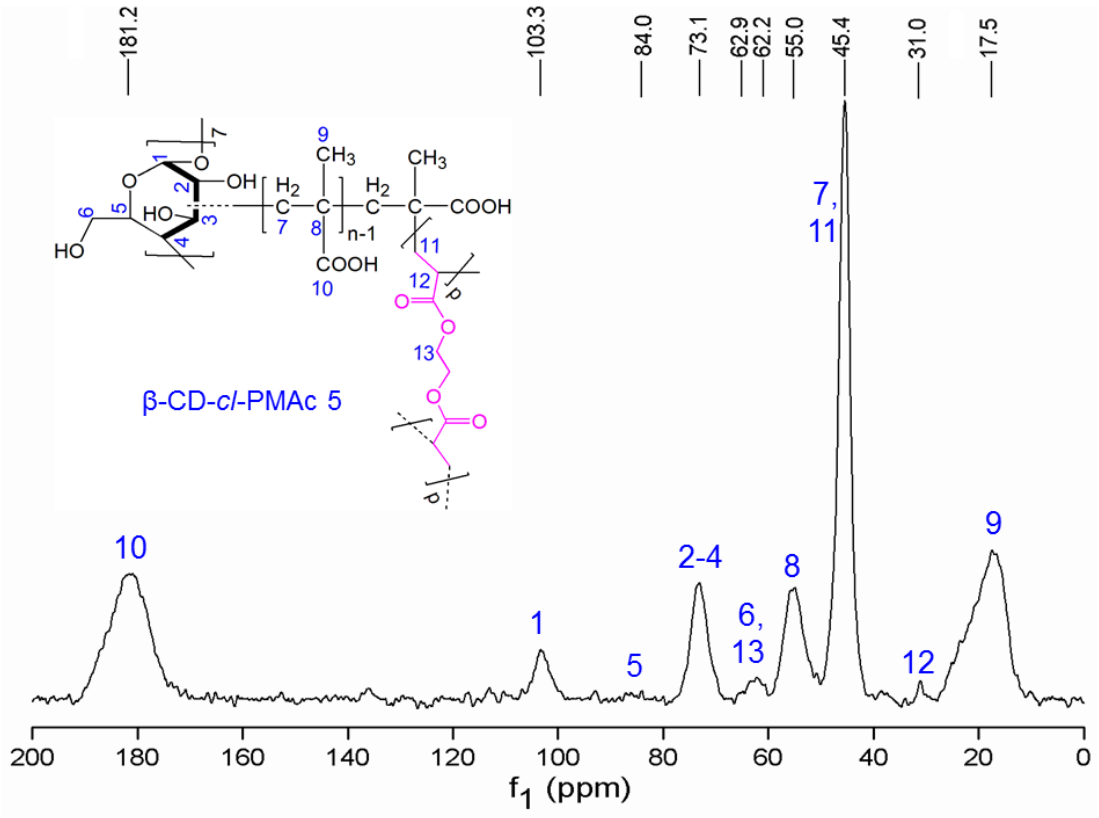


Figure S4. Solid state ^{13}C NMR spectrum of β-CD-*cl*-PMAc 5 hydrogelator.

Table S3: CHN analysis result.

Material	% C	% H	% N
β-CD-*cl*-PMAc 5 xerogel	46.89	8.66	0.00
β-CD-*cl*-PNIPAm 4 xerogel	57.36	12.14	10.21
β-CD-*cl*-(PNIPAm-co-PMAc) xerogel	47.33	9.78	1.35

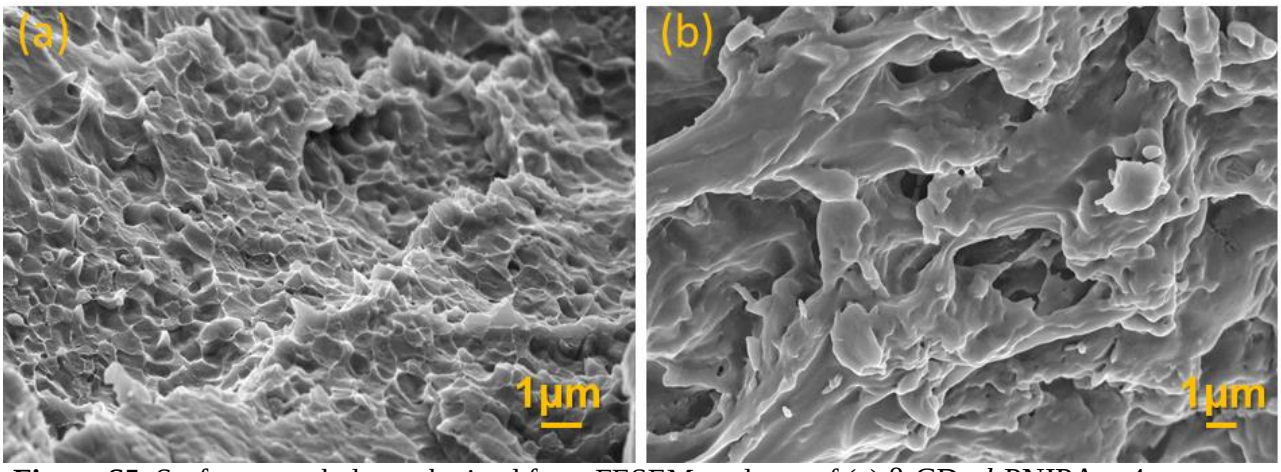


Figure S5. Surface morphology obtained from FESEM analyses of (a) β-CD-*cl*-PNIPAm 4 xerogel and (b) β-CD-*cl*-PMAc 5 xerogel.

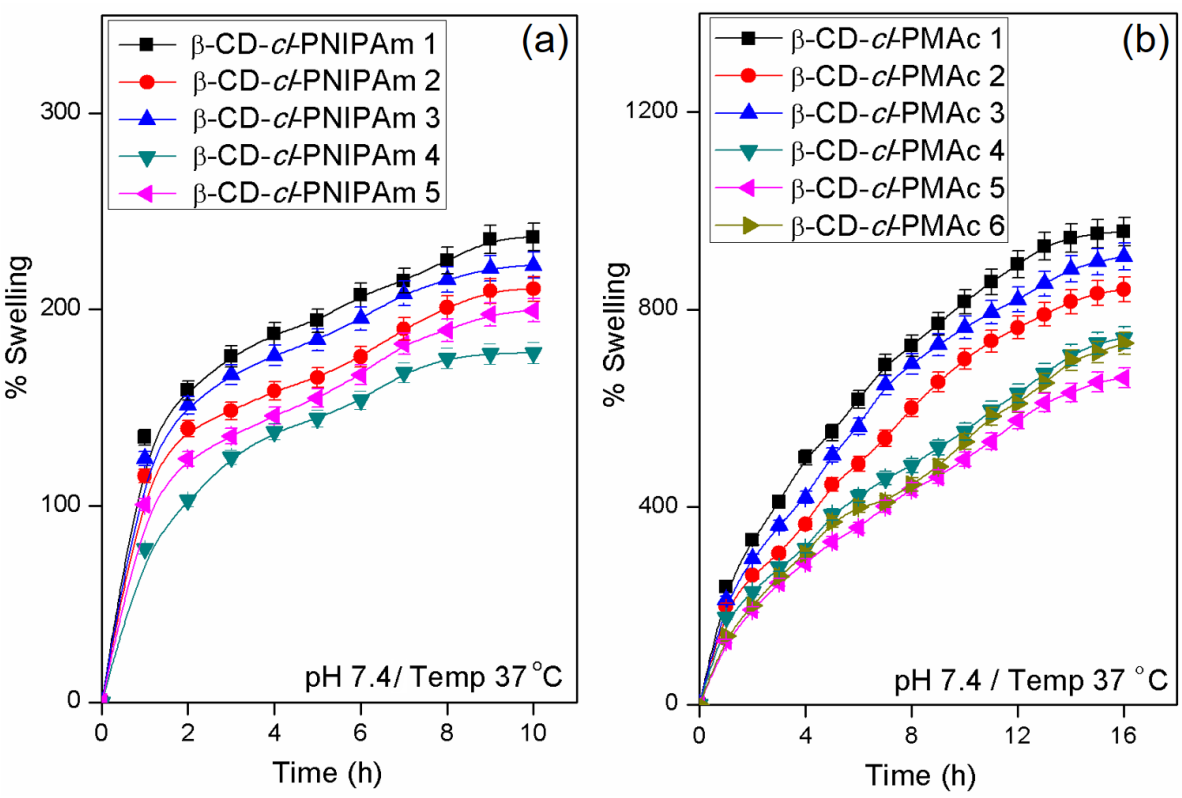


Figure S6. Swelling characteristics of various grades of (a) β-CD-*cl*-PNIPAm hydrogel (b) β-CD-*cl*-PMAc hydrogel at pH 7.4 and 37 °C (Results represented are mean ± SD, n=3).

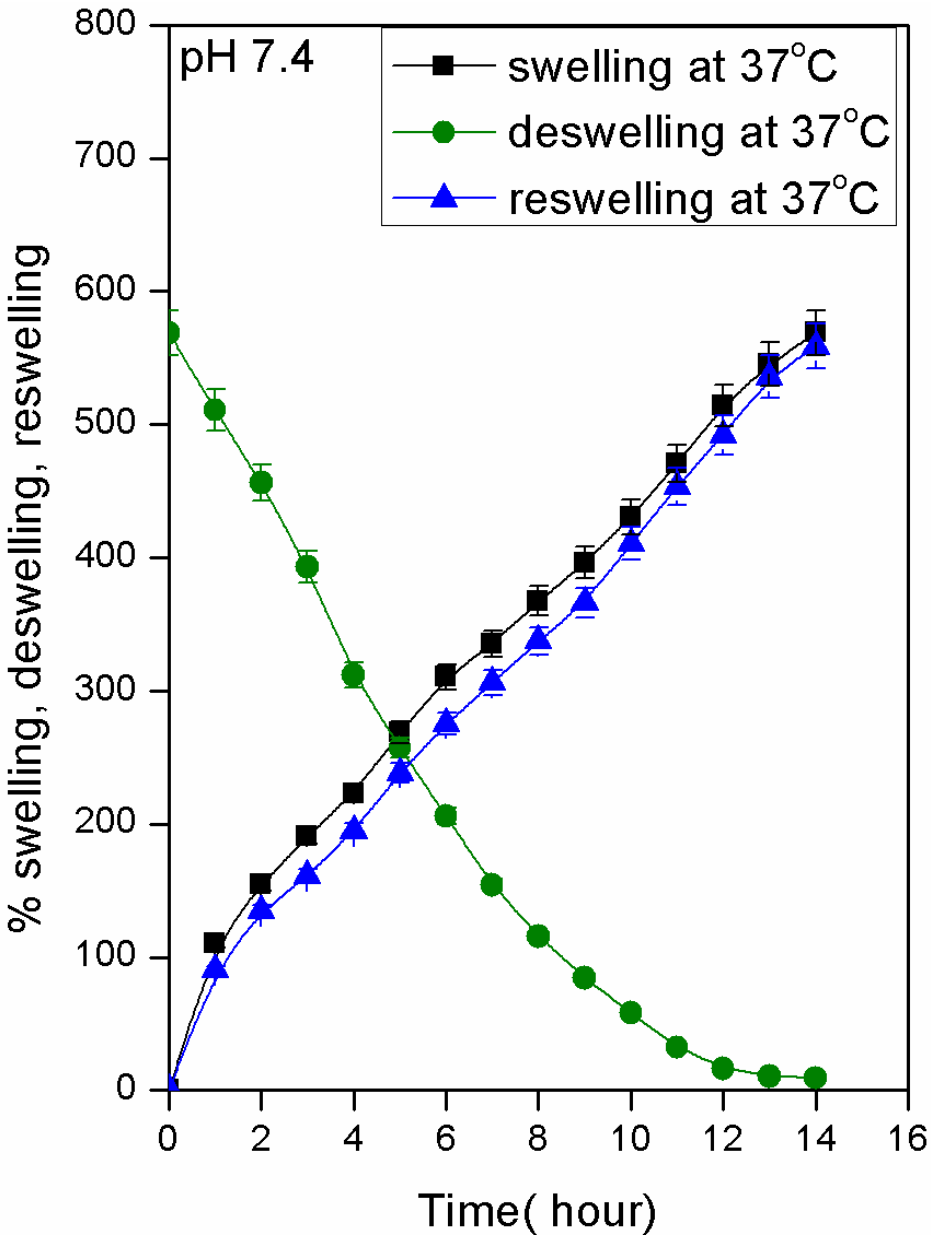


Figure S7. Swelling, deswelling, and reswelling plots of β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel at pH 7.4 and 37 ºC.

Table S4: % ESR for swelling and reswelling, %DSR and τ values for swelling, deswelling and reswelling of β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel at different pH and temperatures

Hydrogel	%ESR			% DSR	% ERSR
	pH 7.4 (37 ^{o}C)	pH 7.4 (25 ^{o}C)	pH 1.2 (37 ^{o}C)	___	pH 7.4 (37 ^{o}C)
β-CD-*cl*-(PNIPAm-co-PMAc)	568.8±17	885.2±26	305.2±15	9.3±0.2	558.8±16

Hydrogel	Swelling rate parameter (τ)			Deswelling rate parameter (τ)	Reswelling rate parameter (τ)
	pH 7.4 (37 ^{o}C)	pH 7.4 (25 ^{o}C)	pH 1.2 (37 ^{o}C)	___	pH 7.4 (37 ^{o}C)
β-CD-*cl*-(PNIPAm-co-PMAc)	709.21	689.65	787.40	- 952.38	724.63

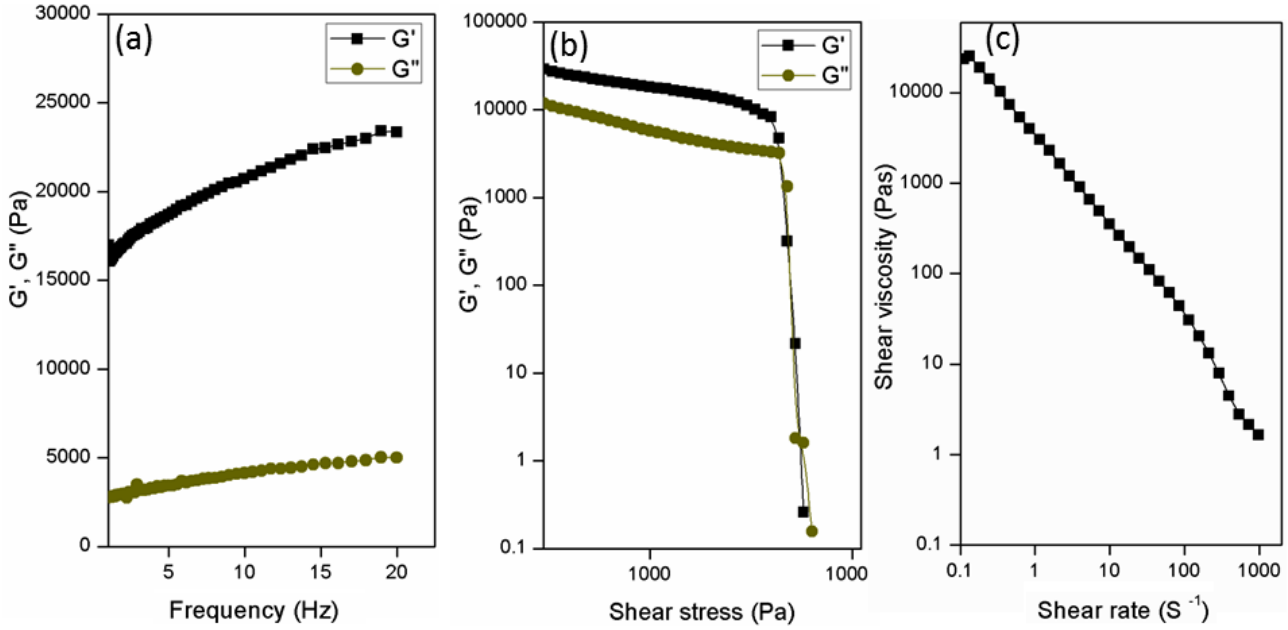


Figure S8. Rheological plots of swollen of β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel (a) G', G" vs. frequency at 1Pa shear stress (b) G', G" vs. shear stress at 1 Hz frequency (c) viscomertic mode at pH 7.4 and 37 ^{o}C.

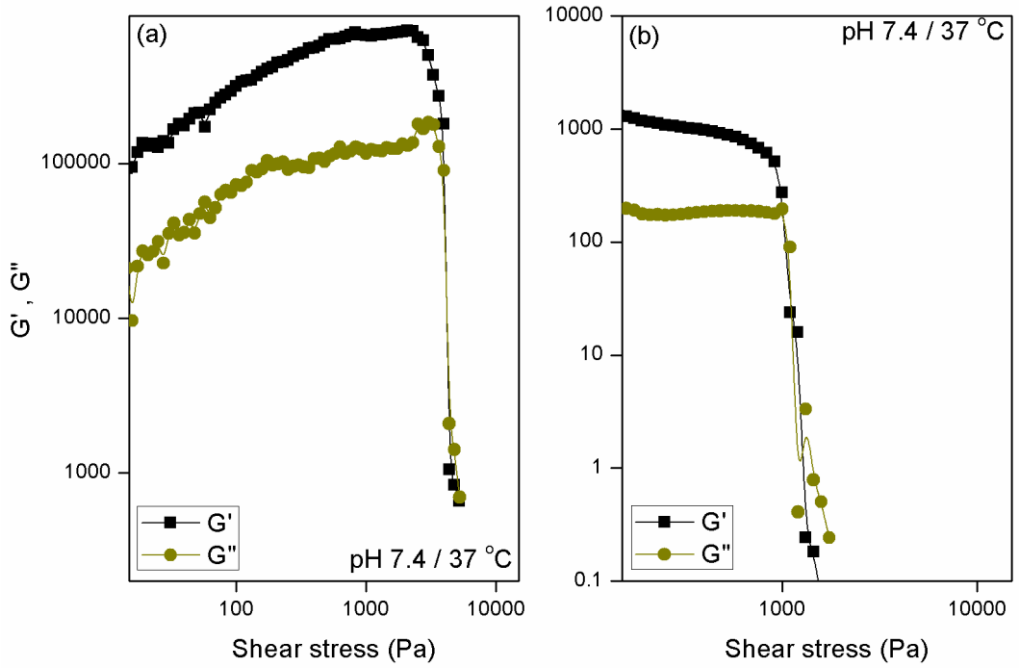


Figure S9. Rheological G', G" vs. shear stress at 1 Hz frequency plots of swollen of (a) β-CD-*cl*-PMAc 5 hydrogel and (b) β-CD-*cl*-PNIPAm 4 hydrogel .

Table S5: Yield stress and gel strength of β-CD-*cl*-PMAc, β-CD-*cl*-PNIPAm and β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel at different pH and temperatures

Hydrogel	Yield Stress (Pa) [pH: 7.4, temperature: 37 ºC]
β-CD-*cl*-PMAc 5	4365
β-CD-*cl*-PNIPAm 4	1096
β-CD-*cl*-(PNIPAm-co-PMAc)	4786

Hydrogel	Parameters	pH: 7.4		pH: 1.2
		37 ºC	25 ºC	37 ºC
β-CD-*cl*-(PNIPAm-co-PMAc)	Yield stress (Pa)	4786	3311	5754

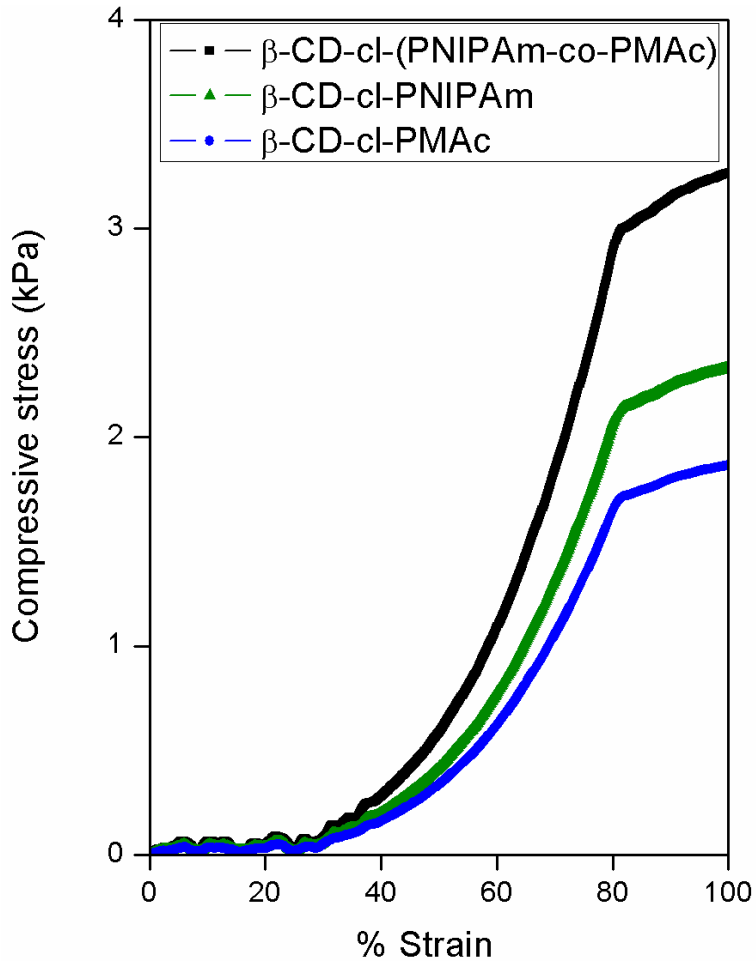


Figure S10. Compressive stress analysis of different hydrogels

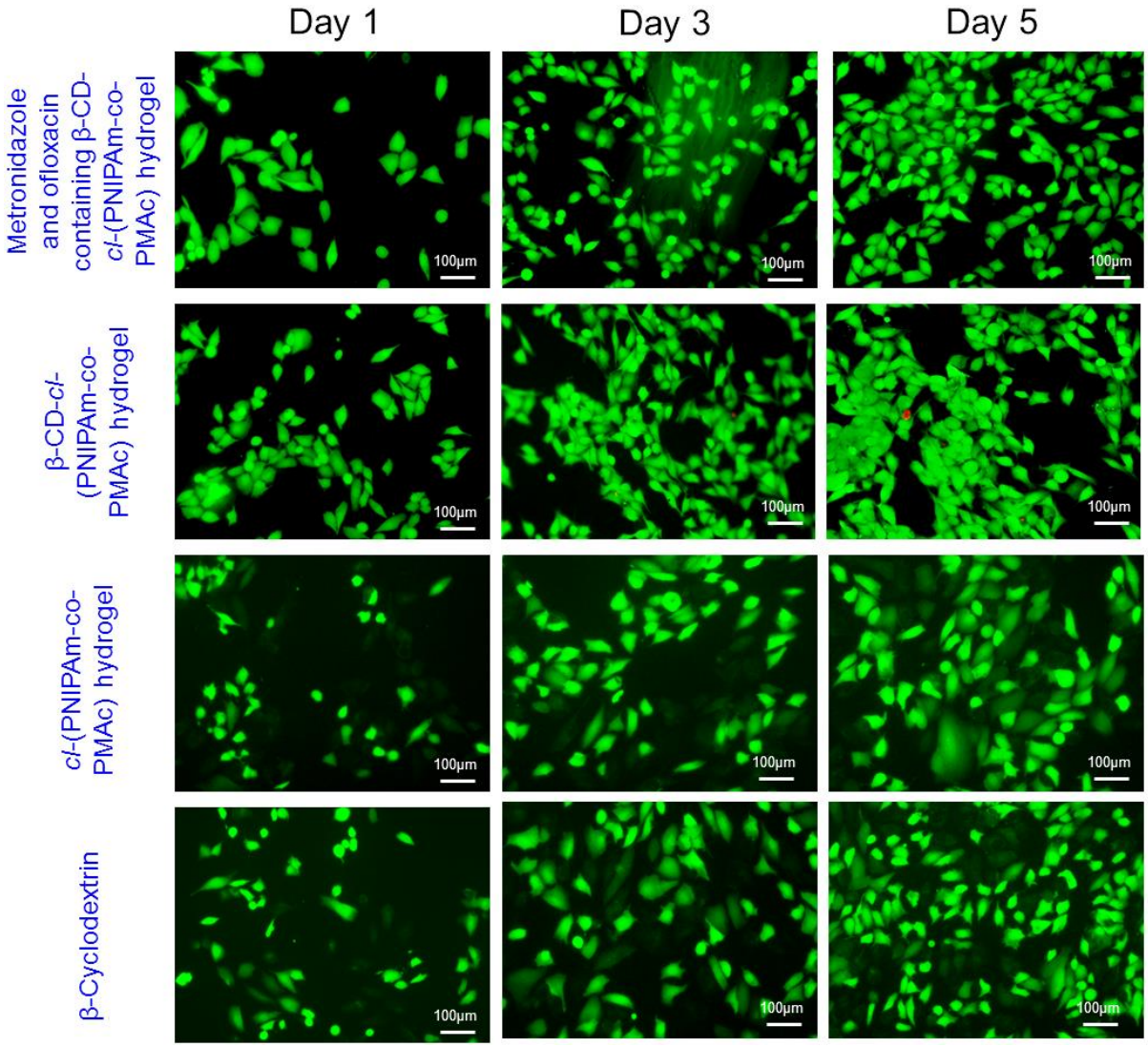


Figure S11. Calcein Et–Br staining results of β-CD, *cl*-(PNIPAm-co-PMAc) hydrogel, β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel and drug loaded β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel based tablet after 1, 3, and 5 days.

FTIR spectral analysis:

The FTIR spectrum of β-CD-cl-(PNIPAm-co-PMAc) xerogel is represented in Fig. S12a, ESI†. The bands at 3479 and 1725, 1652 cm^{-1} are as a result of O–H stretching and merged C=O vibrations of ester and acid groups and C=O stretching vibrations of amide groups, respectively. This suggests the successful attachment of crosslinker and both the monomeric units onto oligosaccharide skeleton.

From the FTIR spectrum of metronidazole (Fig. S12b, ESI†), it is obvious that O–H and C–H bond stretching vibrations are found at 3237 and 2822 cm^{-1}, correspondingly. For C–N stretching and asymmetric stretching of NO_2, the bands were appeared at 1538 cm^{-1}. While the peaks at 1457, 1367 and 1267 cm^{-1} can be attributed to $–CH_2–$ groups scissoring, asymmetric stretching mode of the NO_2 group and C–O stretching vibrations, respectively. In the FTIR spectrum of Ofloxacin (Fig. S12c, ESI†), the characteristics peak at 3041 cm^{-1} can be assigned to stretching vibration of O–H bond. Another band at 2798 cm^{-1} represents alkene and aromatic C–H stretching. The peaks at 1708, 1620, 1295 and 1026 cm^{-1} are responsible for carbonyl (C=O) stretching, N–H bending of piperazinyl ring, bending vibration of O–H bond and C–F stretching, respectively. Finally, the FTIR spectrum of the swollen tablet is shown in Fig. S12d, ESI†. It has been found that all the major bands of both the drugs and β-CD-*cl*-(PNIPAm-co-PMAc) gel were present with slight shifting towards lower wavenumber. This phenomenon is likely due to the existence of H-bonding as well as some physical interactions between xerogel and the drugs (as proposed in Fig S13, ESI†), suggesting the good assembly of drugs and hydrogel in tablet formulation.

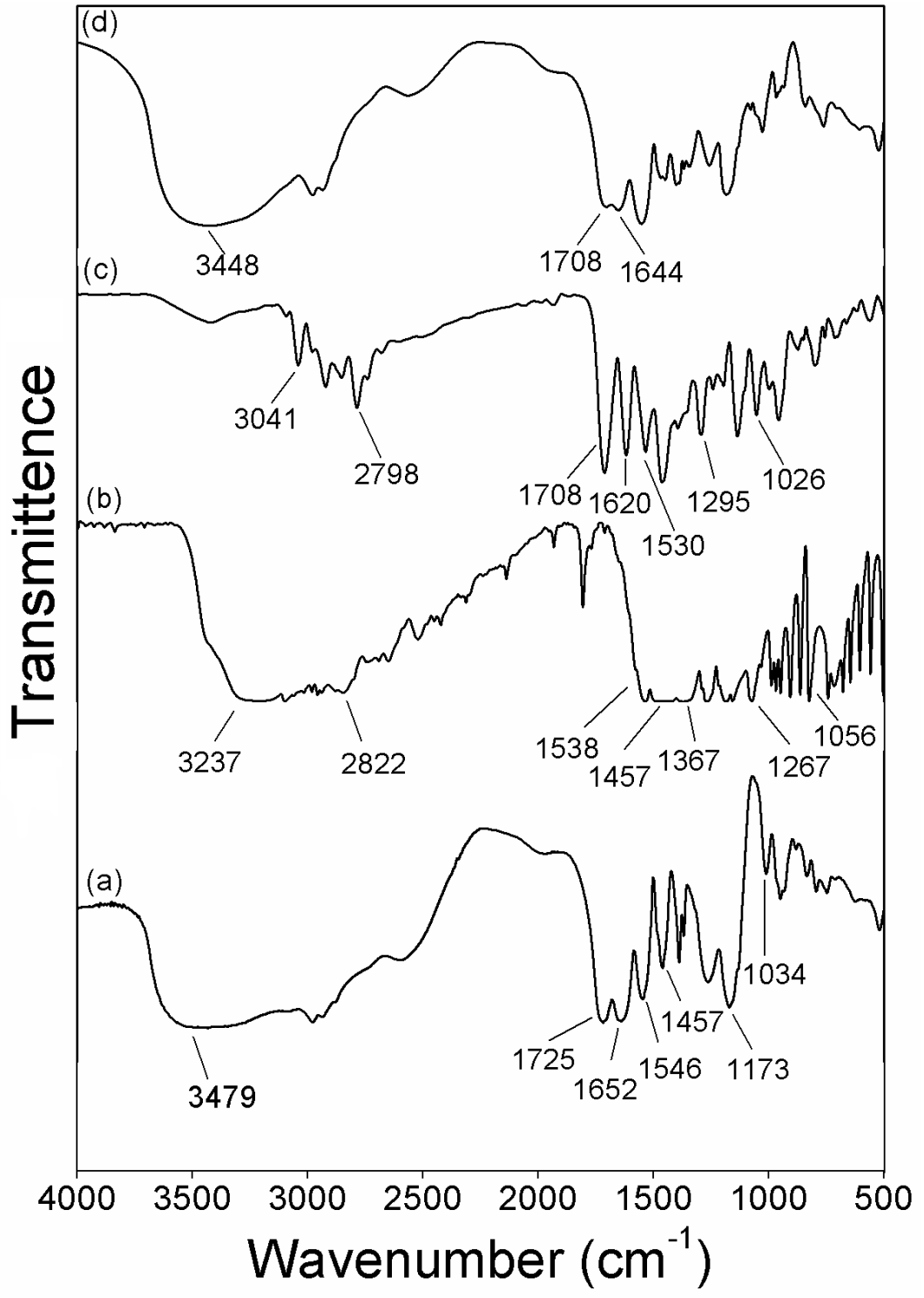


Figure S12. FTIR spectra of (a) β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel, (b) Metronidazole, (c) Ofloxacin, and (c) swollen tablet.

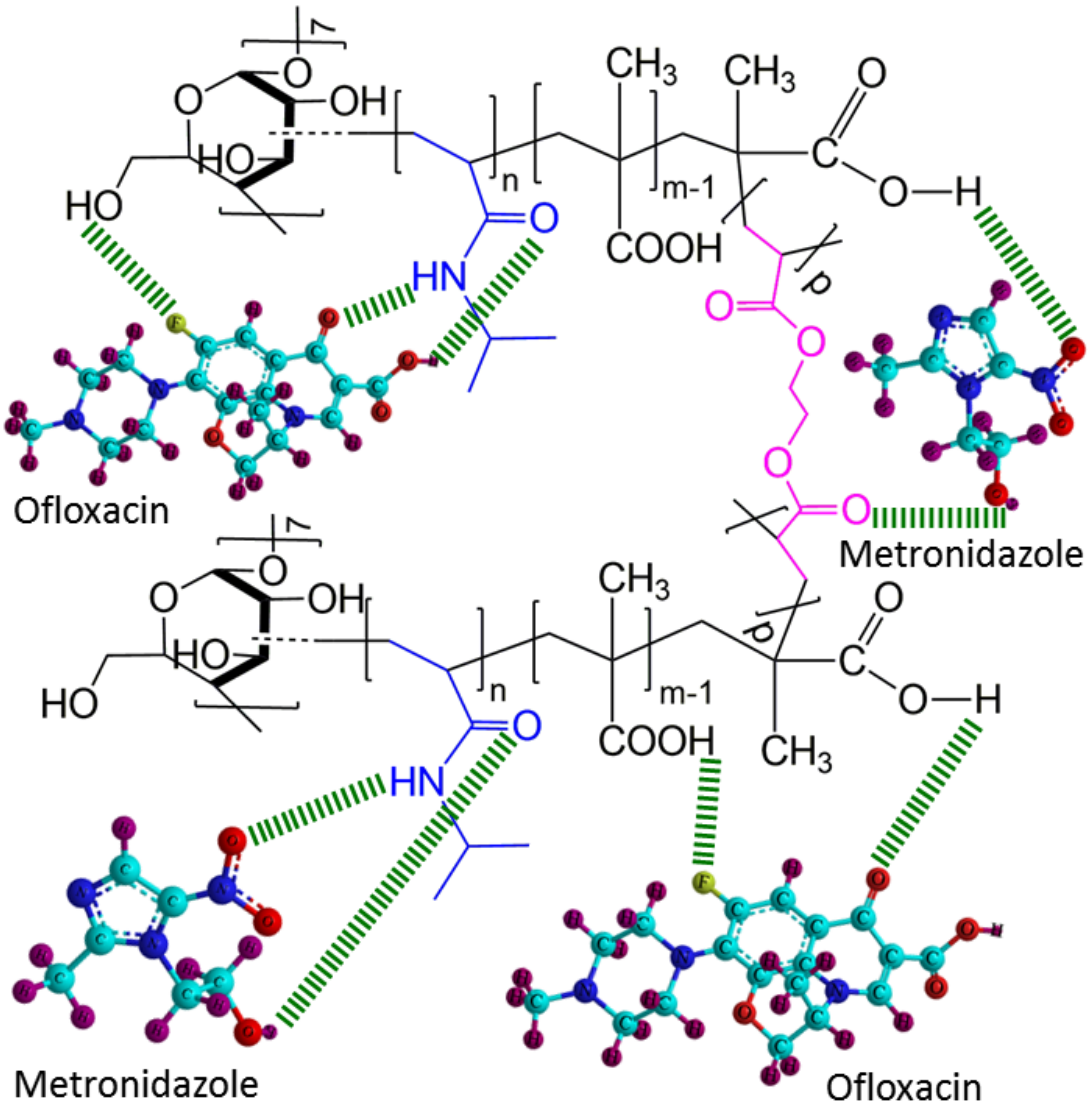


Figure S13. Feasible interactions between β-CD-*cl*-(PNIPAm-co-PMAc) hydrogel and metronidazole and Ofloxacin drug.

Table S6. Metronidazole and Ofloxacin release kinetics and mechanism data.

Matrix	Model Drug	Zero order kinetics	First order kinetics	Korsemeyer-Peppas Model	
		R^2	R^2	R^2	n
β -CD	Metronidazole	0.98	0.78	0.96	0.80
	Ofloxacin	0.97	0.78	0.97	0.82
β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator At 37 °C	Metronidazole	0.82	0.50	0.92	0.78
	Ofloxacin	0.81	0.49	0.86	0.74
β-CD-*cl*-(PNIPAm-co-PMAc) hydrogelator At 25 °C	Metronidazole	0.86	0.47	0.84	0.88
	Ofloxacin	0.85	0.52	0.87	0.86

Table S7. *In vivo* comparative pharmacokinetic parameters of metronidazole and Ofloxacin based tablets in rabbit plasma.

	Metronidazole		**Ofloxacin**	
	Metronidazole (β –CD based tablet)	Metronidazole [β-CD-cl-(PNIPAm-co-PMAc) based tablet)	Ofloxacin (β –CD based tablet)	Ofloxacin [β-CD-cl-(PNIPAm-co-PMAc) based tablet)
C_{max} (µg/mL)	3.77 ±0.061	3.59 ±0.091	16.59 ±0.565	14.44 ±0.229
T_{max} (h)	0.83 ±0.288	3.00 ±0	0.50 ±0	2.00 ±0
AUC_{0-t}	38.27 ±0.111	54.90 ±0.193	77.51 ±0.958	134.10 ±0.852
$AUC_{0-\infty}$	41.57 ±0.107	69.30±1.860	79.15 ±0.951	145.20 ±0.790
K_{el}	0.11 ±0.000	0.06 ±0.004	0.18 ±0.001	0.11 ±8.150
$T_{½}$ (h)	6.53 ±0.027	10.81 ±0.736	3.86 ±0.033	6.09 ±0.004

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