pH-Responsive Hydrogel of Poly(2-Hydroxyethyl Acrylate-Co-2-Acrylamido-2-Methyl-1-Propane Sulphonic Acid-Co-Ethylene Glycol Vinyl Ether): Synthesis, Diffusion Characteristics and Drug Delivery Applications

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Abstract

This study reports the preparation of pH-responsive hydrogels for the controlled release of the non-steroidal anti-inflammatory drug Tapentadol HCl (TPCL). The hydrogels were synthesized through cross-linking of 2-hydroxyethyl acrylate (HEA) and (1,1-Dimethyl-2-sulfoethyl)acrylamide, 2-Acrylamido-2-methylpropane sulfonic acid) (AMPS) with ethylene glycol vinyl ether (EGVE) using N,N'-methylenebis(acrylamide) (NN-MBA) via free radical polymerization.

To elucidate the characterization properties of the hydrogels, FTIR, DSC, XRD and SEM techniques were employed. Diffusion characteristics of hydrogels were evaluated by calculating network parameters. Dynamic swelling and drug release patterns of hydrogels were assessed in pH 1.2 and 7.4 phosphate buffer solutions, with results indicating slight enhanced swelling and drug release in pH 7.4 at 24 hours.

Keywords: pH sensitive hydrogel, Network parameters, Swelling kinetic parameters, Tapentadol HCl, Drug delivery.

Introduction

Hydrogels have significance in various therapeutic areas as drug carriers due to their biocompatibility, penetrability and physical properties. Controlled delivery of drugs and tissue technology are two of the most frequently utilized hydrogel applications.[20] The objective of controlled drug release is to administer medication at a predetermined time and to maintain the body's drug concentration at an optimal level. Hydrogels exhibit a smooth, rubbery surface when swollen, resembling natural tissue and are utilized as drug-carrying vehicles for controlled drug release applications.[29,31] Hydrogels' capacity to respond reversibly to pH, magnetic, light, electric and temperature renders them critical, particularly for specific biomedical applications.[4,21,28]

Among all the polymer frameworks mentioned above, pH-sensitive hydrogels are significant and respond to changes in the environment by altering their volume or shape.[23] They are employed to deliver therapeutic compounds to specific body sites.

Tapentadol HCl (TPCL) is a drug utilised to treat musculoskeletal pain.[12] The conventional oral dosage for musculoskeletal pain treatment involves a controlled-release schedule, with a maximum dose of 600 mg administered every 12 hours.[8] Alternatively, immediate-release tablets in 50, 75 and 100 mg increments may be employed at 4 to 6-hour intervals for pain control.[13] Despite its classification as an opioid analgesic, TPCL is utilized in managing severe pain conditions such as post-operative and cancer-related pain. Notably, TPCL demonstrates a comparatively lower potential for tolerance relative to other opioids, rendering it the preferred option for prolonged delivery formulations.[19] TPCL was chosen as a model drug to assess the proposed hydrogel's drug release characteristics.

According to previous literature, only a few hydrogels have been reported that combine EGVE with other natural polymers.[22] However, EGVE-based hydrogels alone, without combining any polymer, have not been documented in the literature. The present research aims to synthesize pH-responsive EGVE-AMPS-HEA (EGAH) hydrogels from ethylene glycol vinyl ether [EGVE], AMPS monomer and 2-hydroxyethyl acrylate (HEA). Ethylene glycol vinyl ether may function as a deactivating agent and possesses the capability to copolymerize with HEA. HEA contains both a terminal hydroxy group and polymerizable acrylic groups. 2-Acrylamido-2-methyl-1-propanesulfonic acid (AMPS) is a sulfonic acid acrylic monomer with hydrophilic properties.

AMPS exhibits an ionic character due to the sulfonic acid group, which is advantageous for hydrogel applications. The network structure of a hydrogel is developed through the cross-linking of polymer chains with N,N'-methylene bis acrylamide (NN-MBA) via free radical polymerization in the presence of APS, a free radical initiator.[1]

EGVE and AMPS possess hydrophilic groups, namely -OH and $-SO_3H$ respectively. These groups exhibit water absorption properties and are present in the hydrogel.[6,9] The synthesized poly(2-hydroxyethyl acrylate-co-2-acrylamido-2-methyl-1-propane sulfonic acid-co-ethylene glycol vinyl

ether) (EGAH) gels were characterized using FTIR, XRD, DSC and SEM techniques. Various network studies of EGAH gels, including volume fraction (ϕ) at swollen state, the average molecular weight between two adjacent crosslinks of the polymer chains (Mc), Flory χ parameter (χ), mesh size (ξ) and crosslink density (Ve), were evaluated. *In vitro* dissolution tests of TPCL from EGAH gels were conducted in buffer solutions at pH 1.2 and 7.4 at 37°±0.5°C. To investigate the TPCL release mechanism, swelling and drug release data were examined using empirical kinetic models such as the Higuchi model, zero and first-order kinetics and the Korsmeyer-Peppas model.

Material and Methods

Materials: HEA and EGVE were procured from BLD Pharm (India). AMPS and NN-MBA were procured from Tokyo Chemical Industry (TCI) Co. Ltd. APS and HCl were procured from Merck Limited (India), KH_2PO_4 was procured from SRL Chemicals (India) and a gift sample of Tapentadol HCl API was obtained from MSN laboratories located in Hyderabad.

Instrumentation: Fourier-transform infrared spectroscopy (FT-IR) studies were conducted to examine the tapentadol present in hydrogels. FT-IR spectra were analyzed using a Bruker (Spectrum-II model, Germany) for pure tapentadol, plain EGAH hydrogels and tapentadol-loaded hydrogels. The morphology and surface characteristics of hydrogels were examined using Scanning electron microscopy (SEM) (Make: TESCAN, MIRA model) operating at an acceleration voltage of 5-30 kV. EGAH hydrogel samples were coated with gold for 2 minutes to enhance conductivity subsequently mounted on a copper stub. Scanning electron microscope images were captured at various magnifications. The thermal stability was evaluated using differential scanning calorimetry (Make: New Age Instruments, DSC-60 model) for pure tapentadol, plain EGAH hydrogels and TPCL-loaded hydrogels.

Samples were analysed using a nitrogen gas flow of 50 mL/min from 20°C to 360°C at a scanning rate of 20°C/min. After encapsulation, X-ray diffraction studies were employed to evaluate the crystallinity of the TPCL drug. An X-ray diffractometer (Make: Bruker, D8-Advance model, Germany) was utilized to record XRD patterns for pure EGAH gels, TPCL-loaded EGAH gels and pure TPCL. At a temperature of 10°C, each sample was scanned with the 2θ angle adjusted to 60° to examine alterations in the crystalline structure.

Synthesis of EGAH hydrogels: EGAH hydrogels were synthesized by combining EGVE, AMPS, HEA, cross-linker (NN-MBA), using initiator (APS) according to the composition specified in table 1 through free radical polymerization. To achieve a homogeneous mixture, the reactants were continuously agitated for two hours at 25°C in a deoxygenated environment. The reaction mixture temperature was raised to start the free radical polymerization reaction, which was then allowed to run for three hours at 60°C to produce hydrogel networks. After the polymerization, the polymeric hydrogels cooled to room temperature before being sectioned into Petri discs. The synthesis process of EGAH hydrogels is illustrated in the scheme presented in figure 1. The hydrogel discs were immersed in double-distilled water for 48 hours, with frequent water changes to remove any residual reactants, EGVE and monomers. The swollen EGAH hydrogels were air-dried for 48 hours at ambient temperature, followed by an oven at 45°C to obtain consistent weights. The masses of the fresh, dried and swollen gels were recorded and corresponding gel images are shown in figure 2.

Swelling studies: Equilibrium swelling of EGAH gels in water was investigated (Table 1). Dynamic swelling studies (DSR) were performed in deionized water and various buffers at pH levels of 1.2 and 7.4 at 25°C. Predetermined quantities of dried gels were immersed in 50 mL of water/buffer. At regular intervals, the swollen gels were removed and surfaces were carefully blotted with tissue paper and their masses were measured using a balance (Sartorius). % DSR (% Dynamic swelling ratio) and % ESR (% Equilibrium swelling ratio) are calculated using the formulas given in the published sources.[16,17] The swelling kinetic characteristics and diffusion properties of EGAH were determined using the Korsmeyer-Peppas kinetic equation.[10]

Efficiency of encapsulation and drug incorporation: TPCL drug was incorporated into EGAH gels through the equilibrium swelling procedure[17]. Hydrogel samples, each weighing approximately 500 mg, were placed into beakers containing solutions of known drug concentrations. The drug entered the hydrogels after the EGAH gels swelled. Then these EGAH gels were carefully removed from the drug solution. Any residual drug was subsequently removed from the hydrogel's surface using the same drug solution. After filtering the remaining drug solution, an analysis was conducted at λ_{max}=275nm[5] using a UV spectrophotometer (UV-1800, Shimadzu, Japan).

After 48 hours of drying at room temperature, the TPCL-incorporated EGAH was then dried at 40±2°C in oven until their weight remained constant. Using an agate mortar, about 20 mg of dry drug-incorporated EGAH gels was crushed into powder before adding 50 mL of pH-7.4 buffer solution and stirring for 24 hours. The final solution was centrifugated and filtered via Whatmann filter paper.[30] The following formulas were used to calculate the percentage of TPCL drug incorporated in EGAH gels and the percentage of TPCL encapsulation efficiency, as in table 1.

$$\%\ \text{TPCL loading} = \left(\frac{\text{wt. of TPCL in EGAH}}{\text{wt. of EGAH hydrogel}}\right) \times 100 \quad (1)$$

$$\%\text{Encapsulation} = \frac{wt\ of\ TPCL\ in\ EGAH\ hydrogel}{wt\ of\ total\ TPCL}\ X\ 100 \quad (2)$$

EGAH gels network characterization study: Several network-related parameters were calculated for EGAH hydrogels as per literature[17,27] and are presented in table 2.

Drug Release and kinetics: EGAH gels were subjected to *in vitro* drug release experiments at 37 °C ± 0.5 °C in both pH 1.2 and pH 7.4 phosphate solutions. The tablet dissolution tester (Dissolution system, model 2500, DISTEK, USA) with eight baskets was utilized to conduct the dissolution experiment. Each TPCL-loaded hydrogel was weighed to approximately 200 mg and they were all added to a dissolution bowl (USP Apparatus 1 with 100 rpm) containing 600 mL of dissolution medium at 37 °C. Medium volume is maintained constant throughout the experiment by adding 10 mL of new buffer to each basket at regular intervals after withdrawing 10 mL of buffer medium using a syringe.

UV-Vis spectrophotometer at 275 nm was employed to quantify the released TPCL drug from hydrogels at different intervals. The drug release kinetics was determined using the zero-order equation, Higuchi's square-root equation and the Korsmeyer-Peppas equation[11,2] as tabulated in table 3 and table 4. The 'n' values were used to investigate the TPCL distribution mechanism. An n value < 0.45 shows Fickian diffusion; $0.45 \leq n \leq 0.89$ denotes non-Fickian diffusion and $n \geq 0.89$ indicates a case-II transport mechanism.[25]

Results and Discussion

FTIR studies for EGAH hydrogels: The materials used in EGAH preparation contain alkene (C=C) functional groups. Following free radical polymerization, no significant absorption bands were observed in the ranges of 3100-3000 cm^{-1} and 1680-1630 cm^{-1} in the resultant hydrogels, corresponding to C=C-H and aliphatic C=C stretching (Figure 3) respectively. Consequently, it was determined that hydrogels were formed with EGVE, HEA and AMPS with cross-linker NN-MBA through polymerization. Infrared spectroscopy data revealed that key absorption bands associated with the hydrogel and drug remained consistent in both pure EGAH hydrogels and drug-loaded EGAH hydrogels. This observation confirmed that the drug was physically entrapped within the hydrogel matrix without chemical interaction.

DSC studies of EGAH hydrogels: DSC thermograms of the TPCL drug, EGAH hydrogel and drug-loaded EGAH hydrogel are presented in figure 4A. The melting of TPCL is characterized by a sharp peak at 204.34°C, whereas the EGAH hydrogel demonstrates a broad peak in the range of approximately 280–310°C.

In the drug-loaded EGAH hydrogel, the original distinctive endotherm of the TPCL drug was not observed and the broadness of the hydrogel increased, further corroborating the incorporation of the drug. The TPCL drug appears to be molecularly dispersed within the EGAH hydrogel[3].

XRD studies for EGAH hydrogels: Figure 4B presents the X-ray diffractograms of the drug-loaded EGAH hydrogel, pure TPCL drug and the EGAH hydrogel. The crystalline nature of the TPCL drug is evidenced by the more intense peaks observed at 2θ of 15° to 30°. The absence of the characteristic band associated with the drug's crystalline nature in the drug-incorporated EGAH gel network indicates that the TPCL drug was molecularly dispersed throughout the EGAH gel network and no drug crystals were present in the drug-incorporated EGAH gels.

SEM studies for EGAH hydrogels: Figure 5 illustrates the SEM images of the hydrogels captured at different magnifications. The developed hydrogels exhibited a smooth surface with a light glassy finish, as demonstrated in the SEM images in fig. 5 (A and C). Fig. 5 (B and D) reveals the layered structure of the hydrogel. Due to their network spaces, biological molecules, water and other solvents can be more readily absorbed through the network.

Evaluation of EGAH Hydrogels' Network Properties: The network properties of EGAH hydrogels were investigated through modifications in the feed components, EGVE, AMPS and crosslinker. These parameters encompass polymer density (dp), volume fraction (ϕ), Flory-Huggins interaction parameter (χ), the average molecular weight of the chain polymers between two adjacent crosslinks (Mc), crosslinking density (Ve) and mesh size (ξ). The results for these network properties are presented in table 2.

Table 1
Data on EGAH formulations, swelling, drug loading and encapsulation

EGAH code	EGVE (mL)	AMPS (gm)	HEA (mL)	2% NN-MBA (mL)	10% APS (mL)	% ESR ± S.D	% DL ± S.D	% EE ± S.D
EGAH-1	0.5	0.50	1	1	1	2206 ± 0.3	24.20 ± 0.4	62 ± 1.0
EGAH-2	1.0	0.50	1	1	1	2436 ± 0.8	25.60 ± 0.3	65 ± 0.5
EGAH-3	1.5	0.50	1	1	1	2854 ± 0.5	27.54 ± 0.6	70 ± 0.2
EGAH-4	1.0	1.00	1	1	1	2721 ± 0.7	26.60 ± 1.2	68 ± 1.2
EGAH-5	1.0	0.25	1	1	1	2051 ± 1.1	23.35 ± 0.4	60 ± 0.7
EGAH-6	1.0	0.50	1	0.5	1	2660 ± 0.9	26.90 ± 0.7	71 ± 1.3
EGAH-7	1.0	0.50	1	1.5	1	1814 ± 0.4	23.02 ± 0.5	59 ± 0.5

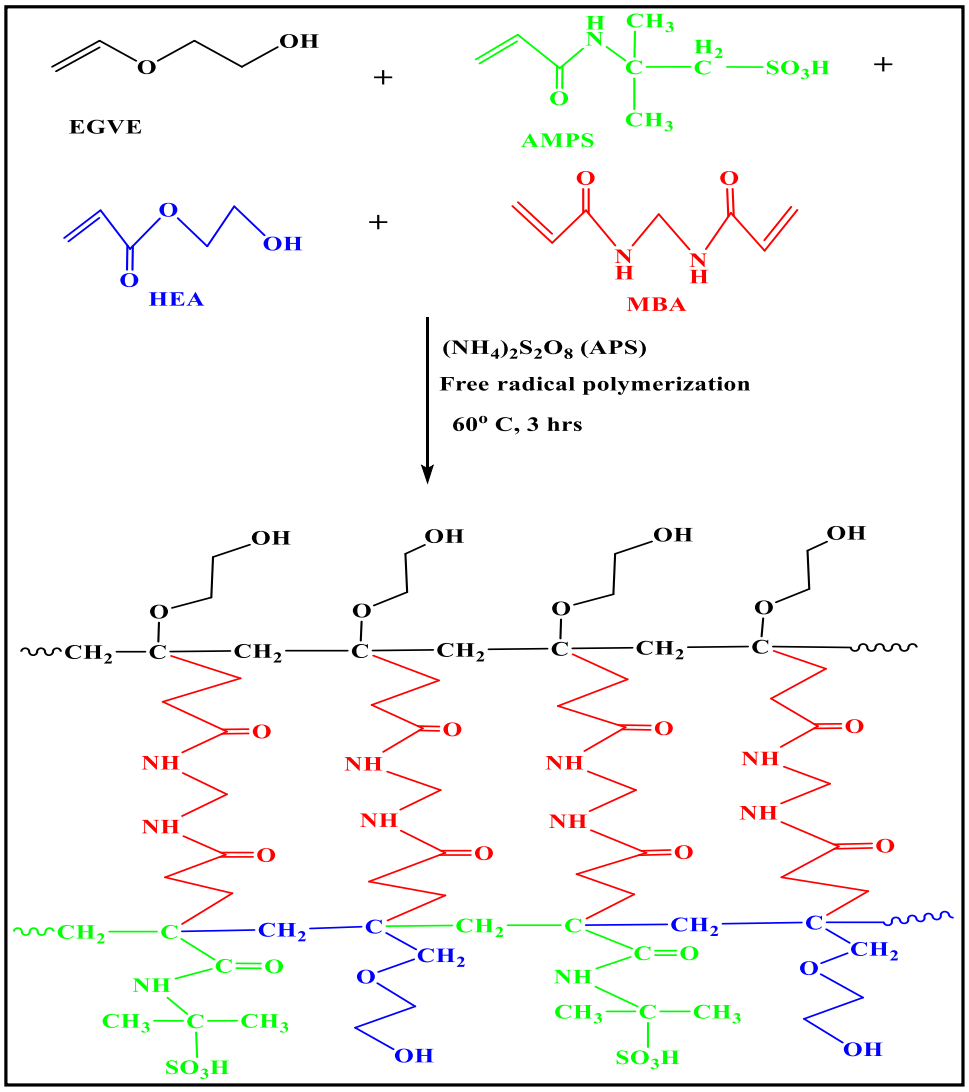

Figure 1: A conceptual illustration of EGAH formation

Table 2
The EGAH hydrogels' network parameters

S.N.	Volume/ Weight	Density (dp) (g/Cm^3)	Equilibrium swelling (Q_e)	Volume fraction (ϕ)	Flory – Huggins interaction parameter (χ)	Mol. wt. adjacent two cross-links (Mc) (g/mol)	Cross-link density (V_e) (mol/cm^3) ×10^{-7}	Mesh size ξ (nm)
Impact of Cross linker [NN-MBA] (2%) (mL)								
1	0.5	1.3670	26.60	0.0268	0.5089	13148982	1.396	859.69
2	1.0	1.2881	24.36	0.0309	0.5103	6570141	1.9605	579.40
3	1.5	1.2066	18.14	0.0437	0.5146	1764376	6.8384	267.48
Impact of AMPS monomer (g)								
4	0.25	0.9327	20.51	0.0497	0.5166	942850	9.8927	187.37
5	0.5	1.2881	24.36	0.0309	0.5103	6570141	1.9605	579.40
6	1.0	1.2180	27.21	0.0293	0.5098	8828426	1.3796	683.57
Impact of EGVE (mL)								
7	0.5	1.4268	22.06	0.0308	0.5103	7165909	1.9911	605.69
8	1.0	1.2881	24.36	0.0309	0.5103	6570141	1.9605	579.40
9	1.5	1.2013	28.54	0.0283	0.5094	8233676	1.459	667.40

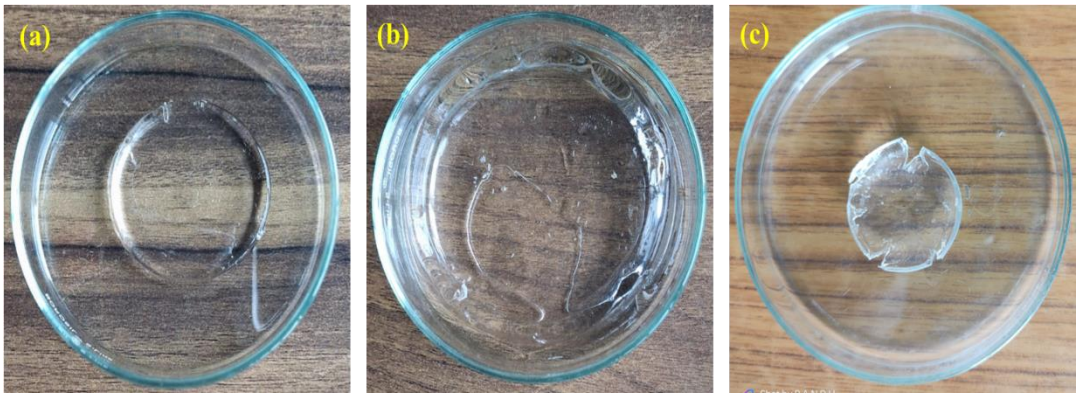

Figure 2: EGAH hydrogels images (a) fresh EGAH hydrogel (b) swollen EGAH hydrogel (c) dried EGAH hydrogel

Table 3
TPCL release kinetics parameters in pH-1.2 dissolution medium at 37 °C

Batch codes	Zero-order (M/min)		First-order (min^{-1})		Higuchi Square-root		Korsmeyer-Peppas		
	K_O	R^2	K_1	R^2	K_h	R^2	n	Kp	R^2
F1	15.8430	0.9696	0.1037	0.8793	1.5186	0.9891	0.5354	0.1961	0.9831
F2	22.4430	0.7956	0.1329	0.6730	2.7201	0.8918	0.5426	0.1005	0.9930
F3	28.6430	0.8352	0.5290	0.7479	12.0900	0.9219	0.5034	0.5114	0.9774
F4	26.2830	0.9003	0.5299	0.8773	5.2725	0.9643	0.5837	0.5040	0.9715
F5	9.4557	0.9160	0.4632	0.8165	13.3240	0.9754	0.6095	0.4202	0.9809
F6	31.3300	0.7943	0.5402	0.7272	10.0990	0.8904	0.5524	0.5214	0.9458
F7	4.0913	0.8922	0.4902	0.7703	23.8750	0.9607	0.6011	0.4464	0.9949

Table 4
TPCL release kinetics parameters in pH-7.4 dissolution medium at 37 °C

Batch codes	Zero-order (M/min)		First-order (min^{-1})		Higuchi Square-root		Korsmeyer-Peppas		
	K_O	R^2	K_1	R^2	K_h	R^2	n	Kp	R^2
F1	16.3043	0.7806	0.0875	0.6731	3.1328	0.8805	0.6708	0.0456	0.9722
F2	21.8000	0.8208	0.1409	0.8060	0.4737	0.9116	0.5918	0.1031	0.9705
F3	24.7830	0.7869	0.1518	0.7634	1.1162	0.9508	0.5589	0.1129	0.9964
F4	23.7430	0.8052	0.1430	0.7104	19.9380	0.9552	0.5480	0.1159	0.9675
F5	26.0170	0.8997	0.1590	0.7914	6.1930	0.9620	0.5701	0.1401	0.9759
F6	26.4170	0.8010	0.1575	0.7105	1.9351	0.8961	0.5597	0.1310	0.9617
F7	18.6480	0.8260	0.1129	0.7138	3.9883	0.9149	0.6525	0.0783	0.9684

Table 5
Results of dynamic swelling study for hydrogels in deionized water

Formulations	Log k	k	n	R^2
EGAH-1	2.1985	0.3421	0.5635	0.9860
EGAH-2	2.2876	0.3593	0.5413	0.9840
EGAH-3	2.3439	0.3699	0.5490	0.9886
EGAH-4	2.2950	0.3607	0.5651	0.9844
EGAH-5	2.2921	0.3602	0.4917	0.9880
EGAH-6	2.3663	0.3740	0.5337	0.9898
EGAH-7	2.2738	0.3567	0.5239	0.9880

Cross-linker [NN-MBA] impact of on network properties: Formation of EGAH gels is significantly influenced by crosslinkers with regard to their concentration as well as their impact on the hydrogel's network structure and functionality. An increase in NN-MBA leads to higher crosslinking density (Ve), reduced mesh size (ξ) and lower molecular weight between cross-links (Mc). This phenomenon is likely attributable to the reduction in pore diameters within the hydrogel network and an increased number of crosslinking connections between polymer chains.[7] Moreover, volume fraction (ϕ) of the EGAH increases with higher NN-MBA concentration. The increase in volume fraction is related to a reduction in equilibrium swelling (from 26.60 to 18.14) as the crosslinker concentration increases. Furthermore, the polymer-solvent interaction parameter (χ) remains approximately 0.51 across all crosslinker concentrations.

AMPS impact on network properties: Hydrogels have been synthesized with varying concentrations of AMPS while maintaining constant levels of all other components to investigate the influence of AMPS on network formation. As the AMPS quantity increases, the cross-link density (**V_e**) decreases. Pore size (ξ) and molecular weight between adjacent cross-links (Mc) values exactly show an opposite trend to the cross-link density. Increasing the AMPS leads to electrostatic repulsive forces and a few cross-links are present per unit volume of hydrogel and the pore size increases.

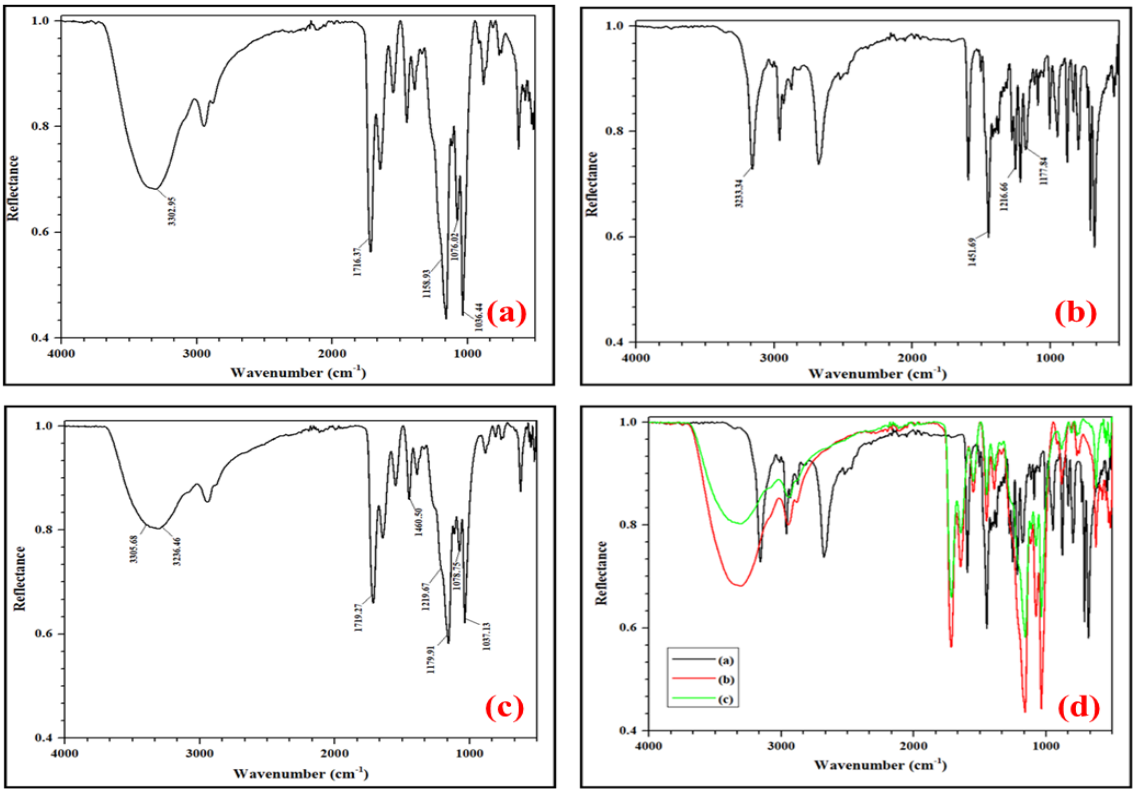

Figure 3: FTIR spectra of (a) TPCL drug, (b) EGAH hydrogel, (c) TPCL-loaded EGAH hydrogel. (d) Overlay IR spectra of (a) EGAH hydrogel, (b) TPCL drug, (c) Drug-loaded EGAH hydrogel

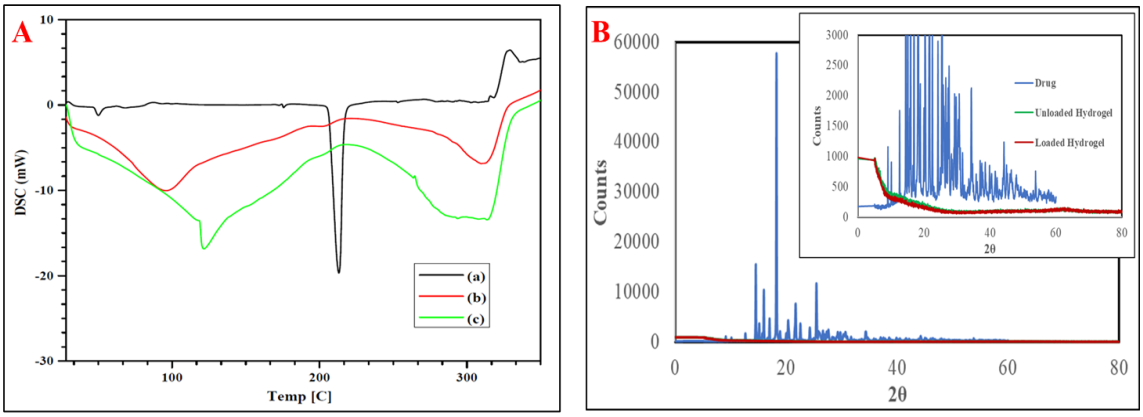

Figure 4: A) DSC thermograms of (a) TPCL drug, (b) EGAH hydrogel and (c) drug-loaded EGAH hydrogel and B) XRD of drug, unloaded hydrogel and drug loaded hydrogel

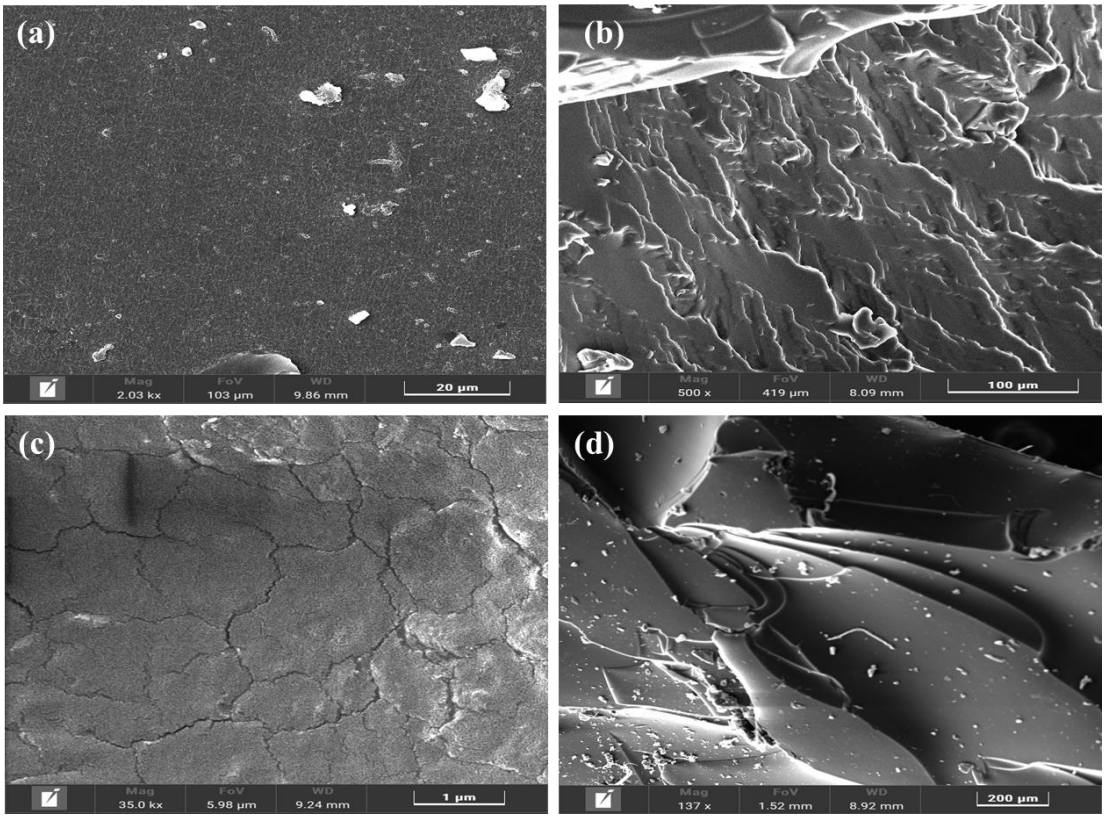

Figure 5: SEM images (a) surface (b) cross section for placebo EGAH hydrogel and (c) surface (d) cross section for drug-loaded EGAH hydrogel

EGVE impact on network properties: The impact of EGVE on network properties was studied by increasing its volume from 0.5 mL to 1.5 mL. On initially increasing the EGVE, slight decrease in cross link density (**V_e**) was observed. Mesh size (ξ) and average molecular weight between crosslinks (Mc) decrease and increase. Initially, EGVE slightly reduces crosslink density and disrupts efficient network formation, leading to decreased mesh size (ξ) and average molecular weight between crosslinks (Mc). However, EGVE acts as a flexible spacer at higher concentrations, increasing Mc and ξ by expanding the network and reducing effective crosslinking.

Swelling Studies of EGAH Hydrogels: In hydrogel drug delivery applications, swelling studies constitute the most critical property.[26] Various formulations of EGAH gels were synthesized by varying the quantities of HEA, AMPS, EGVE, NN-MBA and APS and dynamic swelling parameters were evaluated using deionized water. The kinetic swelling parameters were determined and presented in table 5 based on the dynamic swelling results.

pH impact on equilibrium swelling and dynamic studies: Swelling studies (Figure 6a and Figure 6b) of EGAH-5, EGAH-2 and EGAH-4 hydrogels, which were synthesized by increasing the AMPS quantity to 1.0 g from 0.25 g while maintaining the other conditions same, were conducted to evaluate the influence of feed composition of monomer AMPS. The Q_e of EGAH gels increased from 19.5 to 24.6 g/g in pH-1.2 and 20.0 to 25.2 g/g in pH-7.4 respectively, as the feed AMPS concentration increased during the 48-hour dynamic and equilibrium experiments. EGAH-5, EGAH-2 and EGAH-4 hydrogels exhibited a higher swelling in pH-7.4 media. This may be due to AMPS's polar nature, function as an organic acid and ability to dissociate to form free sulfonate ions[33]. The presence of free ions results in an osmotic pressure differential between the gel and solvent phases[18].

Cross-linker impact on equilibrium swelling and dynamic studies: Hydrogel synthesis requires the presence of crosslinkers which are molecules with two or more sites of reactions that allow bridges to be formed between chains. In order to evaluate the influence of the crosslinker on the swelling behaviour, the crosslinker volume (2% MBA) was raised from 0.5 to 1.5 mL (Figure 6c). The increase in crosslinker volume decreases the equilibrium swelling ratio (26.27–20.23 g/g). The EGAH-6 hydrogels exhibit the highest dynamic swelling ratio of 2627% at low crosslinker concentrations. The increased cross-linking density reduces the hydrogels' mesh size, resulting in a more complex and rigid network structure that limits the absorption of solvent molecules[32].

EGVE impact on equilibrium swelling and dynamic studies: The volume of EGVE in the polymerization mixture was increased from 0.5 mL to 1.5 mL while maintaining constant levels of other reaction parameters. EGAH-1 with a lower volume (0.5 mL) has a lower swelling ratio of 21.92 g/g and EGAH-3 with a higher volume (1.5 mL) has a higher

swelling ratio of 28.22 g/g and EGAH with 1.0 mL shows between EGAH 1 and EGAH 3 (Figure 6d).

Efficiency of encapsulation and drug loading: Table 1 presents the percentage encapsulation efficiency (% EE) and percent drug loading (% DL) of various EGAH hydrogels. Multiple factors, including the degree of crosslinking, the drug's nature and the monomers, influence the % EE and % DL. For EGAH-6, EGAH-2 and EGAH-7, the % EE decreased (71 to 59) as the crosslinker (NN-MBA) concentration increased. An increase in crosslinking density results in a downward trend in % EE, rendering the hydrogel network more rigid and reducing the available free space. The % EE of TPCL was observed to increase 60, 65 and 68 for formulations EGAH-5, EGAH-2 and EGAH-4 corresponding to alterations in the monomer (AMPS) concentration.

The % EE was recorded as 62, 65 and 70 for EGVE volumes of 0.5 mL (EGAH-1), 1.0 mL (EGAH-2) and 1.5 mL (EGAH-3) respectively. It could be due to the swelling properties of EGAH hydrogels. For EGAH-6, EGAH-2 and EGAH-7, the % DL decreased (26.9 to 23.0) as the crosslinker (NN-MBA) concentration increased.

Studies of drug release of EGAH hydrogels: This study investigates how pH and crosslinker density influence the release of TPCL from EGAH gels.

Impact of pH: Figures 7(a) and 7(b) graphically depict the low pH response behaviour of EGAH gels. The percentage of TPCL drug release from EGAH-2, EGAH-4 and EGAH-5 hydrogels, which were developed by varying the monomer (AMPS) concentration, was approximately 90%, 94% and 83% respectively, in pH-1.2 and approximately 93%, 96% and 88%, in pH-7.4 dissolution mediums respectively over a 24-hour period. The EGAH gels exhibited a higher quantity of TPCL released in pH-7.4 media compared to pH-1.2 media. These findings may be attributed to AMPS being a strong organic acid with high polarity[14] and possessing the ability to dissociate to form free sulfonate ions. This results in an increase in absorption of solution at pH-7.4 through enhancement of the hydrogel's free space.[15]

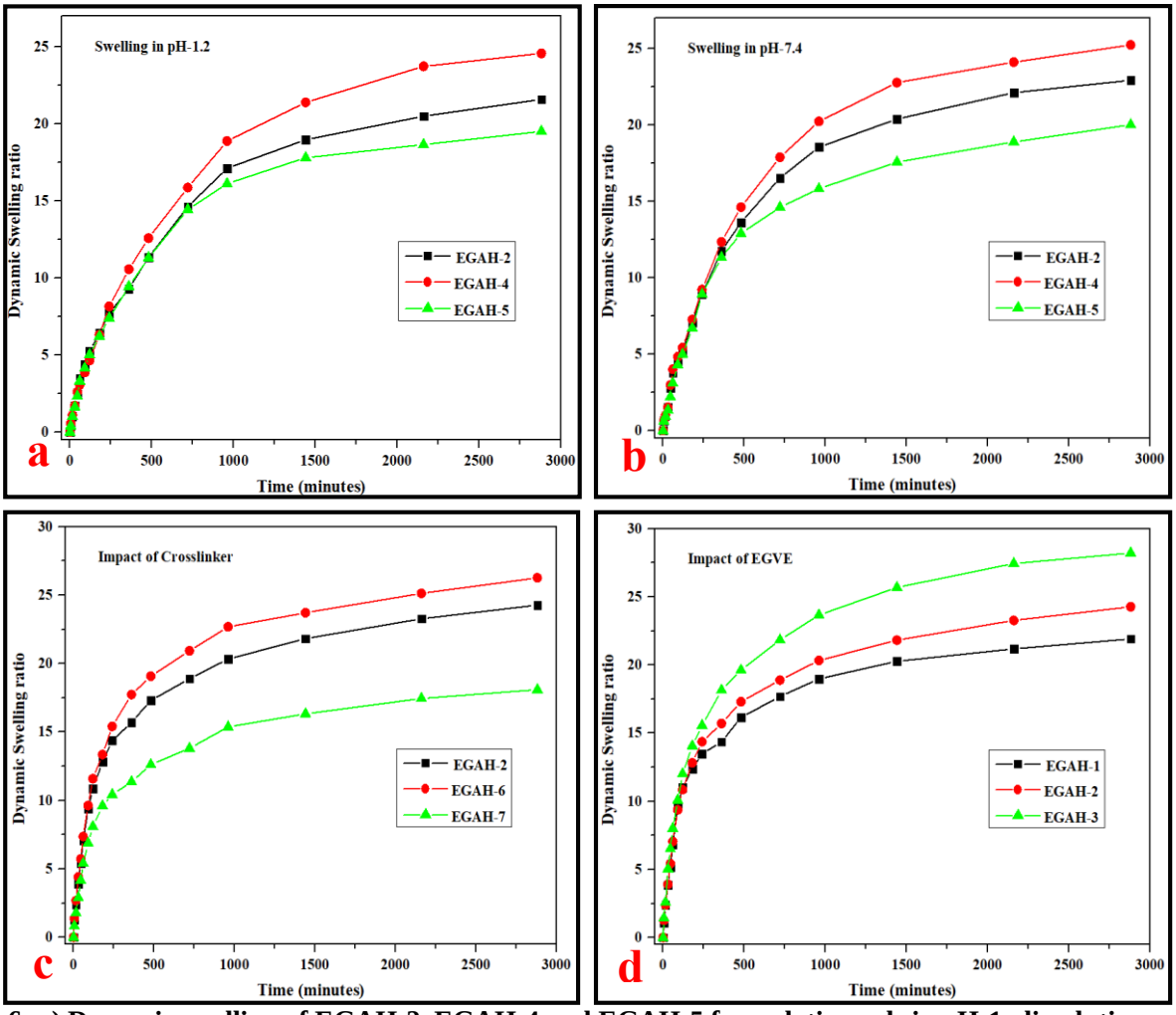

Figure 6: a) Dynamic swelling of EGAH-2, EGAH-4 and EGAH-5 formulation gels in pH-1. dissolution medium. b) Dynamic swelling of EGAH-2, EGAH-4 and EGAH-5 formulation gels in pH-7.4 dissolution medium c) Dynamic swelling of EGAH-2, EGAH-6 and EGAH-7 formulation gels in water. d) Dynamic swelling of EGAH-1, EGAH-2 and EGAH-3 formulation gels in water

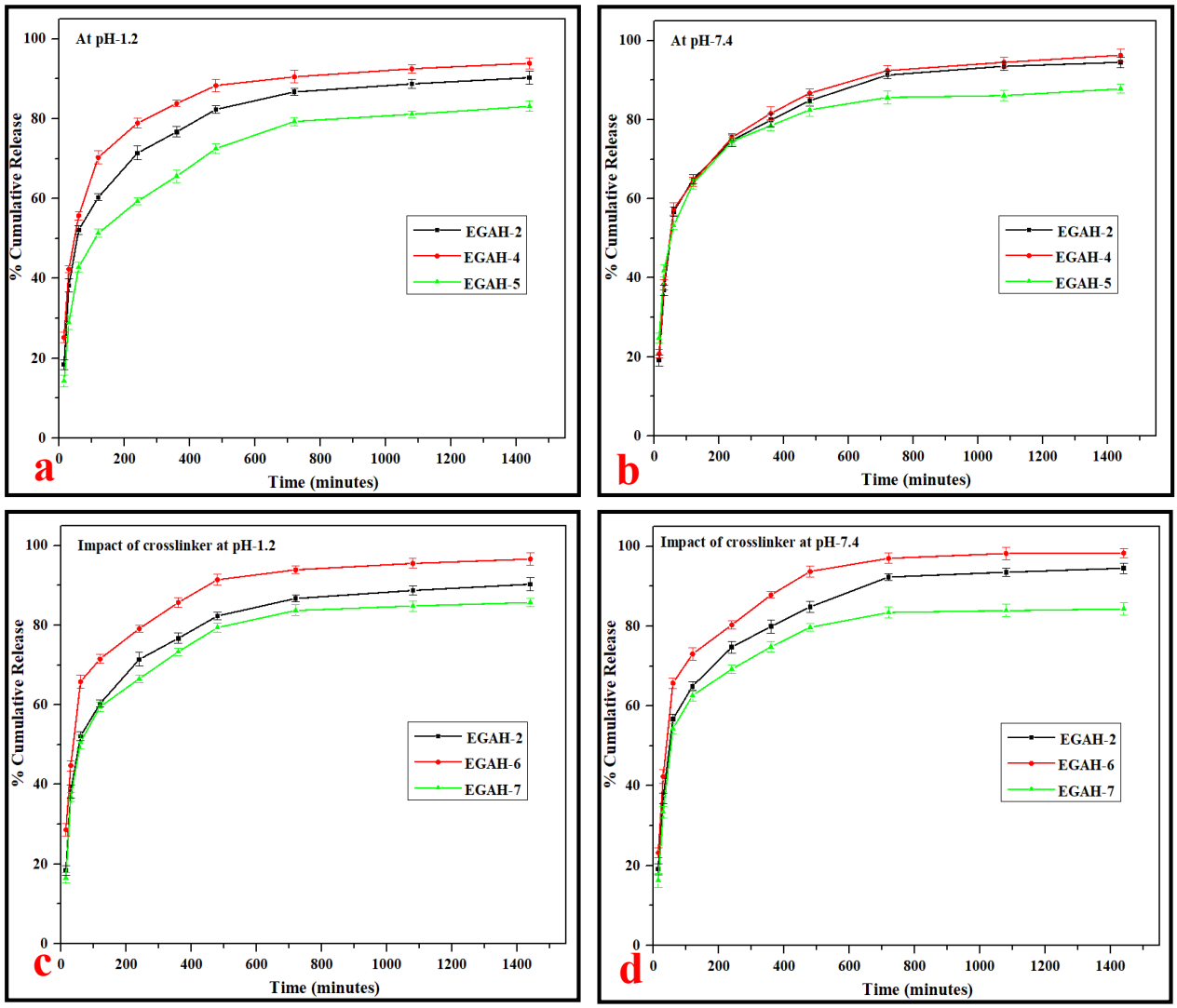

Figure 7: a) and b) Cumulative release of TPCL from EGAH-2, EGAH-4 and EGAH-5 gels in pH-1.2 and pH-7.4 dissolution medium at 37 °C. c) and d) Cumulative release studies of TPCL from EGAH-2, EGAH-6 and EGAH-7 gels in pH-1.2 and pH-7.4 dissolution medium at 37 °C

Impact of NN-MBA (cross linker): The influence of crosslinking of EGAH on TPCL *in vitro* release was studied by altering the NN-MBA concentration and the resulting graphs are presented in figures 7(c) and 7(d). In comparison to the EGAH-2 (1.0 mL) and EGAH-7 (1.5 mL) hydrogels with higher crosslinker concentrations, the EGAH-6 formulation, which has a lower crosslinker concentration (0.5 mL), exhibited enhanced drug release[24]. This phenomenon can be attributed to the low crosslinker density and loose polymer network, which facilitate more rapid diffusion of drug molecules. The EGAH-7 hydrogels demonstrate a lower cumulative release percentage due to their higher crosslinker density. EGAH-2 hydrogels exhibited moderate release. It could be associated with the higher number of crosslinks in the EGAH networks, resulting in smaller pore size within the network polymer and hence, slower diffusion of TPCL molecules[14].

Kinetics analysis for drug release: The data obtained by fitting the results with different kinetic models are presented in table 3 and table 4. Regression coefficient (R^2) values were determined for different proportions of EGVE, AMPS and NN-MBA based on the results of all kinetic models. It was determined that the Koresmeyer-Peppas model with the highest value best fits the R^2 values. The diffusion exponent (n) values in pH-1.2 and pH-7.4 media for EGAH hydrogels were calculated using the Koresmeyer-Peppas equation. The values of n were found to range from 0.5034 to 0.6095 in pH-1.2 media and from 0.5480 to 0.6708 in pH-7.4 medium. The observation that n values are $0.5 < 1$ in both basic and acidic media indicates that the TPCL released from EGAH gels follows a non-Fickian diffusion mechanism, in which the TPCL is released simultaneously by polymer chain relaxation and diffusion.

Conclusion

In this study, a novel pH-responsive polymeric hydrogel was synthesized from ethyl vinyl ether (EGVE), 2-acrylamido-2-methylpropane sulfonic acid (AMPS) and hydroxyethyl acrylate (HEA) through cross-linking with N,N'-

methylenebisacrylamide (NN-MBA) using ammonium persulfate (APS) as an initiator via free radical polymerization. Fourier-transform infrared spectroscopy (FTIR), Scanning electron microscopy (SEM), Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) were employed to characterize the structural, morphological, thermal and chemical interaction properties of the EGAH hydrogels.

Seven distinct formulations were developed by varying the concentrations of crosslinker, EGVE and monomers. The non-steroidal anti-inflammatory drug TPCL was effectively incorporated into the EGAH-6 formulation, achieving an optimal encapsulation efficiency of 71%. The EGAH-6 formulation, containing a lower crosslinker content, exhibited the highest drug release rate of 98%. *In vitro* release studies demonstrated that the maximum percentage (98%) of TPCL drug was released from formulation EGAH-6 over 24 hours in a pH 7.4 buffer at 37°C.

Kinetic modeling revealed that drug release from EGAH hydrogels best fit the Korsmeyer-Peppas equation, exhibiting the highest R^2 values. The release mechanism of TPCL from EGAH gels was determined to follow non-Fickian diffusion. Consequently, these hydrogels demonstrate potential for various formulations as controlled drug delivery systems.

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