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Development and evaluation of gelatin/polyacrylamide/carboxymethyl tamarind kernel gum hydrogel for delivery of ampicillin sodium

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Gelatin-based hydrogels, despite their excellent biocompatibility, face limitations in their utility for targeted drug release due to low mechanical strength. Thus, this research is directed towards the fabrication of pH-responsive hydrogels based on gelatin, polyacrylamide (PAM) and carboxymethyl tamarind kernel gum (CMTKG), followed by their loading with ampicillin sodium drug. The hydrogel has been optimized by varying crosslinker, and initiator amounts to observe their effect on swelling. The swelling is increased with an increase ininitiator, reaching a maximum of 1371% at pH 7.4 and 1218% at pH 1.2. The hydrogels are analyzed through Scanning Electron Microscopy (SEM), Powder X-ray Diffraction (PXRD), and Attenuated Total Reflection-Fourier Transform Infrared Spectroscopy (ATR-FTIR) techniques. Various parameters such as drug loading, porosity, and gel fraction are evaluated. The *in vitro* drug release is evaluated in both pH 1.2 and 7.4 buffer, with higher drug release (63.3%) observed under alkaline pH. The kinetic modeling data validates the Korsmeyer-Peppas model (R^2= 0.9871) to be the suitable model for the explanation of the drug release mechanism, suggesting the Fickian diffusion (n<0.5, pH 1.2) and non-Fickian diffusion (n>0.5, pH 7.4). Therefore, the Gelatin/PAM/CMTKG hydrogel shows potential for targeted release of ampicillin sodium in response to varying pH.

Keywords: Biopolymer, Drug Release, Gelatin, Hydrogel, Kinetic modelling

Introduction

Hydrogel is a three-dimensional framework composed of hydrophilic polymer chains, physically or chemically crosslinked. The hydrophilic groups such as -COOH, -SO_3H, -OH and -$CONH_2$ etc., facilitate the absorption of fluid into the matrix[1]. The surface tension and capillary forces facilitate the swelling characteristics of the hydrogel. Hydrogels are renowned for their biocompatibility and environmental friendliness and are widely used in industrial, pharmaceutical, and agricultural fields[2]. Various synthetic and natural polymers, including polyacrylamide[3], collagen[4], gelatin[5–7], hyaluronic acid etc., have been employed to fabricate hydrogel networks[8]. The cross-linking within the hydrogel structure serves as a crucial factor in preventing their dissolution in aqueous environments[9]. These polymeric networks exhibit a distinctive characteristic similar to living tissues, depicted by their soft and rubbery nature. This feature renders them well-suited for various biomedical applications. Hydrogels, also known as intelligent or smart hydrogels, exhibit responsiveness to different chemical and physical stimuli, such as magnetic field, pH, ionic strength, etc.[10].

In biomedical applications, pH plays a very crucial role in the design and implementation of targeted drug delivery systems. The pH-responsive hydrogels are categorized as either anionic or cationic based on their response to changes in pH. Anionic hydrogels exhibit higher swelling in alkaline pH as they undergo ionization at a pH greater than their pKa. However, cationic hydrogels show a greater swelling in acidic pH, as it ionizes at a pH lower than their pKa[10]. Polyacrylamide (PAM), is a non-toxic, pH-sensitive polymer known for its excellent biocompatibility [11,12]. It contains the –$CONH_2$ group, which fosters swelling and drug-release behavior at various pH conditions[13]. Nowadays, PAM have been combined with biopolymers such as chitosan[12], carboxymethyl cellulose[11], carboxymethyl tamarind kernel gum[14] etc. to formulate hybrid hydrogels with improved biocompatibility, swelling and mechanical properties.

Tamarind Kernel Gum (TKG) is an economical polysaccharide, procured from the Tamarindus indica L. plant seeds. It's carboxymethylated derivative, carboxymethyl tamarind kernel gum (CMTKG) is a biopolymer with molar proportions of xylose, glucose and galactose as 1:3:2(Ref.14). It is an anionic polymer with high swelling capacity and pH-dependent release properties, making it suitable for drug delivery applications[15].

Gelatin is another biopolymer, derived from the partial hydrolysis of collagen, obtained from animal tissues i.e., skin, ligament, bones, blood vessels, and heart. Its primary components include glycine, proline, and 4-hydroxyproline[16]. Gelatin emerges as a remarkable preference for drug delivery applications owing to its non-toxic nature, excellent gel-forming ability, good biodegradability and highly biocompatible[17].

Ampicillin sodium, a model drug, is a β-lactam antibiotic, that belongs to the class of penicillin. It is widely employed in addressing infections arising from gram-negative and gram-positive bacteria, in both humans and animals. This versatile drug is efficient in treating a range of infections such as gastrointestinal, meningitis, and urinary tract infections[18,19].

Numerous studies have explored hydrogel-based delivery systems for hydrophilic drugs. However, these approaches often encounter limitations such as challenges in achieving release at targeted pH in the gastrointestinal tract and having low mechanical strength, leading to burst drug release. For instance, gelatin/ß-cyclodextrin/dextran hydrogels were investigated for the release of 5-fluorouracil, but it exhibited approximately 50% drug release at *p*H 1.2 and around 80% at pH 7.4(Ref.20). Hence to minimize the release at untargeted sites, this study explored the fabrication of a series of gelatin, PAM and CMTKG based hydrogels for pH-dependent release of model drug ampicillin sodium. The novelty of this work is that the Gelatin/PAM/CMTKG hydrogel has been fabricated and tailored for the first time for the controlled release of ampicillin sodium. The synthesized hydrogels were analyzed by PXRD, ATR-FTIR, and SEM techniques. In addition, the impact of initiator, and cross-linker amount on the swelling of synthesized hydrogels was studied in pH 1.2 and 7.4 buffer. The evaluation of the drug release kinetics was done with different mathematical models comprising Hixson-Crowell, Korsmeyer-Peppas, Higuchi, Zero order and First order.

Experimental Section

Materials

Gelatin (Fischer Scientific), Potassium persulphate [KPS, MW=270.30 g/mol, (Fischer Scientific, Mumbai, India)], Acrylamide [AM, MW=71.08 g/mol, (CDH, New Delhi, India)] and N, N′-methylene-bis(acrylamide) [MBA, MW=154.17 g/mol (Merck, Germany)] were used as provided. CMTKG [0.20º substitution, MW=9.14 $\times 10^5$ g/mol] was generously given by Hindustan Gum and Chemicals Ltd., Haryana, India and Ampicillin sodium [MW=371.39 g/mol], was gifted by Unicure India Pvt Ltd, Noida, India.

Synthesis of Gelatin/PAM/CMTKG hydrogels

The series of Gelatin/PAM/CMTKG hydrogels (A-1 to A-9) were fabricated with different amounts of initiator KPS (14-38 mg), and crosslinker MBA (10-30 mg), as detailed in Table 1. A required amount of CMTKG, AM and gelatin were dissolved in distilled water while continuously stirring for 1 h. Besides this, KPS and MBA were added to the solution and stirred for an hour. Then poured into the test tubes and heated for 1h in a water bath at 60°C. The synthesized hydrogels were removed from the test tube, sliced, and oven-dried at 60°C. Fig. 1 shows the illustration of the fabrication of hydrogel[21].

Table 1 — Composition of Gelatin/PAM/CMTKG hydrogels

Sample code	CMTKG (g)	AM (g)	MBA (mg)	KPS (mg)	Gelatin (g)
A-1	0.2	0.5	10	32	0.5
A-2	0.2	0.5	15	32	0.5
A-3	0.2	0.5	20	32	0.5
A-4	0.2	0.5	25	32	0.5
A-5	0.2	0.5	30	32	0.5
A-6	0.2	0.5	10	14	0.5
A-7	0.2	0.5	10	20	0.5
A-8	0.2	0.5	10	26	0.5
A-9	0.2	0.5	10	38	0.5

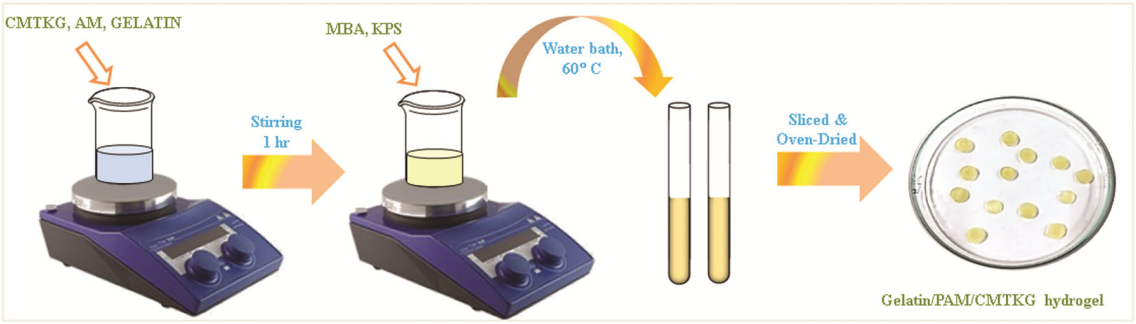


Fig. 1 — Synthesis of Gelatin/PAM/CMTKG hydrogel

Swelling studies

The swelling behavior of fabricated hydrogels was assessed in pH 7.4 and 1.2 buffer over 24 h. Dried hydrogel discs were accurately weighed (W_d) and subsequently immersed in the appropriate solutions. After 1 h, the hydrogel disc was extracted, gently blotted with filter paper, weighed (W_S), and subsequently re-immersed in the solution[22]. Swelling was conducted in triplicate and assessed using the given equation[23].

$$\text{Equilibrium Swelling (\%)} = \frac{(W_s - W_d)}{W_d} \times 100 \quad (1)$$

Gel fraction

To calculate the gel fraction (crosslinked portion) of all synthesized hydrogels, the weighed hydrogel disc (W_i) was dipped in distilled water for 24 h and then taken out, dried in an oven at 60°C and weighed (W_e) again. The gel fraction (%) was calculated using the following equation[24].

$$\text{Gel fraction (\%)} = \frac{W_e}{W_i} \times 100 \quad (2)$$

Porosity

The porosity of the fabricated hydrogels was evaluated using hexane as the solvent. The dried hydrogel discs (M_i) were dipped in 10 mL of hexane for 2 h. After removing the hydrogel disc from the hexane and wiping it with filter paper, the final weight (M_f) was recorded. The porosity of the hydrogel disc was calculated using the following equation:

$$\text{Porosity (\%)} = \frac{M_f - M_i}{\rho V} \times 10 \quad (3)$$

Here, ρ and V represent the density of hexane (0.659 g/mL), and volume of the hydrogel[25,26].

Drug loading and drug entrapment efficiency

The drug loading was carried out for formulation (A-1) as it exhibited the highest swelling among all the hydrogels. Ampicillin sodium-loaded Gelatin/ PAM/CMTKG hydrogel was formulated as mentioned in the synthesis procedure with the minor variation that drug ampicillin sodium (35 mg) was also added during the addition of MBA and KPS in the solution and the rest process remains the same. The calculation of drug loading and drug entrapment efficiency was performed for ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel. A hydrogel was immersed in a pH 7.4 buffer for 24 h, then the 3 ml solution was withdrawn, and the absorbance at λ_{max} 203 nm was measured through a UV-vis spectrophotometer (Model: Cary 300 UV–Vis). The amount of drug loaded was calculated following the Beer-Lambert law, using the calibration curve drawn with the known concentration of the drug solution. The equations employed for the determination of drug loading (DL%) and drug encapsulation efficiency (DEE%) were as follows[27,28]

$$DL(\%) = \frac{Amount\ of\ drug\ loaded\ in\ hydrogel}{Weight\ of\ hydrogel} \times 100 \quad (4)$$

$$DEE(\%) = \frac{Amount\ of\ drug\ loaded\ in\ hydrogel}{Initial\ amount\ of\ drug\ added\ in\ hydrogel} \times 100 \quad (5)$$

***In vitro* ampicillin sodium release**

The *in vitro* studyfor ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel was conducted in an orbital incubator shaker under pH 1.2 and pH 7.4buffer solutions. A precise quantity (0.1 g) of the ampicillin sodium-loaded hydrogel disc was immersed in 100 mL of pH 7.4 and 1.2solutions at 37 °C. At the interval of1 hour, 3 mL of the solution was taken out, and an equal volume of fresh buffer was added to it. Subsequently, the absorbance of the solution was measured employing a UV spectrophotometer (Model: Cary 300 UV-Vis) at the λ_{max} 203 nm. The drug amount was determined through the calibration curve drawn with the known concentration of the drug solution[29].

Kinetic modeling of ampicillin sodium

Various mathematical models have been employed to analyze drug release mechanisms, including the Korsmeyer-Peppas, Hixson-Crowell, Higuchi, Zero-order and First-order models. The regression coefficient (R^2) values were correlated and the model with an R^2 value closest to 1 was considered the most fitted one[30].

Characterization

Powder X-ray diffraction (PXRD) was performed for ampicillin sodium, Gelatin/PAM/CMTKG and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel, using a high-resolution Bruker D8 diffractometer at 2θ range of 10-70° with CuKα radiation. Attenuated Total Reflection-Fourier Transform Infrared Spectroscopy (ATR-FTIR) spectra were recorded for MBA, Gelatin/PAM/CMTKG hydrogel and ampicillin sodium-loaded Gelatin/ PAM/CMTKG hydrogel within a wavenumber range of 4000-450 cm^{-1}, using the ATR-FTIR spectrophotometer (Model: Nicolet iS50 FTIR Tri-detector). Scanning Electron Microscopy (SEM) images of Gelatin/ PAM/CMTKG and ampicillin sodium-loaded Gelatin/ PAM/CMTKG hydrogels were captured using an SEM (JEOL Japan Mode: JSM 6610LV).

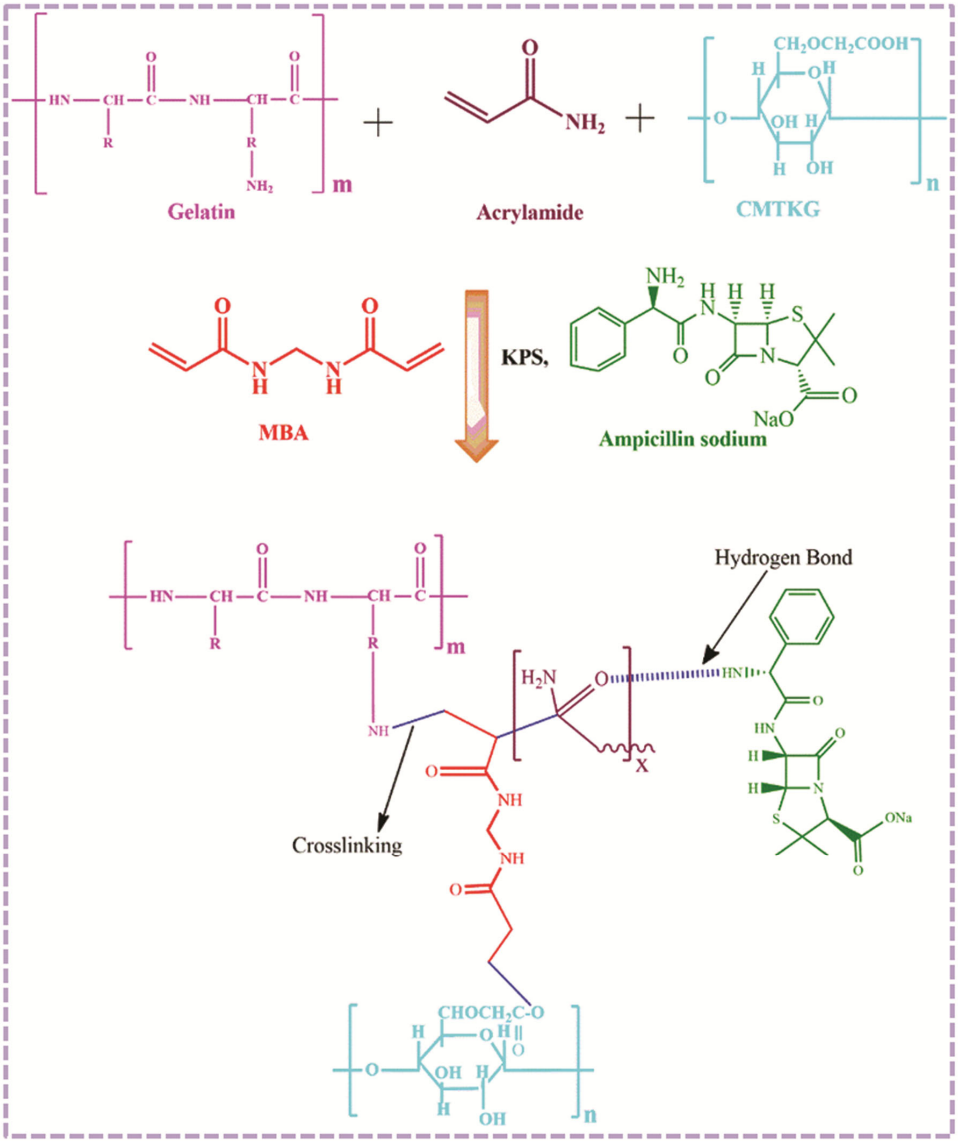
Statistical analysis

Each experiment was carried out thrice (n=3), and the results are reported as mean ± standard deviation. Statistical analysis was performed using ANOVA (One-way analysis of variance), with significance set at $p < 0.05$ for all studies.

Results and Discussion

Mechanism of Gelatin/PAM/CMTKG hydrogels and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel formation

Various hydrogel formulations are fabricated by varying amounts of KPS and MBA using free radical polymerization (as displayed in Table 1). The initiator KPS, decomposes to generate sulfate radicals at 60°C. The decomposition of the vinyl bond of AM in the existence of sulfate radicals leads to the formation of acrylamide radicals. These radicals-initiated chain formation, propagation, and finally termination, lead to the formation of PAM. The sulphate radical also abstracts the H atom from the COOH group of CMTKG and the -NH_2 group of Gelatin, generating radicals on polymeric chains. The MBA acted as a cross-linker, connecting the free radicals present on the Gelatin, CMTKG, and PAM chain, thus leading to the formation of a three-dimensional polymeric hydrogel network[31]. Moreover, in ampicillin, sodium-loaded Gelatin/PAM/CMTKG hydrogel, the hydrogen bonding among ampicillin sodium (drug) and PAM contributed to the development of ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel as displayed in Scheme 1.



Scheme 1 — Mechanism of synthesis of ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel

Swelling studies

Swelling analysis was conducted in pH 7.4 and pH 1.2 buffers for all fabricated hydrogels. Fig. 2 illustrates the impact of the initiator (KPS) and crosslinker (MBA) quantities on the equilibrium swelling (%) of the hydrogel.

Impact of cross-linker

The swelling of synthesized hydrogels was significantly affected by the concentration of MBA (Fig. 2a). The synthesized hydrogel (A-1) displayed the highest swelling of about 1371±0.75% at pH 7.4 and 1218±0.76%at pH 1.2 with 10 mg MBA, compared to all other formulations, as listed in Table 1. The swelling capacity decreased when the amount of MBA was increased from 10 mg to 30 mg. This reduction in swelling ($p < 0.05$) was attributed to higher concentrations of cross-linker, which minimized the free volume within the polymeric network, thereby decreasing the capacity for fluid absorption. Moreover, decreasing the MBA by 10 mg resulted in a gel-like structure due to insufficient cross-linking in the polymer network [32].

Impact of Initiator

The concentration of MBA is held constant at 10 mg, while variations in initiator (KPS) content (14-38 mg) are examined for their swelling effects, as illustrated in Fig. 2 (b). Initially, an increase in initiator content leads to a rise in the swelling (%), having a maximum swelling of 1371±0.75% at pH 7.4 and 1218±0.76% at pH 1.2 with 32 mg of KPS. However, a decrease occurs below 32 mg, attributed to unreacted monomers, resulting in a less compact polymer network and a subsequent reduction in swelling ($p < 0.05$). Additionally, initiator content exceeding 32 mg causes swelling to decrease again, due to the formation of a soluble oligomer chain instead of a polymeric chain which leads to a reduction in swelling[14]. For all the formulations, higher swelling ($p < 0.05$) was observed in alkaline pH 7.4 compared to acidic conditions (pH 1.2). In an

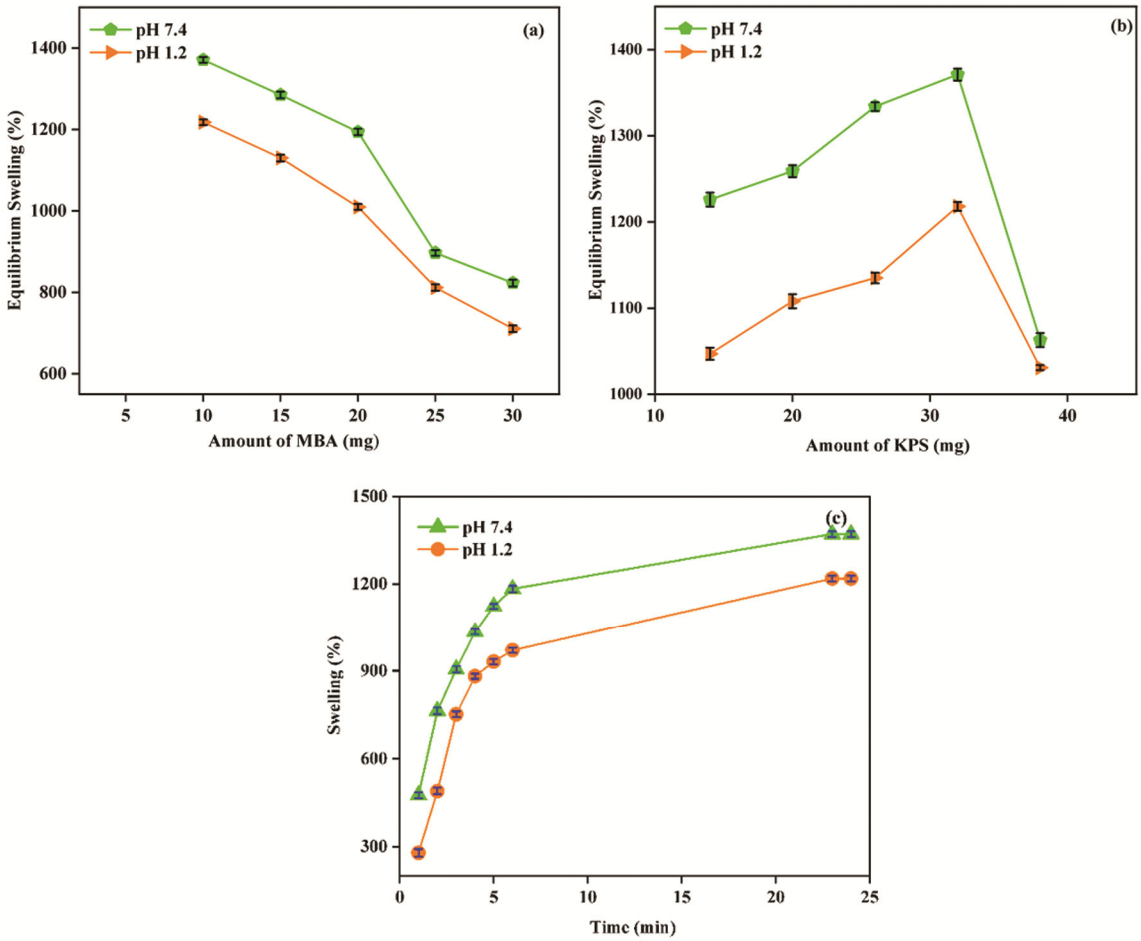


Fig. 2 — Impact of (a) cross-linker, (b) initiator on equilibrium swelling (%), and (c) swelling (%) vs time plot for A-1 formulation

alkaline pH, deprotonation of the COOH groups of polymeric chains happens, and the electrostatic repulsion among the COO^- ions leads to the polymeric chain relaxation and adopt an elongated conformation. This elongation generates extra space, allowing biofluid to penetrate the hydrogel matrix and increase swelling (%). Moreover, at pH 1.2, protonation of COOH groups occurs, leading to the hydrogen bonding among CMTKG, PAM, and gelatin, resulting in the contraction of the hydrogel network, thus reducing the swelling (%) of the hydrogel[31].

Gel fraction analysis

The gel fraction plot revealed that increasing the quantities of crosslinker MBA (A-1 to A-5) and initiator KPS (A-6 to A-8) significantly increases chain entanglement and cross-linking density, leading to a more compact structure, hence higher gel fraction ($p < 0.05$) (Fig. 3). However, exceeding 32 mg of initiator (A-9) results in decreased gel fraction ($p < 0.05$) due to oligomer formation. The presence of these uncross-linked soluble oligomer chains reduces the overall crosslinked gel content of the hydrogel. The highest gel fraction observed was 89.28±0.65% with 32 mg of KPS and 30 mg of MBA in the Gelatin/PAM/CMTKG hydrogel[33].

Porosity

The porosity analysis revealed an increase in the quantity of the crosslinker MBA (A-1 to A-5) results in a decrease in porosity ($p < 0.05$), due to increased crosslinking between Gelatin, PAM, and CMTKG chains, which leads to a denser structure with fewer voids. Moreover, as the amount of initiator KPS (A-6 to A-8) increases, porosity also increases ($p < 0.05$), due to more reaction, which provides more voids between chains. However, beyond 32 mg of KPS (A-9), excessive polymer chain formation, resulting in a reduction in porosity, as illustrated in Fig. 4[34].

Characterization

PXRD analysis was carried out for the ampicillin sodium, Gelatin/PAM/CMTKG hydrogel and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel to gain insights into the crystalline nature (Fig. 5). The sharp crystalline peak of ampicillin sodium was observed at 2θ value of 12.7, 15.5, 17.3, 18,19.3, 19.8, 21.8, 23.9, 25.8, 26.3, 26.7° (Ref.35). Moreover, the broad band observed in the PXRD spectrum of Gelatin/PAM/CMTKG and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel indicates that the synthesized hydrogel exhibits amorphous nature. Additionally, in the PXRD of the ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel, there is an absence of peaks related to ampicillin sodium, revealing that ampicillin sodium is evenly distributed within the cross-linked network of polymer[30].

ATR-FTIR spectra for the Gelatin/PAM/CMTKG hydrogel, ampicillin loaded-Gelatin/PAM/CMTKG hydrogel, and MBA are shown in Fig. 6. In both Gelatin/PAM/CMTKG and ampicillin loaded-Gelatin/PAM/CMTKG hydrogel, the band at 3321 cm^{-1} & 3196 cm^{-1} and 3317 cm^{-1} & 3194 cm^{-1} respectively, correspond to -NH and -OH overlapping stretching vibration. The peak at 1649 cm^{-1} and 1647 cm^{-1}

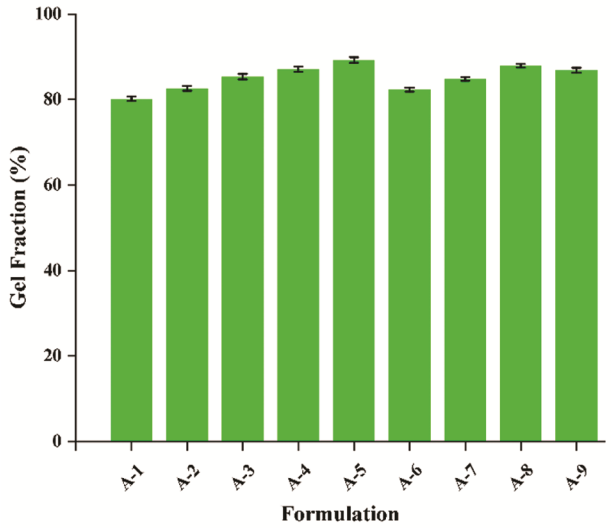


Fig. 3 — Gel Fraction analysis of all Gelatin/PAM/CMTKG hydrogels

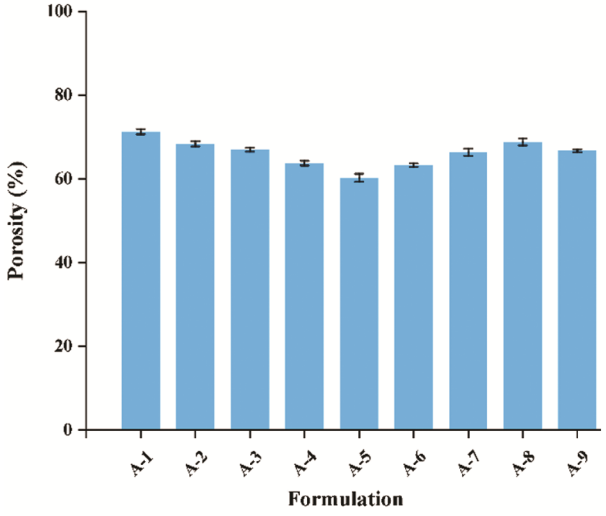


Fig. 4 — Porosity studies of all fabricated Gelatin/PAM/CMTKG hydrogels

signifies the C=O stretch in Gelatin/PAM/CMTKG hydrogel and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel[36]. The peaks at 2926 cm^{-1} and 2931 cm^{-1} are related to the C-H stretch in Gelatin/PAM/CMTKG and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel. Additionally, the peak assigned to the C-O-C group is sighted at 1094 cm^{-1} and 1106 cm^{-1} in Gelatin/PAM/CMTKG and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel[15].

In the ATR-FTIR spectrum of MBA, the peak at 1307 cm^{-1} ascribed to C-N stretch, is moved to 1323 cm^{-1} and 1321 cm^{-1} in the Gelatin/PAM/CMTKG hydrogel and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel, shows the decline in conjugation due to cross-linking and successful development of cross-linked hydrogel network[14]. Additionally, in the ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel, the absence of any additional peaks as compared to Gelatin/PAM/CMTKG hydrogel, indicates that there is likely only a weak or physical interaction between the drug and hydrogel.

SEM images of the Gelatin/PAM/CMTKG hydrogel and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel are presented in Fig. 7. The Gelatin/PAM/CMTKG hydrogel features a highly uneven and porous surface, facilitating the capacity of effective encapsulation of ampicillin sodium crystals within the polymer matrix. However, an SEM micrograph of ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel shows a smoother and less porous surface, as the entrapped drug captures the pores of the hydrogel matrix[10].

Drug loading and drug encapsulation efficiency

The drug loading and drug encapsulation efficiency for the Gelatin/PAM/CMTKG hydrogel (A-1) were examined. The drug encapsulation efficiency (%) was determined to be 61.16% and drug loading (%) was 19.54% for the Gelatin/PAM/CMTKG hydrogel.

***In vitro* Ampicillin sodium release**

An *in vitro* study was conducted for ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel, as

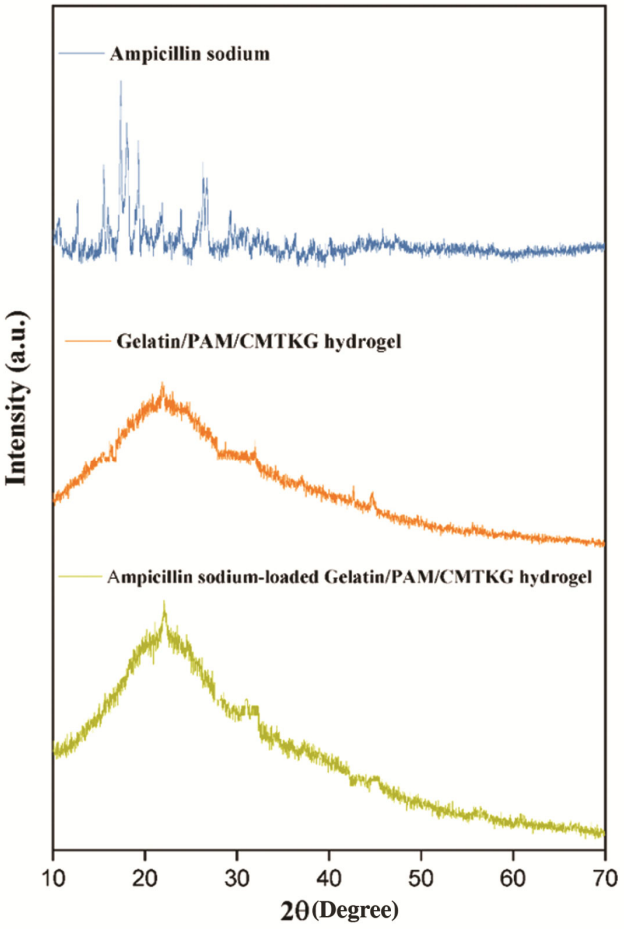


Fig. 5 — PXRD patterns of ampicillin sodium, Gelatin/PAM/CMTKG hydrogel and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel

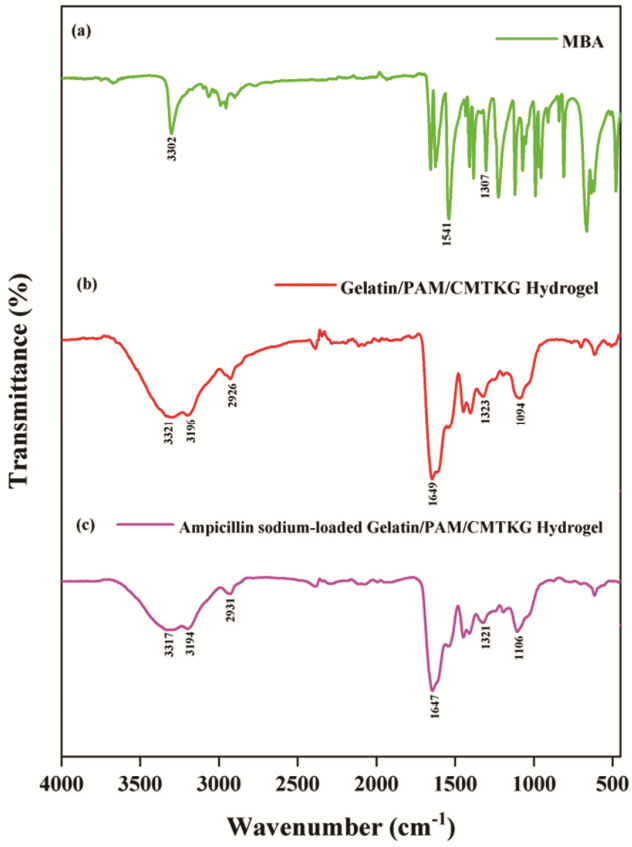


Fig. 6 — FTIR spectra of MBA, Gelatin/PAM/CMTKG hydrogel and ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel

Table 2 — Kinetic modelling data of ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel

Model	Equation	Coefficient of Regression (R^2)		Ref.
		pH 7.4	pH 1.2	
Zero Order	$W_t = W_\infty + k_0 t$ k_0 = zero-order constant	0.9012	0.9327	38
Higuchi	$W_t/W_\infty = k_{HG} t^{1/2}$ k_{HG} = Higuchi constant	0.9762	0.9809	24
First Order	$\text{Log}W_t = \text{Log}W_\infty + \frac{kt}{2.303}$ k = first order constant	0.7268	0.7831	39
Hixson-Crowell	$(W_t)^{1/3} - (W_\infty)^{1/3} = k_{HX} t$ k_{HX} = Hixson Crowell constant	0.8172	0.8239	39
Korsmeyer–Peppas	$W_t/W_\infty = kt^n$ k = kinetic constant n = diffusion exponent	0.9871	0.9892	22

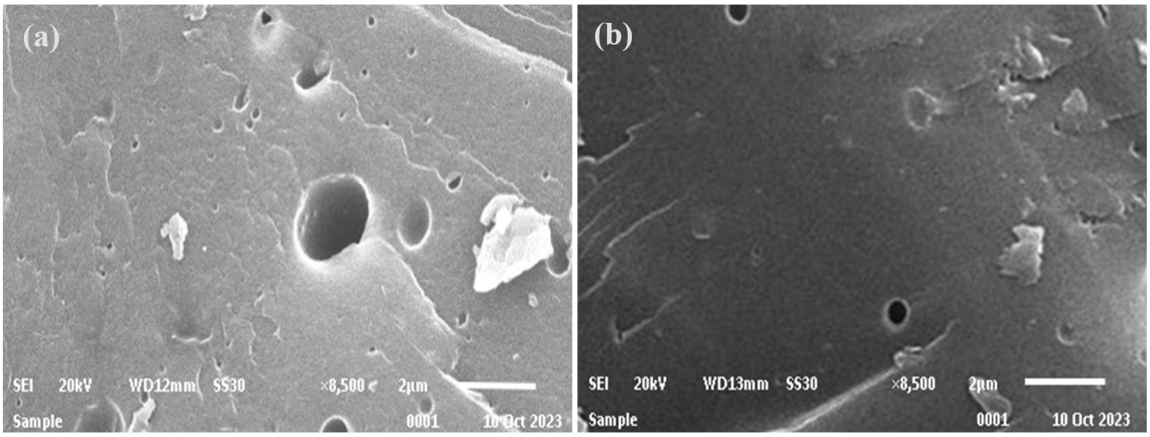


Fig.7 — SEM images of (a) Gelatin/PAM/CMTKG hydrogel and (b) ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel

shown in Fig. 8. The study revealed a higher drug release under pH 7.4 compared to pH 1.2, due to deprotonated COO^- ion present in hydrogel. At pH 7.4, these COO^- ions exhibit repulsion, causing the polymer chain to expand, leading to an increased drug diffusion ($p < 0.05$) from the hydrogel matrix. Under pH 1.2, the COOH group undergoes protonation, which facilitates the formation of hydrogen bonds among the CMTKG, Gelatin, and PAM chains, resulting in a contracted polymeric network, and lower drug release from the hydrogel. The release profile of ampicillin sodium from the hydrogels showed a gradual and prolonged release pattern without any burst release, ensuring optimal drug levels over extended periods and reducing the need for frequent dosing. The maximum ampicillin sodium release was observed to be 63.3±0.69% at pH 7.4, and 14.6 ±0.75% at pH 1.2 from the synthesized ampicillin sodium loaded Gelatin/PAM/CMTKG hydrogel. Hence, the synthesized ampicillin sodium loaded-Gelatin/PAM/CMTKG hydrogel can be utilized for pH-dependent controlled release of ampicillin sodium[30].

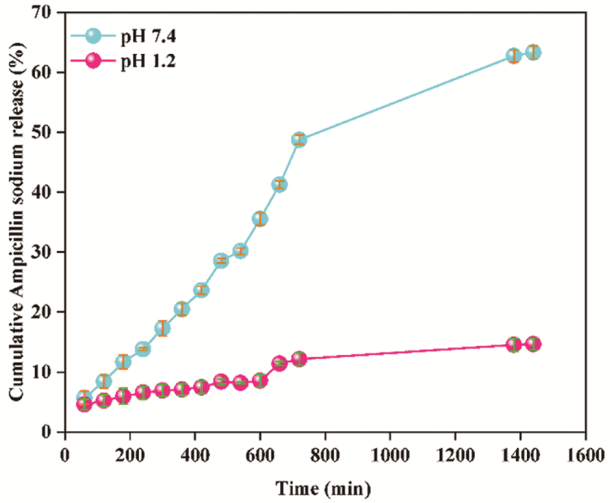


Fig. 8 — Ampicillin sodium release from Gelatin/PAM/CMTKG hydrogel in pH 7.4 and 1.2

Kinetic modelling of ampicillin sodium

The kinetic modelling was done for ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel using various kinetic models, as detailed in Table 2. The results demonstrated that the data closely fit the Korsmeyer-Peppas model under both pH conditions as illustrated in Fig. 9. At pH 7.4, an R^2 value of 0.9871 and an n value of 0.7847 indicated a non-Fickian diffusion mechanism, which revealed that drug release due to the diffusion and polymeric chain relaxation. However, at pH 1.2, the R^2 value was observed as 0.9892, with an n of 0.2557, indicating

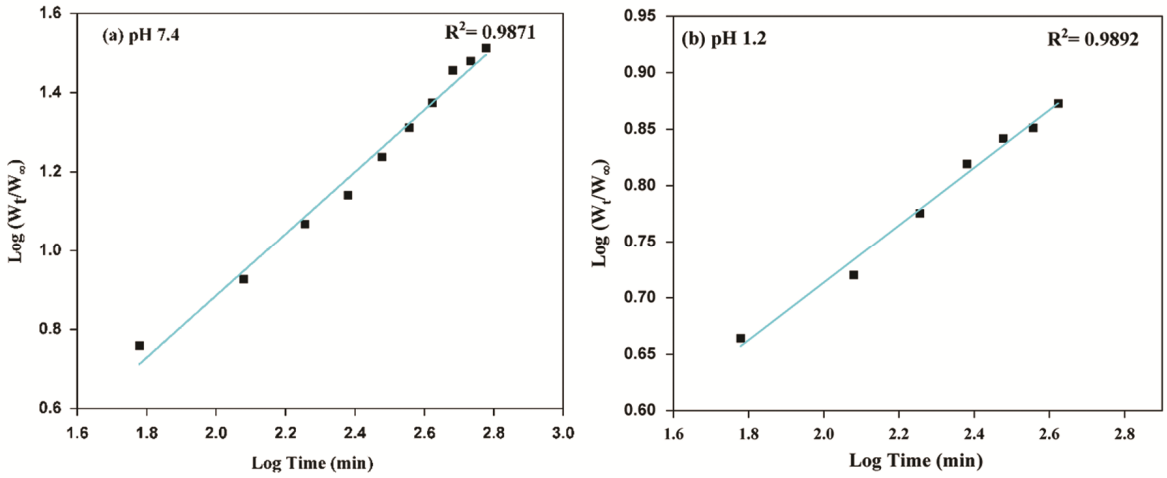


Fig. 9 — Kinetic modelling plot of ampicillin sodium as per Korsmeyer-Peppas model in (a) pH 7.4 and (b) 1.2

the Fickian diffusion mechanism, suggesting that drug release occurred primarily through the diffusion process alone[37].

Conclusion

In this study, the synthesis of pH-responsive ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel was successfully achieved using MBA as a crosslinker and KPS as the initiator. The swelling analysis revealed that an increase in KPS leads to an increase in swelling ($p < 0.05$), but increases in MBA result in decreased swelling values. The porosity of the hydrogels showed an increasing trend ($p < 0.05$) with higher KPS content and a decreasing trend with higher MBA content. Moreover, the gel fraction data showed an increase in gel fraction with higher KPS and MBA content. The swelling and *in vitro* drug release analysis were conducted in pH 1.2 and 7.4 buffer, revealing higher swelling and drug release at pH 7.4, making it suitable for targeted drug delivery. Moreover, the kinetic modelling data of drug release aligned well with the Korsmeyer–Peppas model with R^2 value of 0.9871 at pH 7.4 and 0.9892 at pH 1.2, indicating a Fickian diffusion mechanism ($n<0.5$) at pH 1.2 and a non-Fickian diffusion mechanism ($n>0.5$) at pH 7.4. Therefore, the synthesized ampicillin sodium-loaded Gelatin/PAM/CMTKG hydrogel shows promise for the pH-dependent release of ampicillin sodium.

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