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DEVELOPMENT AND OPTIMIZATION OF PH-RESPONSIVE HYDROGEL FOR CONTROLLED GASTROINTESTINAL DELIVERY OF ATENOLOL

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Abstract

Atenolol is a widely prescribed β1-adrenergic receptor blocker for the management of hypertension, angina, and cardiac arrhythmias; however, its low oral bioavailability, short elimination half-life, and frequent dosing requirements limit its therapeutic effectiveness and patient compliance. This study aims to develop a pH-responsive hydrogel based on κ-carrageenan and methacrylic acid (MAA) using the free-radical polymerization technique for the controlled and colon-targeted delivery of atenolol. The hydrogel matrix is designed to remain stable in the acidic environment of the stomach and swell at the higher pH of the intestine and colon, enabling sustained and site-specific drug release. The proposed system is expected to enhance atenolol bioavailability, reduce dosing frequency, and eliminate the need for conventional enteric coating. The developed hydrogels will be loaded with atenolol and evaluated through in vitro characterization to assess their swelling behavior, drug-loading efficiency, and controlled-release performance. This approach offers a promising strategy for improving the efficacy, safety, and patient compliance of long-term cardiovascular therapy.

Introduction

Cardiovascular diseases (CVDs) remain one of the leading causes of morbidity and mortality worldwide, necessitating the development of effective long-term drug delivery strategies. Atenolol, a selective β1-adrenergic receptor antagonist, is widely used in the management of hypertension, angina pectoris, and cardiac arrhythmias(Frishman, 1980). Despite its clinical efficacy, conventional oral formulations of atenolol exhibit several limitations, including low oral bioavailability (40–50%), extensive first-pass metabolism, a short elimination half-life (6–7 hours), and the need for multiple daily doses(Cruickshank, 1980). These drawbacks may lead to fluctuating plasma drug concentrations, reduced therapeutic efficacy, and poor patient compliance.

Recent advances in novel drug delivery systems have focused on improving the pharmacokinetic and pharmacodynamic properties of therapeutic agents through controlled and targeted drug release. Among these systems, hydrogels have attracted considerable attention because of their

three-dimensional cross-linked polymeric networks, high water content, biocompatibility, biodegradability, and tunable swelling behavior(Caló & Khutoryanskiy, 2015). In particular, pH-responsive hydrogels can undergo reversible swelling in response to changes in gastrointestinal pH, enabling site-specific and sustained drug release while protecting drugs from premature degradation in the stomach(Peppas, Bures, Leobandung, & Ichikawa, 2000).

Kappa-carrageenan (κ-carrageenan), a naturally occurring sulfated polysaccharide obtained from red seaweed, possesses excellent gel-forming ability, biocompatibility, and pH-responsive properties, making it an attractive polymer for oral drug delivery(Campo, Kawano, Silva, & Carvalho, 2009). Incorporation of methacrylic acid (MAA), a monomer containing ionizable carboxylic acid groups, further enhances the pH sensitivity of the hydrogel by promoting swelling under neutral to alkaline conditions(Minhas, Ahmad, Ali, & Sohail, 2013). Such hydrogels are particularly suitable for colon-targeted drug delivery, where they remain stable in the acidic gastric environment and release the drug at the higher pH of the intestine and colon.

The present study aims to develop and characterize a κ-carrageenan/MAA-based pH-responsive hydrogel via free-radical polymerization for the controlled oral delivery of atenolol. The developed hydrogel is expected to improve drug bioavailability, provide sustained and site-specific release, reduce dosing frequency, eliminate the need for enteric coating, and ultimately enhance therapeutic efficacy and patient compliance. Furthermore, the prepared hydrogels will be evaluated in vitro to determine their physicochemical properties and drug-release performance.

Materials Overview

Kappa-carrageenan is a naturally occurring sulfated polysaccharide with excellent gel-forming ability, thermoreversible behavior, and pH-responsive properties, making it suitable for controlled drug delivery. Methacrylic acid (MAA) is a pH-sensitive monomer that enhances hydrogel swelling and drug release under intestinal and colonic pH conditions. N, N′-Methylenebisacrylamide (MBA) serves as the crosslinking agent, providing mechanical strength and stability to the hydrogel network. Atenolol, a selective β_1-adrenergic receptor blocker used to treat hypertension and cardiovascular disorders, was selected as the model drug because its low oral bioavailability and short half-life make it an ideal candidate for sustained, colon-targeted delivery.

Materials and Method

Materials

Kappa-carrageenan (κCG), methacrylic acid (MAA), ammonium persulfate (APS), N, N′-methylenebisacrylamide (MBA), atenolol, hydrochloric acid, sodium hydroxide, potassium chloride, ethanol, and deionized distilled water were used for hydrogel preparation. All chemicals were of analytical grade. Experimental studies were performed using standard laboratory equipment, including a UV–Visible spectrophotometer, dissolution apparatus, pH meter, FTIR spectrometer, scanning electron microscope (SEM), thermogravimetric analyzer (TGA), differential scanning calorimeter (DSC), and X-ray diffractometer (XRD).

Preparation of Hydrogels

pH-responsive κCG-co-poly(methacrylic acid) hydrogels were synthesized by the aqueous free-radical polymerization method. κ-Carrageenan was dissolved in phosphate buffer, followed by the sequential addition of APS, methacrylic acid, and MBA as the crosslinking agent. The reaction mixture was purged with nitrogen gas and polymerized under controlled temperatures (45–65°C). The obtained hydrogels were removed from the molds, cut into discs, washed with an ethanol–water mixture (70:30) to remove unreacted materials, and dried at room temperature, followed by oven drying.

Drug Loading and Characterization

Atenolol was loaded into the dried hydrogels by the swelling–diffusion method using phosphate buffer (pH 7.4). The prepared hydrogels were characterized for equilibrium swelling, drug loading, drug entrapment efficiency, in vitro drug release at pH 1.2, 6.8, and 7.4, porosity, water absorption, apparent density, and sol–gel fraction. Atenolol concentration was determined by UV–Visible spectrophotometry at 220 nm using a previously prepared calibration curve.

Physicochemical Characterization

The chemical interactions, thermal behavior, surface morphology, and crystallinity of the hydrogels were evaluated using Fourier Transform Infrared Spectroscopy (FTIR), Thermogravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), and X-ray Diffraction (XRD), respectively.

Statistical Analysis

Experimental data were analyzed using GraphPad Prism 5. Results were expressed as mean ± standard deviation, and statistical significance between groups was determined using an unpaired *t*-test, with $p < 0.05$ considered statistically significant.

Results

Physical Appearance

Ready hydrogels had an overall smooth morphology and a milky appearance, except at high methacrylic acid concentrations. The concentration of methacrylic acid increased, thereby increasing the transparency of the fabricated hydrogels.

When the hydrogels became dry, there was a slight color change in all of them, changing to transparent. The figure shows the physical appearance of κCG-co-poly (methacrylic acid) hydrogels.

Sol-Gel analysis

Sol-gel analysis was performed to evaluate the proportion of sol and gel in fabricated hydrogel formulations.

Table 1: Sol-gel analysis of K-CG-co-poly(methacrylic acid) hydrogel

Formulation	M_b	M_a	$\textbf{Gel} = \frac{M_b}{M_a} \times 100$	$\textbf{Sol} = 100 - \textbf{Gel}\ \%$
KMA-1	0.419	0.372	88.783	11.217
KMA-2	0.399	0.298	74.687	25.313
KMA-3	0.446	0.309	69.283	30.717
KMA-4	0.67	0.573	85.522	14.478
KMA-5	0.912	0.814	89.254	10.746
KMA-6	0.914	0.841	92.013	7.987
KMA-7	0.758	0.663	87.467	12.533
KMA-8	0.649	0.598	92.142	7.858
KMA-9	0.695	0.678	97.554	2.446

Water Absorption Study

Hydrogel Water absorption and apparent density were carried out, and the difference between all formulations of hydrogel is shown in Figure 1.

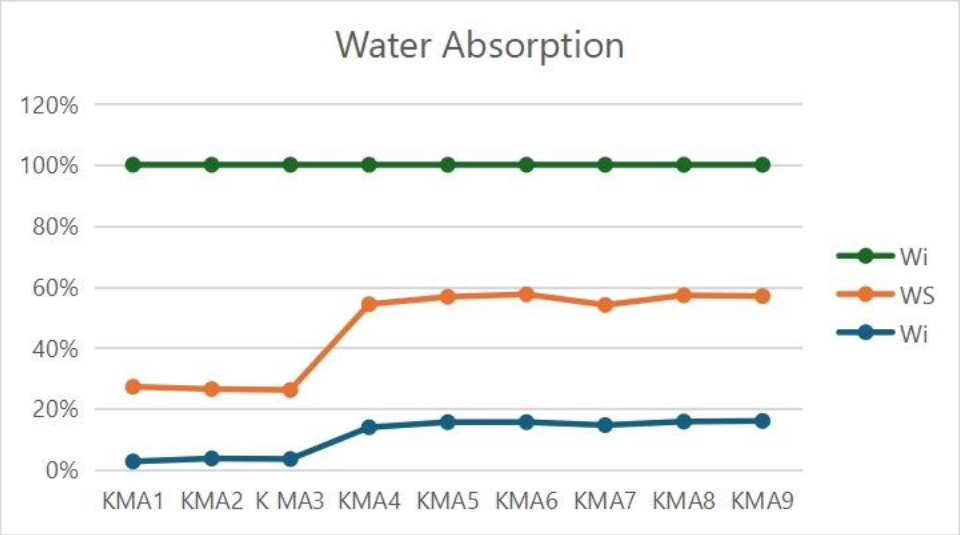


Figure 1: Effect of different formulations with various contents of K-Carrageenan, MAA, and MBA on the percent water absorption of hydrogel.

Porosity measurement

The pore size and volume of the prepared hydrogels were assessed using porosity measurements

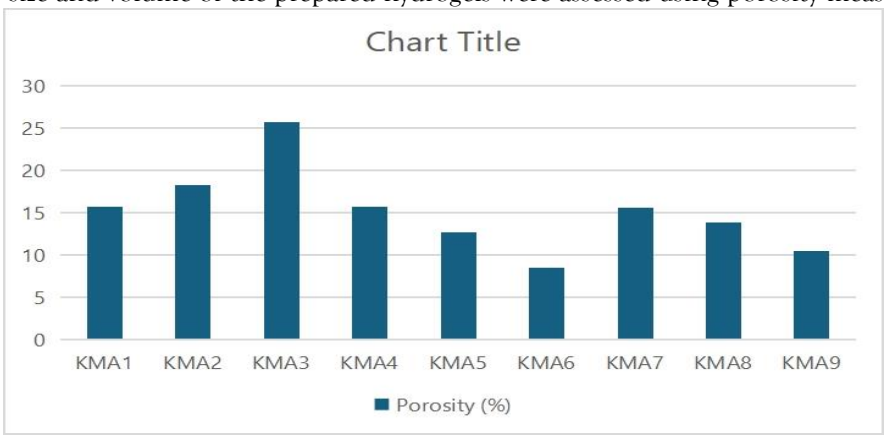


Figure 2: Porosity (%) Measurement

Swelling Index

Analysis of the dynamic swelling index of K-Carrageenan-co-poly (methacrylic acid) Hydrogels with varying concentrations of K-Carrageenan, MAA, and MBA (KMA-1 to KMA-9) was tested at pH 1.2, pH 6.8, and pH 7.4. The results are shown in Figures provide graphical representations.

Standard curve of Atenolol

The stock solution was diluted (1, 2, 4, 6, 8 and 10 ug/mL-1) in series, and the absorbance of the dilution was determined at 220 nm with a UV - visible spectrophotometer.

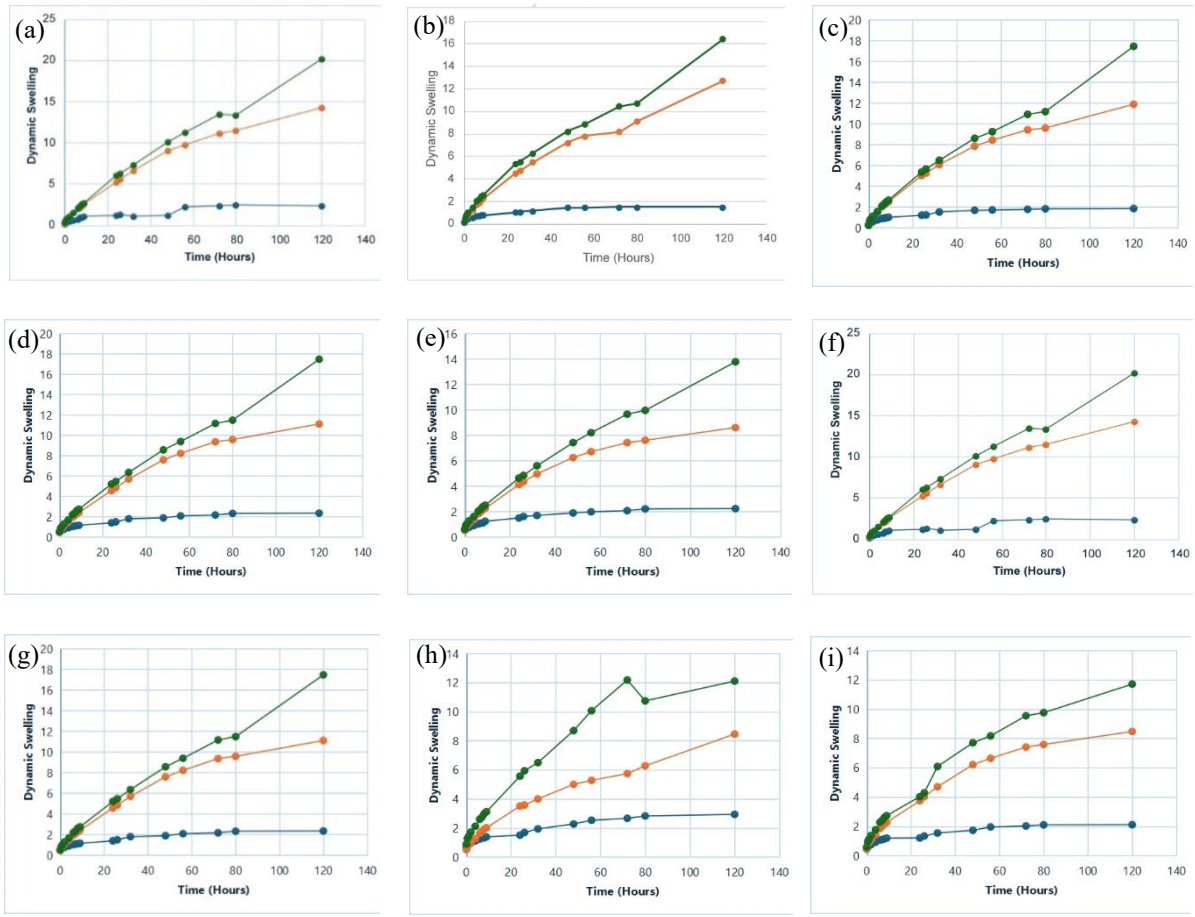


Figure 3: Swelling index of various hydrogel formulations at pH 1.2, 6.8 and 7.4
(a) KMA-1 (b) KMA-2 (c) KMA-3 (d) KMA-4 (e) KMA-5 (f) KMA-6 (g) KMA-7 (h) KMA-8 (i) KMA-9

Table 2: Absorbance of Atenolol at various concentrations

S. No	Concentration of Sample (µg/ml)	Absorbance
1	1	0.032
2	2	0.061
3	4	0.109
4	6	0.152
5	8	0.192
6	10	0.229

In-vitro Drug Release Studies

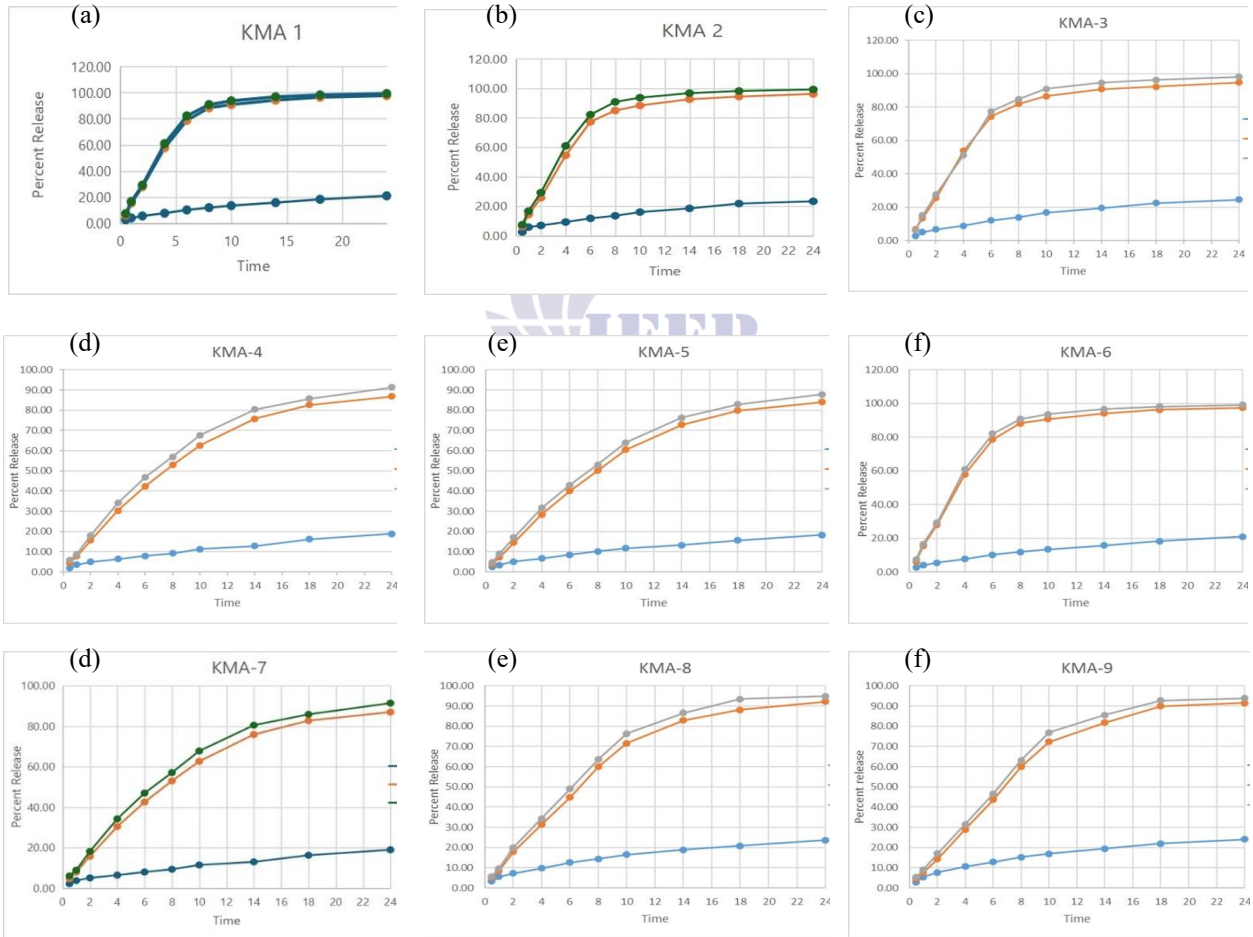


Figure 4: In-vitro release profile of Atenolol from various hydrogel formulations at pH 1.2, 6.8 and 7.4

(a) KMA-1 (b) KMA-2 (c) KMA-3 (d) KMA-4 (e) KMA-5 (f) KMA-6 (g) KMA-7 (h) KMA-8 (i) KMA-9

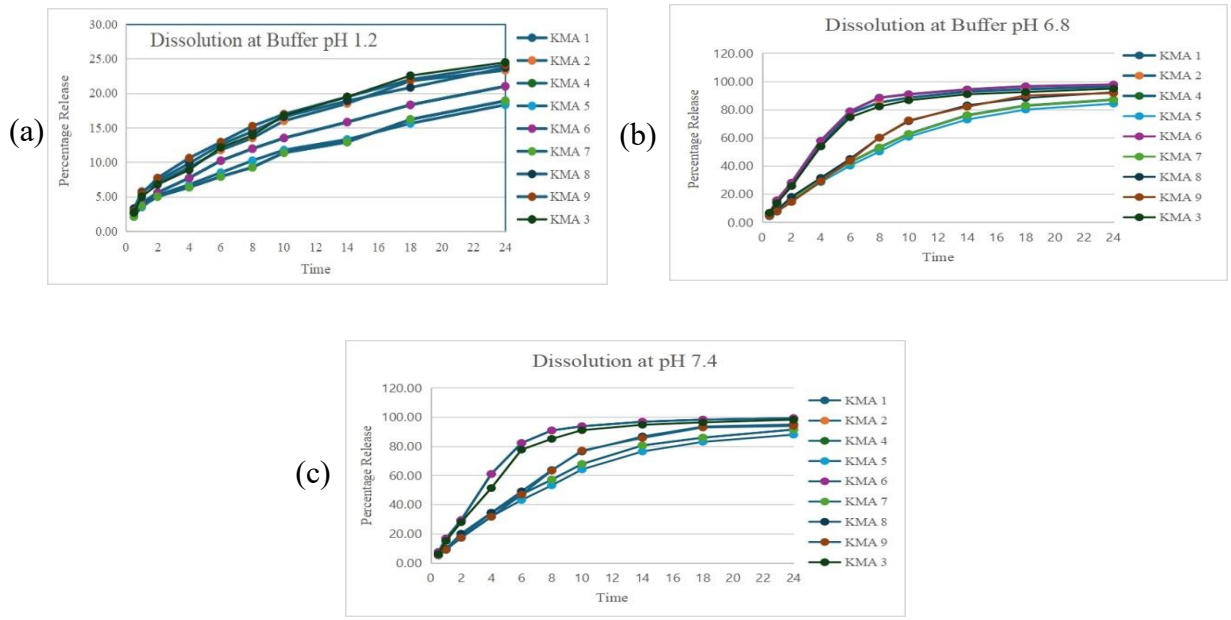


Figure 5: Cumulative In-vitro release profile of KMA-1 to KMA-9, at (a) pH 1.2 (b) pH 6.8 (c) pH 7.8

Release Kinetic Models

The data of the dissolution tests conducted on all the formulations between KMA-1 and KMA-9 was subjected to different release kinetic models and the patterns of drug releases were determined using different release models as shown in tables.

Table 3: Drug release kinetic models of κ-Carrageenan-co-poly(methacrylic acid) hydrogel formulation with changing κ-Carrageenan concentration.

Sample Codes	κ-Carrageenan contents (/30g)	pH	Zero Order kinetics (R2)	First Orders kinetics (R2)	Higuchi Model (R2)	Korsmeyer Peppas (n)
	0.12g	1.2	0.9562	0.9676	0.5732	0.9987
KMA-1	0.12g	6.8	0.6688	0.9287	0.8482	0.9108
	0.12g	7.4	0.6536	0.9616	0.8363	0.9116
	0.15g	1.2	0.9367	0.9509	0.9912	0.9727
KMA-2	0.15g	6.8	0.6818	0.9164	0.8569	0.9194
	0.15g	7.4	0.6536	0.9616	0.8363	0.9116
	0.18g	1.2	0.9411	0.9552	0.8848	0.991
KMA-3	0.18g	6.8	0.6958	0.9107	0.8716	0.9428
	0.18g	7.4	0.697	0.9561	0.8682	0.9208

Table 4: Drug release kinetic models of κ-Carrageenan-co-poly(methacrylic acid) hydrogel formulation with changing MAA concentration.

Sample Codes	MAA contents (/30g)	pH	Zero Order kinetics (R2)	First Orders kinetics (R2)	Higuchi Model (R2)	Korsmeyer Peppas (n)
KMA-4	9ml	1.2	0.9793	0.9854	0.9114	0.9896
	9ml	6.8	0.898	0.987	0.9809	0.9835
	9ml	7.4	0.8864	0.9941	0.9779	0.981
KMA -5	12ml	1.2	0.9628	0.9717	0.9972	0.9978
	12ml	6.8	0.9021	0.9839	0.9815	0.9838
	12ml	7.4	0.8987	0.9903	0.9821	0.9844
KMA -6	6ml	1.2	0.9562	0.9676	0.5732	0.9987
	6ml	6.8	0.6688	0.9287	0.8482	0.9108
	6ml	7.4	0.6536	0.9616	0.8363	0.9116

Table 5: Drug release kinetic models of κ-Carrageenan-co-poly(methacrylic acid) hydrogel formulation with changing MBA concentration.

Sample Codes	MBA contents (/30g)	pH	Zero Order Kinetics (R2)	First Order Kinetics (R2)	Higuchi Model (R2)	Korsmeyer Peppas (n)
KMA-7	0.012g	1.2	0.9793	0.9854	0.9114	0.9896
	0.012g	6.8	0.898	0.987	0.9809	0.9835
	0.012g	7.4	0.8864	0.9941	0.9779	0.981
KMA -8	0.015g	1.2	0.9301	0.9459	0.996	0.9936
	0.015g	6.8	0.8747	0.986	0.9681	0.980
	0.015g	7.4	0.861	0.9793	0.9627	0.9783
KMA -9	0.018g	1.2	0.9153	0.9335	0.9934	0.9866
	0.018g	6.8	0.8736	0.9743	0.9604	0.9759
	0.018g	7.4	0.8583	0.9706	0.9567	0.9792

Invitro characterization

Fourier Transform Infrared Analysis

FTIR analysis was performed for κ-Carrageenan, MAA, kCG-co-poly(methacrylic acid) hydrogel, Atenolol and Atenolol loaded kCG -co-poly(methacrylic acid) and is shown in Figure 3.28, 3.29, 3.30, 3.31, 3.32 respectively.

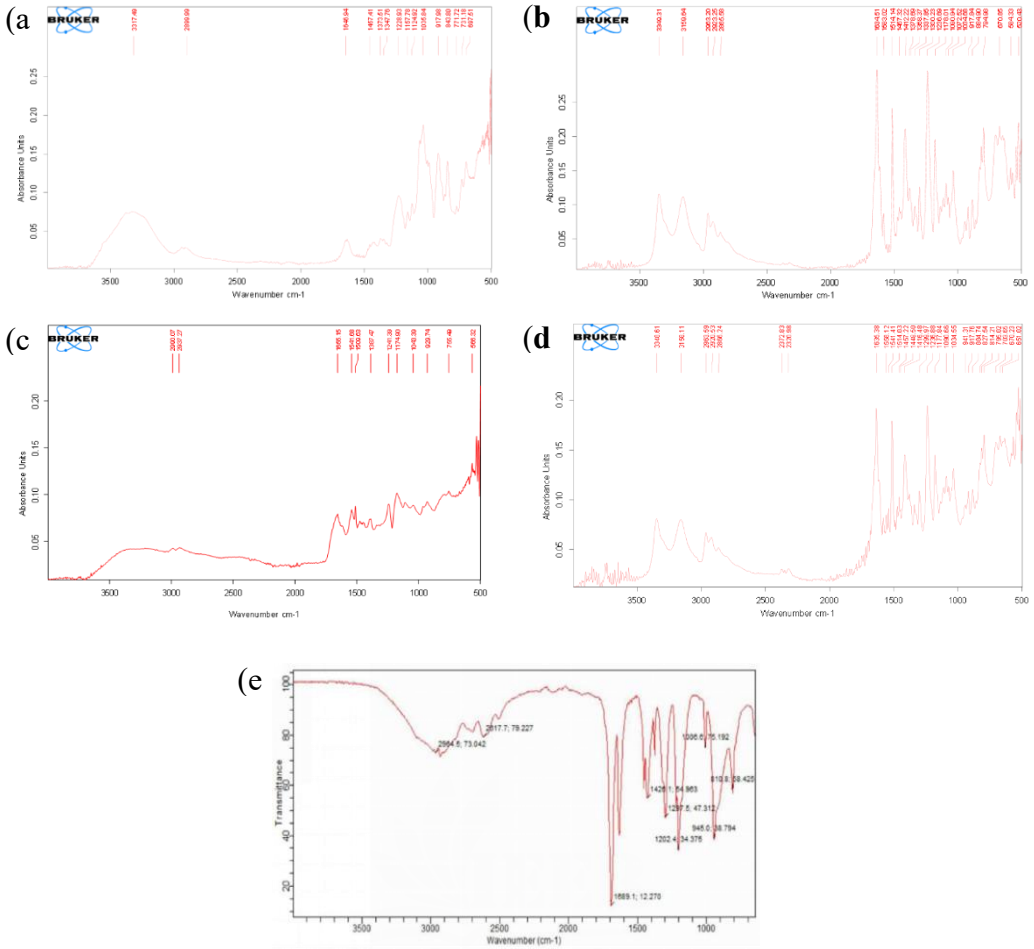
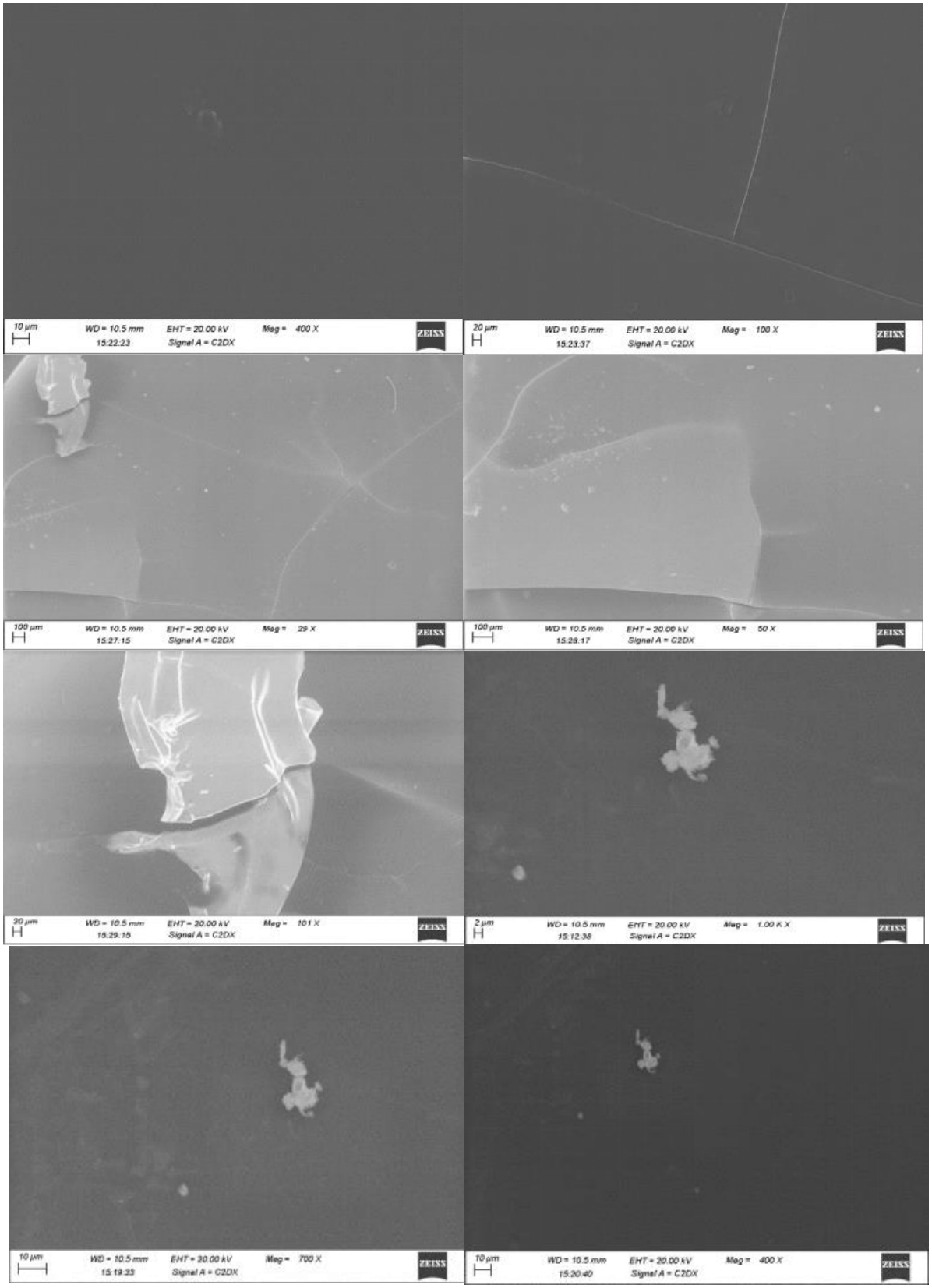


Figure 6: FTIR spectra of (a) κ-Carrageenan (b) Atenolol (c) κ-Carrageenan-co-poly(methacrylic acid) Hydrogel (d) FTIR spectra of Atenolol Loaded κ-Carrageenan-co-poly(methacrylic acid) Hydrogel (e) Methacrylic Acid (MAA)



Scanning Electron Microscope (SEM) Analysis

Thermogravimetric Analysis

Thermal stability of hydrogel and its contents was analyzed using thermogravimeter.

Differential Scanning Calorimetry Analysis (DSC)

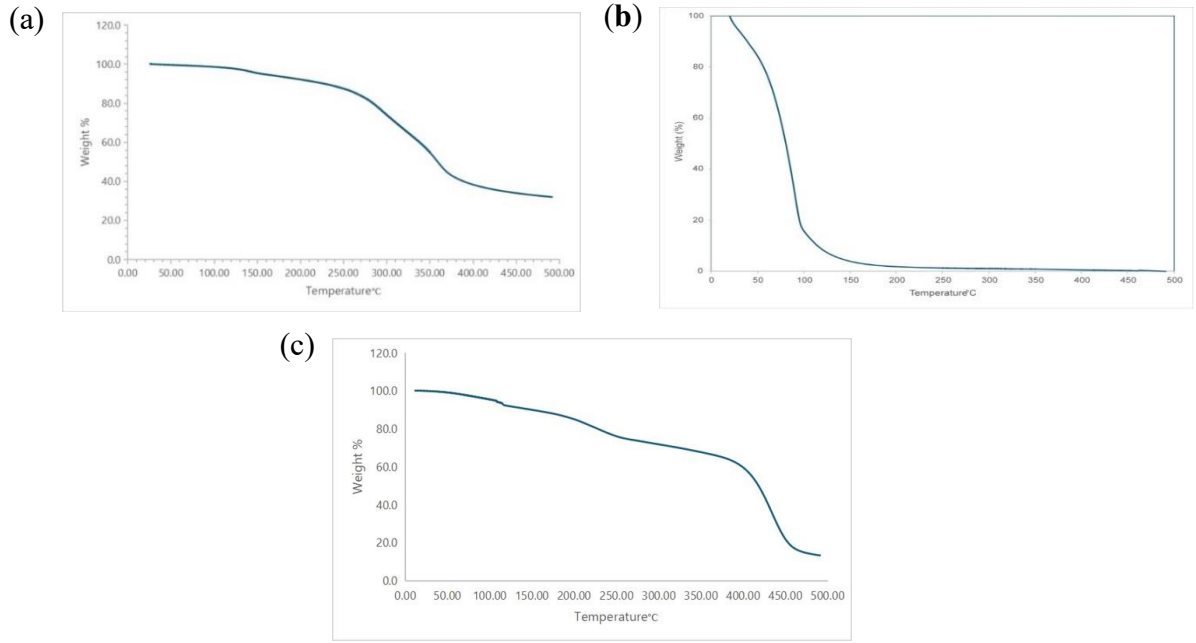


Figure 7: TGA of (a) K-Carrageenan (K-CG) (b) Methacrylic Acid (MAA) (c) K-CG-co-poly(methacrylic acid) Hydrogel

Effect of heat flow was checked on various contents and hydrogel for the evaluation of thermal stability of prepared hydrogel.

X-ray diffraction (XRD)

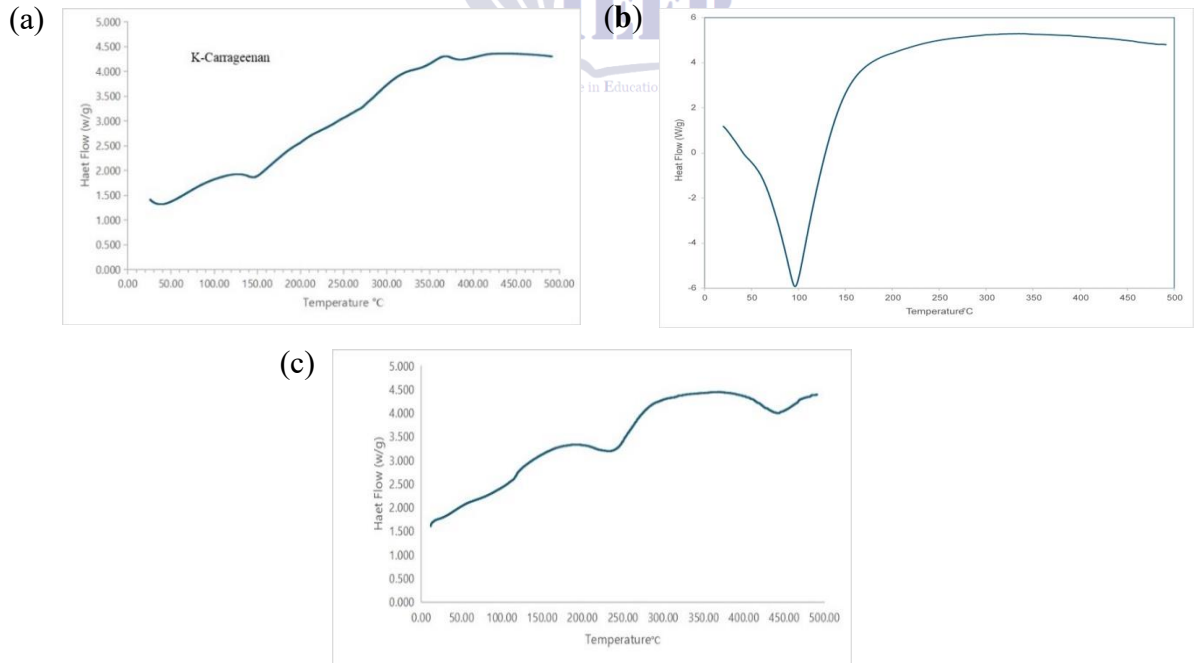


Figure 8: DSC of (a) K-Carrageenan (b) Methacrylic Acid (MAA) (c) K-CG-co-poly(methacrylic acid) Hydrogel

Using a diffractometer, the crystallinity and amorphous nature of κ-CG-co-poly (methacrylic acid), pure drug, and drug-loaded κ-Carrageenan-co-poly (methacrylic acid) were examined.

Discussion

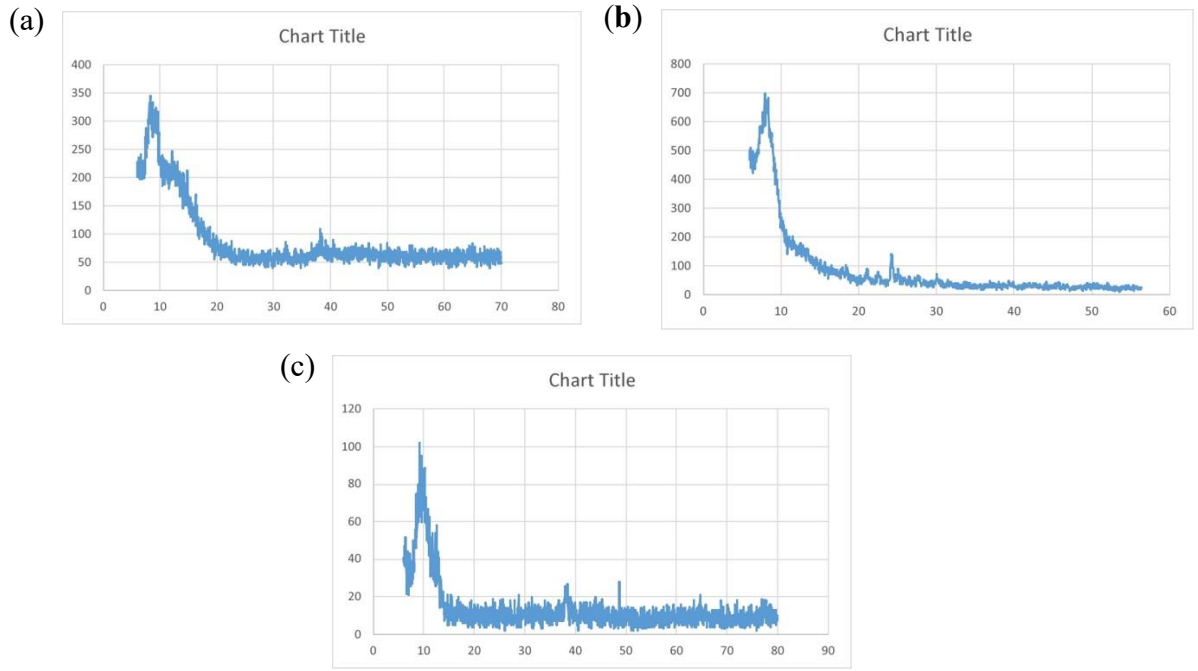


Figure 9: X-ray diffraction pattern of (a) κ-Carrageenan-co-poly(methacrylic acid) hydrogel (b) Atenolol (c) Atenolol loaded κ-Carrageenan-co-poly(methacrylic acid) hydrogen

The determination of uncross linked fraction of monomer or polymer was calculated using sol-gel fraction method. K-CG-co-poly(methacrylic acid) Hydrogel formulations were studied to calculate the effect of different content of hydrogel on sol-gel fraction.

The amount of κ-Carrageenan in hydrogel effects the concentration of gel fraction. Gel proportion was decreased as increasing the amount of κ-Carrageenan because polymer directly affect the process of crosslinking in hydrogel. This fraction of unreacted polymer directly increases the sol fraction of hydrogel.

The increases in the monomer and cross-linker concentration caused an increase in the gel fraction. This can be explained by the fact that unreacted components and the proportion of the solution decreased due to a high level of crosslinking, as shown in table 1.

The percentage of water absorption measured shows that the absorption rate of water by hydrogels depends on the availability of pores in the polymeric structure, which ultimately reflects to the mechanical properties of the copolymer. The hydrogel contains a larger volume of pore which enables more water to be retained.

The addition of polymer concentration to 0.6% was noted to increase water absorption capacity which can be explained by the fact that the density of crosslinking decreased, whereas increasing monomer content to 40 percent of the overall weight increased water absorption further as it formed a more interconnected pore architecture.

As concentration of MBA increased from 0.04-0.06% caused reduction in water absorption due to reduction in pore volume and strong cross linking.

Porosity of the hydrogel was measured using the porosity measurement method. Table 3.3 shows that, the porosity of the hydrogel rises with increasing concentrations of κ-Carrageenan and MAA; however, it falls with increasing MBA concentration.

Nanda et al. (2013) indicate that porosity is determined by the amount of pores that are contained in the hydrogel. A rise in both the percentage porosity and polymer concentration has been shown to correlate with the viscosity of the polymer solution, high viscosity inhibits the removal of entrained bubbles but a reduction in monomer concentration leads to concomitant increase in the percentage porosity.On the other hand, the decrease in percent porosity due to

meth acrylic acid is the decrease in the solution viscosity as the monomer concentration of 20% v/w is raised to 40% v/w.

A growth in the ratio of MBA leads to a slow decrease in the pore mass of hydrogel, due to improved entanglement between the polymer and the monomer. This strong crosslinking decreases the occupied volume (Jalil et al., 2017). The maximum pore volume as a result of reduced MBA level is seen in the KMA-7 formulation, and the opposite is seen in the KMA-9 formulation in which the cross-linker level incorporated in the polymer matrix is increased thus reducing the pore volume as a result.

Three different sets of copolymers were made to evaluate the effect of polymer and monomer and cross-linker content on swelling index of the hydrogels.The copolymers produced were found to swell depending on the pH, and at high PH, the weight of the hydrogel was reported to increase significantly. Hydrogen bonding between the CH3CO - and -COOH groups caused the hydrogels to collapse at pH 1.2 but the hydrogel expanded the most at pH 6.8 and 7.4, the point at which the electrostatic repulsion was created by protonating the gels (Shi et al., 2017). The swelling behavior as a pH-dependent phenomenon is due to the existence of ionizable functional groups in the polymer (Minhas et al., 2013).

Three hydrogel formulations were performed as KMA -1, KMA -2 and KMA -3 based on κ-Carrageenan concentrations of 0.4 -0.6 w/w.Sulfate ester functional groups within the κ-Carrageenan polymer gave the hydrogel hydrophilic properties also with the addition of hydroxyl group which increases hydration.To begin with, the rise of polymer concentration should lead to an increased pore volume in the hydrogel, which would allow more water to penetrate the polymer network and, therefore, increase the swelling capacity of the κ-CG-co-poly (methacrylic acid) system (Anwar et al., 2017; Chang et al., 2009).

Effect of Monomer on Swelling

κ-CG-co-poly (methacrylic acid) hydrogel formulations containing increasingly high monomer concentrations (30 per cent v/w) (KMA-4), (40 per cent v/w) (KMA-5), and (20 per cent v/w) (KMA-6) of the monomer were subjected to swelling experiments at a range of pH values. The correlation between methacrylic acid (MAA) concentration and swelling was found to be inverse; the highest swelling index was attained in the formulations of the least monomer concentration, and the lowest swelling was observed at the highest monomer loading.

κ-CG-co-poly (methacrylic acid) hydrogels formulations with different polymer concentrations (KMA-1, KMA -2, and KMA -3) were used for the percent drug release study. An increasing trend of drug release was seen as the concentration of κ-Carrageenan increased from 0.4 to 0.6% w/w. This could be because higher polymer contents provide more hydrophilic functional groups for the interaction with solvent molecules. The increased hydrophilicity will cause the solvent to rush towards the disc, increasing penetration and causing more swelling, which will ultimately result in the drug diffusing out of the hydrogel.

On different κ-CG-co-poly (methacrylic acid) hydrogel formulations, the percentage drug release was calculated as a function of monomer. Drug release decreased when the monomer concentration was increased from 20% v/w to 40% v/w. This decrease in release could be caused by the fact that, above a certain point, methacrylic acid reduces the system's reactivity, which in turn reduces solvent interaction and, ultimately, diffusion phenomena and drug release.

The percent drug release was measured for formulations KMA-7, KMA-8, and KMA-9 with increasing MBA concentrations. The percentage of drug release in both acidic and basic pH is directly impacted by increasing the cross-linker concentration. High crosslinking between the monomer and polymer, which reduces the interconnect pore, solvent penetration, and diffusion process, was found to be the cause of this decrease in drug release.

On κ-CG-co-poly (methacrylic acid), several release kinetic models, including zero order, first order, Higuchi, and Korsmeyer-Peppas models, were used. All formulations exhibit higher R2 values (Regression coefficient) at pH 1.2, 6.8, and 7.4, with the exception of a few values as indicating that κ-CG-co-poly (methacrylic acid)

hydrogels are following first order release kinetics when compared to zero. Higuchi models yield more results that fit a regression line with a value closest to 1.

The Korsmeyer-Peppas model is also used to describe drug release from polymer systems (Korsmeyer et al., 1983). Plotting release data in the Korsmeyer-Peppas model sheet allowed for the calculation of "n." This model states that if n is less than or equal to 0.45 ($n \leq 0.45$), it corresponds to the Fickian diffusion mechanism. Non-fickian diffusion or transport will occur if the value of n is greater than 0.45 and less than 0.89 ($0.45 > n < 0.89$); case II transport is associated with $n = 0.89$, and super case II drug transport is associated with $n > 0.89$ (Dash, 2010; Korsmeyer et al., 1983). Since all the values in Tables 3.23, 3.24, and 3.25 were greater than 0.89 that shows all formulations follows super case II drug transport.

The FTIR spectrum of κ-carrageenan also has a strong band in the 3200-3600 cm^{-1} -OH regions, which can be attributed to a lack of hydrogen bond to hydrophilicity, and it indicates a high degree of hydrogen bonding and hydrophilicity. The apparent minor peaks measured between 2800-2950 $cm^{-1}$are aliphatic C-H functionalities of the polysaccharide backbone. The presence of sulfate substituents is indicated by a separate band at the 1210-1260 cm^{-1}range, and glycosidic C -O -C bonds are recorded at the 1000-1150 -1 range. Other bands at 925-935 cm^{-1} and 840-850 cm^{-1}also support the existence of 3, 6 -anhydro -galactose and sulfate groups, respectively.

The presence of a carboxylic acid functional group is confirmed in the FTIR spectrum of the methacrylic acid as the carboxyl group has a broad OH stretch at 2500-3300 cm^{-1} and a large C=O stretch at 1689 cm^{-1}. Peaks in 1630-1680 cm^{-1} and 900-1000 cm^{-1} areas are indicative of C=C and =C–H vibrations respectively thus confirming the typical methacrylic acid structure.

FTIR analysis of pure atenolol confirms its molecular structure through characteristic absorption bands: the amide carbonyl stretch at 1635 cm^{-1} and N–H bending at 1538 cm^{-1}, aromatic C=C vibrations at 1514 cm^{-1}, aliphatic C–H stretches between 2960–2860 cm^{-1}, and C–O stretches indicative of ether and alcohol functionalities. The spectral profile is consistent with the known structure of atenolol, providing a reference for subsequent analysis of drug-loaded hydrogel systems.

The FTIR spectrum of the κ -carrageenan -co-poly (methacrylic acid) hydrogel indicates that it has a broad band at 3200-3500 cm^{-1}, which is the O-H -stretching of the hydroxyl groups and hydrogen bonds in the hydrogel system. The high peak of about 1700 cm^{-1} is the carboxylic groups of the carboxyl acid that forms as a result of the presence of methacrylic acid, thus indicating the successfulness of grafting. Bands typical of κ -carrageenan sulfate esters occur in the ranges of 1220-1260 cm^{-1} and C–O–C stretching of the backbone polysaccharide occurs at 1000-1100 cm^{-1}.These spectral patterns confirm the establishment of the κ -carrageenan -co-poly (methacrylic acid) hydrogel.

Sample	Wave number (cm-1)	Findings
K-Carrageenan	3200–3600 cm^{-1}	O—H angle vibration or stretching.
	2800–2950 cm^{-1}	C—H stretching
	1210–1260 cm^{-1}	S=O Sulfate Ester
	1000–1150 cm^{-1}	C—O—C stretch
	925–935 cm^{-1}	C–O stretching of 3,6-anhydro-D-galactose
	840–850 cm^{-1}	C–O–S vibration of sulfate groups
MAA	2500–3300 cm^{-1}	O–H Carboxylic Acid Stretch
	2950–2850 cm^{-1}	C–H Stretching

	1689 cm^{-1}	C=O (Carboxylic Acid Carbonyl) Stretch
	1630–1680 cm^{-1}	C=C stretching vibration
Atenolol	2960–2860 cm^{-1}	C-H stretching
	3300 cm^{-1}	Broad O–H stretch
	1635 cm^{-1}	C=O stretching (carboxylate group)
	1514 cm^{-1}	aromatic C=C stretching
	1034 cm^{-1}	C -O stretching
κ-CG-co-poly	4000-3600	O—H weak stretching
(methacrylic acid)	2900	C—H asymmetric stretching
	1650-1720	C=O group
Atenolol Loaded	1736	COOH
κ-CG-co-poly	1634	C=O stretching of cyclopentanone
(methacrylic acid)		

The TGA and DSC analyses revealed the successful formation and improved thermal stability of the κ-CG-co-poly(MAA) hydrogel. κ-Carrageenan exhibited an early moisture loss below 150 °C and a significant degradation at 200-300 °C, while MAA showed a single mass-loss step in the range of 150-200 °C as a result of evaporation. On the contrary, the hydrogel exhibited a higher degradation onset (220–250°C), wider degradation range and larger char residue, indicating a better thermal stability due to cross-linking. The formation of hydrogels was also supported by the DSC thermograms. κ-carrageenan showed water loss and degradation peaks. MAA showed evaporation and polymerization transitions. The hydrogel showed a glass transition (50–100 °C), water-loss peak (100–150 °C) and decomposition peak (200–400 °C) confirming the formation of a stable cross-linked polymer network.

Incorporation of atenolol into the κ-CG-co-poly(MAA) hydrogel was confirmed by XRD analysis. The dry hydrogel showed a broad amorphous halo at about $2\theta = 20°$, which is typical for a cross-linked amorphous polymer network. On the other hand, pure atenolol exhibited sharp crystalline peaks between 10°–50° indicating the highly crystalline nature of the drug. These characteristic drug peaks in the atenolol-loaded hydrogel disappeared and only the amorphous halo remained indicating the molecular dispersion of atenolol in the hydrogel without recrystallization. This amorphous dispersion is anticipated to enhance drug solubility, dissolution and diffusion-controlled drug release.

SEM analysis revealed that the κ-CG-co-poly(MAA) hydrogel exhibited a smooth surface and dense internal structure, confirming successful cross-linking between κ-carrageenan and MAA. The compact morphology indicates the formation of stable polymeric network and successful hydrogel synthesis.

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