

DESIGN AND DEVELOPMENT OF PH-SENSITIVE MICROGELS FOR ENHANCED CONTROLLED RELEASE OF SULFASALAZINE

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Abstract

This research will focus on the design and development of pH-sensitive microgels for the controlled delivery of Sulfasalazine, aiming to improve the treatment of irritable bowel syndrome (IBS). Using the gelling properties of carboxymethyl cellulose (CMC), microgels will be synthesized via free-radical polymerization and tailored to release the drug in a pH-dependent manner. The system will be intended to protect Sulfasalazine from early degradation, enhance its bioavailability, and reduce gastrointestinal side effects commonly associated with conventional formulations. Characterization studies, such as swelling behavior, drug entrapment efficiency, and in vitro drug release at different pH levels, will be conducted to assess the performance of the microgels. Advanced analytical techniques, including FTIR, SEM, XRD, TGA, and DSC, will be employed to evaluate the structural, morphological, and thermal properties of the developed system. FTIR studies show the confirms successful drug loading confirms the chemical integrity of both the polymeric microgel and the encapsulated drug. The XRD analysis supports that pure Sulfasalazine remains highly crystalline, the CMC-cool(methacrylic acid) microgel is largely amorphous, and the drug-loaded microgel exhibits diminished drug crystalline peaks, consistent with drug incorporation and dispersion within the hydrogel matrix. Swelling behavior studies show that the higher swelling occurs on 7.4 pH. Ultimately, the study will aim to establish an efficient, sustained-release drug-delivery platform that improves patient compliance and therapeutic outcomes in the management of IBS.

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a very common functional disorder of gastrointestinal abnormalities discovered worldwide (Vahedi et al., 2010). Irritable bowel syndrome (IBS) is considered a functional disorder of the digestive system, which means its symptoms, which are recognizable, are not linked to any structural and metabolic abnormalities. The identification of IBS is made by using the Rome IV criteria which gives the conditions related to the IBS, including recurrent abdominal pain occurring, on average,

the symptoms occur at least on day per week from the past three months go with at least two of the following symptoms: which is related to the defecation, acetone change in stool frequency, appearance of the stools is also changed. Irritable bowel syndrome can also be classified into subtypes using the Bristol Stool Form Scale (BSFS), which rates stool consistency from 1 to 7, from hard to soft.

It has been shown that hydrogels are highly effective drug carriers that control fluid absorption upon exposure to external stimuli, including pH,

ionic concentration, and enzymes. When made with stimuli-responsive polymers, hydrogels are cohesive, three-dimensional polymer networks that exhibit pH- and temperature-sensitive responses. In drug delivery systems, sensitivity to pH and temperature can be advantageous, as it allows Hydrogels to release medication selectively when the appropriate pH or temperature range is required.

One of the newer types of polymer-based controlled-release medication delivery methods is hydrogel. Hydrogel displays stimulus- to swelling-controlled drug release. pH-responsive alterations in their structure and network, and consequently in drug release, have been investigated. Responsive polymeric networks have been extensively investigated due to significant fluctuations in physiological pH across different body locations under both healthy and diseased conditions. This review emphasizes the use of Hydrogels, a family of polymeric materials, for stimuli-responsive drug release, particularly pH-responsive release, and for controlled drug delivery. (P. Gupta et al., 2002)

Three-dimensional, hydrophilic polymeric matrices known as Hydrogels s can hold large amounts of water and, when swollen, mimic biological tissues. The hydrophilic functional groups (such as -OH, -CONH₂, -CONH, and -SO₃H) present in polymer segments confer Hydrogels s their hydrophilic properties. Crosslinking in these polymers arises from both physical entanglements and chemical interactions, including covalent bonds, hydrogen bonding, and Van der Waals forces. Microgel particles, also known as microgels, offer an adaptable, tissue-friendly, hydrophilic system with enhanced longevity and efficient targeting. (Zia et al., 2020)

When creating microgels, polysaccharides—such as chitosan, cellulose, carrageenan, and dextran—are the most commonly used natural polymers. Non-covalent interactions, such as electrostatic interactions, can crosslink them, and the processes for creating physically crosslinked microgels are comparatively easy. (X. Yang & Kim, 2010)

The solvent in which they dissolve causes the macromolecular networks known as microgels to swell. These are special systems that differ

significantly from typical colloids, such as flexible macromolecules. (Plamper & Richtering, 2017)

Three-dimensional hydrophilic polymeric matrices, called Hydrogels, can mimic biological tissues and retain a large amount of water when swollen. Hydrophilic moieties (such as OH, CONH₂, CONH, and SO₃H) incorporated into the polymer segment endow Hydrogels with hydrophilic properties.

Crosslinks in these structures are formed through polymer entanglements and chemical interactions, including covalent and hydrogen bonds. These systems can be used in a variety of applications since they respond to diverse stimuli and exhibit a dynamic phase shift that can be caused by a variety of variables, such as pH, ionic concentration, temperature, and electromagnetic field, and Van der Waals interactions. Microgel particles, also known as microgels, are micron-sized particles that offer a long-lasting, hydrophilic, biocompatible, adaptable, and efficient targeting mechanism. (Zia et al., 2020)

The drawbacks of traditional drug formulations have been addressed by controlled drug delivery systems, which are designed to give medications at predefined rates for predefined durations of time.

Environmental cues for responsive drug release may be provided by the pH range of fluids in different gastrointestinal tract segments. The pH and ionic composition of the outer solution to which the polymer is exposed determine its charge density.

The polymer will swell or deswell when the solution pH is changed. As a result, drug release from devices composed of these polymers will exhibit pH-sensitive release rates. (Balamurali et al., 2010)

Ionic Hydrogels with charge-carrying pendant groups exhibits pH-sensitive swelling, which is influenced by several factors, including ionic charge, the pK_a or pK_b values of ionizable groups, degree of ionization, hydrophilicity, polymer content, and the pH of the swelling media. The two most important variables that regulate the pH-sensitive Hydrogels 's characteristics are pH and the type of pendant groups.

This characteristic of Hydrogels can be used to deliver drugs to the colon at pH 7.4. The degree of

swelling in Hydrogels with acidic or basic pendant groups depends on the surrounding medium's pH in relation to the groups' pKa and pKb values. (Rizwan et al., 2017)

Materials and Methods

Materials

The pH-sensitive microgel was formulated by using the Active pharmaceutical Ingredients and excipients. The materials used in the microgel formulation are listed below with their sources. Metha Acrylic Acid, carboxy methyl cellulose were purchased from Daejung, Korea; (APS)Ammonium peroxodisulfate were purchased from Sigma-Aldrich, UK; Meta Bisulphite, (NAOH)Sodium hydroxide was purchased from Daejung, Korea 7; (HCl)Hydrochloric acid were purchased from Daejung, Korea 8; (KCl)Potassium Chloride was purchased from Daejung, Korea; Sulfasalazine was purchased from China; Absolute Ethanol was purchased from Merck, Germany 15.

Instruments & equipments

The major instruments and equipments used for preparation and evaluation of BLT includes, Analytical Weighing Balance (Sartorius, Germany), UV Spectrophotometer (Shimadzu, Japan), FTIR (Bruker, Germany), Vernier Caliper (Mitutoyo, Japan), Filtration Assebmly (Cryste), pH meter (HANNA, USA), Dissolution Apparatus (Dawn), Water Bath (Cryste), Oven (Galvano Scientific), Incubator (Cryste), Centrifuge (Pyrex), Scanning electron microscope (Vega 3, Tescan), Thermogravimetric Unit (TA instrument (Q2000 series), X-ray diffractometer (Cu Ka Radiation Analytical expert diffractometer).

Methods

Formation of pH-modulated CMC-co-poly(methacrylic acid) microgels. In our study, CMC-co-poly(methacrylic acid) microgels were prepared via aqueous free-radical polymerization. A measured amount of carboxymethyl cellulose (CMC) was combined with phosphate buffer (pH 6.8), stirred constantly, and heated gradually for

10 to 15 hours, or until the solution turned translucent. The solution could cool to ambient temperature once the CAP was completely soluble. After preparing ammonium peroxodisulfate (APS) separately in distilled water, a precise amount of methacrylic acid was added dropwise. If methacrylic acid is added all at once, APS will precipitate. To prevent this, the subsequent drop of methacrylic acid was added only after the solution had become clear. Deionized distilled water was added to reach the final volume. To start the crosslinking process, a certain quantity of the crosslinker Methylene bisacrylamide (MBA) was injected at the end. After a minute of thorough swirling, the entire system was transferred to glass tubes.

The entire mixture was moved to Pyrex glass test tubes that had been previously labeled once a clear solution had formed.

The nitrogen gas stream was used to extract dissolved oxygen from the mixture. After that, the glass tubes were submerged in a thermostatic water bath, and to minimize the generation of cavities, the temperature was increased gradually. The water bath was maintained for incremental temperatures of 45, 50, 55, 60, and 65 °C for 1, 2, 4, 6, and 12 hours, respectively.

Washing and cutting

After removing the glass tubes from the water bath, the gelled structure was extracted from the molds. After cutting the Hydrogels into 8mm discs, they were cleaned with a 70:30 ethanol-water or methanol-water mixture to remove the water-soluble oligomer, unreacted monomers, and uncrosslinked polymer.

Drying of Hydrogels

Small particles were obtained by passing wet Hydrogels through sieve no. 60. These particles were first allowed to dry at ambient temperature for 24 hours before being baked for another 24 hours at 37 degrees Celsius. To create uniformly sized microgels, dried particles were further crushed with a mortar-pestle assembly before screening through a 120-mesh sieve.

Table 1 CMC-co-poly(methacrylic acid) microgels formulation contents

Formulation	CMC	MAA	APS	MBA
AN-1	1g	4mL	0.008	0.008
AN -2	0.8g	4mL	0.008	0.008
AN -3	0.6g	4mL	0.008	0.008
AN -4	0.6g	4mL	0.008	0.008
AN -5	0.6g	5mL	0.008	0.008
AN -6	0.6g	6mL	0.008	0.008
AN -7	0.6g	4mL	0.008	0.010
AN -8	0.6g	4mL	0.008	0.012
AN -9	0.6g	4mL	0.008	0.014

In-vitro Studies of Hydrgel

Swelling Ratio

The effect of pH on the swelling ratio was examined using a hydrochloric acid solution adjusted to pH 1.2 and phosphate buffer solutions at pH 6.8 and 7.4, all maintained at $37 \pm 0.2^\circ\text{C}$ to simulate physiological conditions. Following precise measurements, the dehydrated microgels were encased in the dialysis membrane (Mol. 274 M. A. ZIA ET AL. Wt. 15,000 Dalton), trimmed at both terminal points, and subsequently kept in buffer solutions with different pH values.

Equilibrium Swelling Ratio

$$= \frac{W_t - W_i}{W_i} \times 100$$

Drug loading

The diffusion-supported swelling method was used to load drugs into microgels. The model medicine used was ketoprofen. 10g of Sulfasalazine was dissolved in 1000 ml of phosphate buffer (pH 7.4) to create the standard drug solution (1%). The solution was allowed to soak the microgels for 72 hours at ambient

temperature. Afterward, the particles were separated from the solution by filtration, and distilled water was used to wash away any remaining surface residue. The drug-loaded microgels were first dried at ambient temperature before being baked at 40 degrees Celsius. (Zia et al., 2020).

In-vitro Drug Release Studies

Dissolution tests were conducted using a calibrated six-station USP II dissolution apparatus at pH 1.2, 6.8, and 7.4. In vitro release behavior of the drug was assessed at low pH, simulating the stomach, and at higher pH, representing the intestine. To ensure consistent sink conditions throughout the experiments, samples were periodically collected at set levels and substituted employing the same volume of the corresponding buffer. Using a UV-visible spectrophotometer, the samples were examined three times to determine the amount of ketoprofen at 260 nm. (Zia et al., 2020)

Porosity Measurements

The solvent replacement method was used to assess the porosity of the microgel compositions. Following an overnight immersion in 100% ethanol to remove any remaining ethanol from the surface, the dried microgel particles were weighed. Particle porosity was determined using the equation below:

$$\text{Porosity} = \frac{M_2 - M_1}{\rho V} \times 100$$

Water Absorption Studies

The microgels were soaked in distilled water at room temperature overnight to examine their water-absorption capacity. The following formula was used to calculate the water percentage.

$$\% \text{ Water Absorption} = \frac{Ws - Wi}{Wi} \times 100$$

Sol-gel Fraction

To determine and examine the quantity of reactants utilized in the CMC-co-poly (MAA) microgel synthesis, a sol-gel fraction analysis of the generated microgel was conducted. Deionized water served as the solvent; Soxhlet extraction was performed on the microgel samples for 4 hours to ensure thorough extraction. The unreacted polymer in the gel was removed by this extraction procedure.

The gel was then dried once again in a vacuum oven at room temperature until it reached a constant weight (W_i). The proportions of sol and gel were computed using the following formulas.

$$\text{sol fraction} = \frac{W_o - W_i}{W_o} \times 100$$

$$\text{gel fraction (\%)} = 100 - \text{sol fraction}$$

In-vitro Characterization of Hydrogel**Fourier transform infrared spectroscopy (FTIR)**

FTIR Spectroscopy is an analytical technique that measures the absorption and transmission of infrared light by a sample across different wavelengths. A pressure of 65 kN will be applied for 1 minute to transform the mixture into a semitransparent disk measuring 12 mm after complete drying at 45 °C. The wavelength range in which the spectra were recorded was 4000–400 cm^{-1} . (Zia et al., 2020).

Thermogravimetric Analysis (TGA)

The thermal stability of the microgels was evaluated using a simultaneous thermal analyzer by monitoring mass loss as the temperature increased (TGA). Accurately weighed samples were placed on the TGA pan, and the temperature was raised gradually from 25 °C to 500 °C at 20 °C/min under a continuous flow of nitrogen at 20 mL/min. The mass of the microgel samples was continuously recorded throughout the temperature ramp. (Zia et al., 2020).

Differential Scanning Calorimetry (DSC)

To assess the thermal stability of CAP-co-poly (methacrylic acid), DSC was used. Samples weighing between 0.5 and 3 mg were heated to temperatures between 0 and 400 °C. The nitrogen flow and heating rate were maintained at 20 milliliters per minute and 20 degrees Celsius, respectively. Every sample was scanned three times. (Zia et al., 2020)

Scanning electron microscopy (SEM)

The surface morphology of CAP-co-poly(HEMA) microgels was investigated using a scanning electron microscope (SEM, Vega 3, Tescan Analytics, France). Dried microgel particles were mounted on aluminum stubs using conductive carbon tape. The samples were then sputter-coated with gold to an approximate thickness of 300 Å. Imaging was performed at 10 kV to examine the surface features of the coated microgels. (Zia et al., 2020)

X-ray diffraction (XRD)

X-ray diffraction (XRD) analysis was performed to investigate the physical structure of the prepared microgel particles and the individual formulation components. The samples were placed in plastic holders, and the surface was leveled using glass slides. Scanning was carried out with a copper $K\alpha$ radiation source over a range of 10–100° using an Analytical Expert powder diffractometer. (Zia et al., 2020).

Results

Physical Appearance

All of the prepared Hydrogels, except those with a higher methacrylic acid concentration, appeared milky and smooth. The produced Hydrogel becomes more transparent as the MAA

concentration rises. All Hydrogels showed a minor shift in color from milky to transparent after drying. The figure displays the physical characteristics of CMC-co-poly(methacrylic acid) Hydrogel.

Percent of Water Absorption

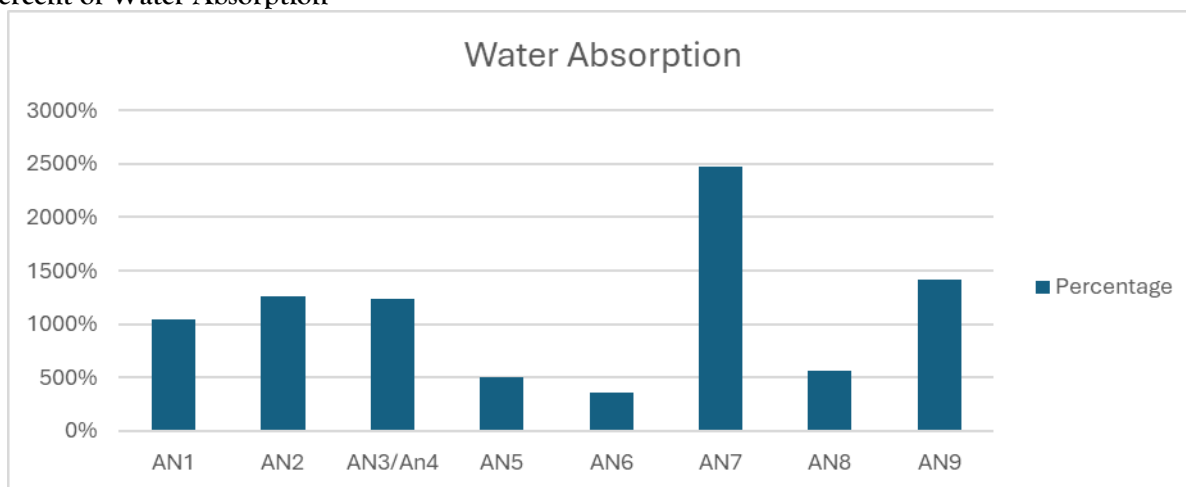


Figure 1: Effect of formulations with various contents of CMC, MAA, and on the percent water absorption of hydrogel

Water absorption and apparent density of the hydrogels were measured, and the differences among all formulated Hydrogel are graphically represented in Figure 1.

Porosity measurement

The produced Hydrogel's pore size and volume were assessed using porosity measuring techniques.

Swelling Index

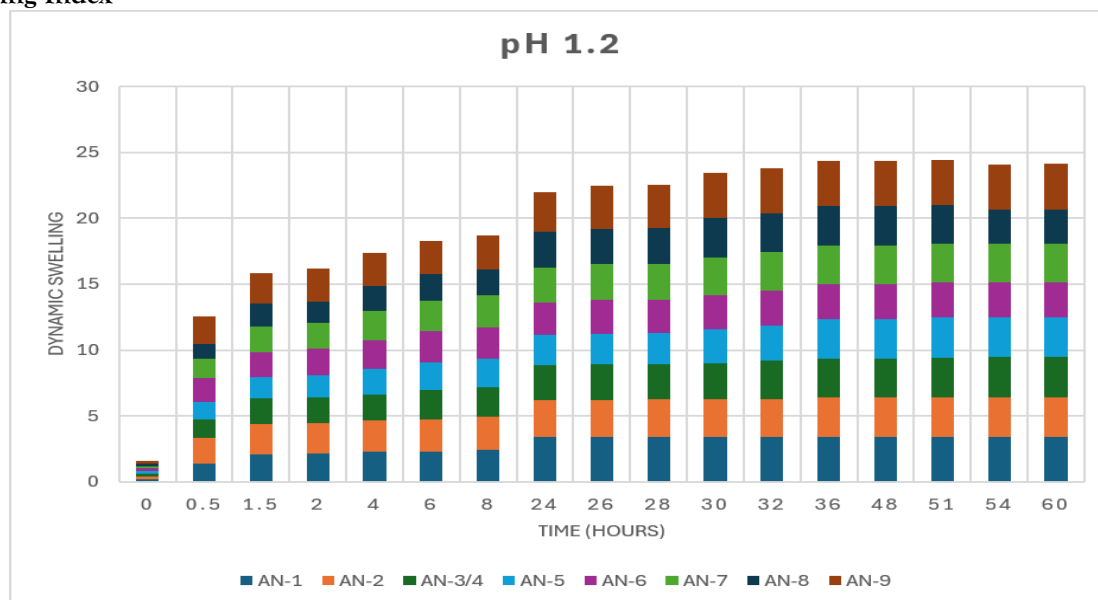


Figure 2 Extent of swelling of AN-1-AN-9 Hydrogel at pH 1.2

Study of the CMC-co-poly's dynamic swelling index (methacrylic acid) Hydrogel with varying amounts of CAP, MAA, and MBA (AN-1 to AN-

3.12, and Figure 2-8) were tested at pH 1.2, pH 6.8, and pH 7.4.

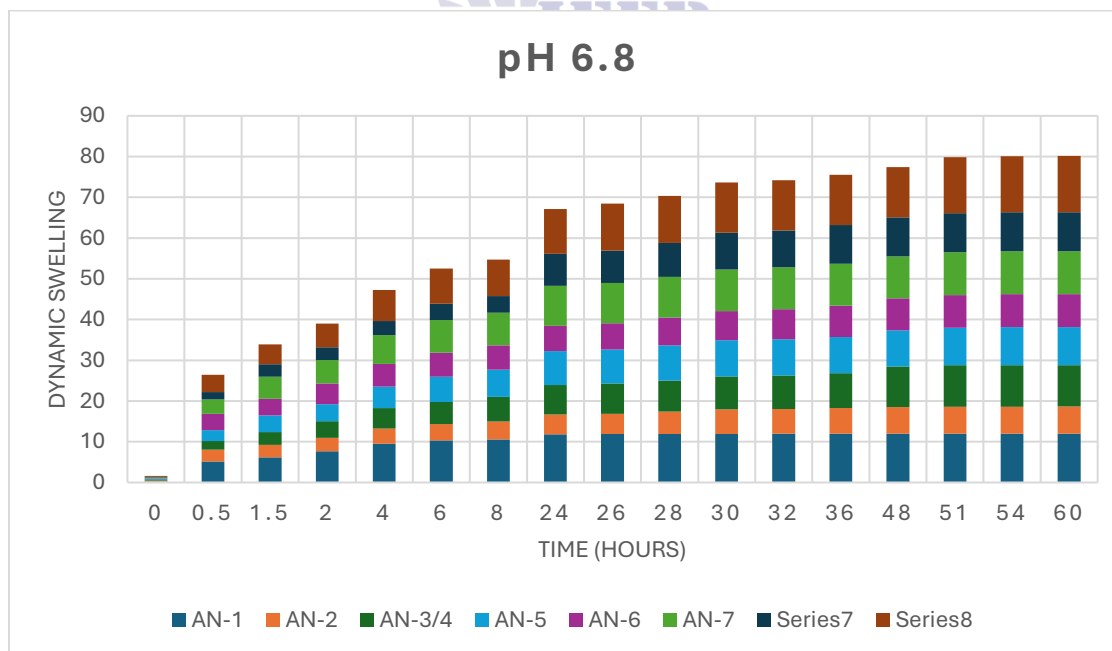


Figure 3 Extent of swelling of AN-1-AN-9 Hydrogel at pH 6.8

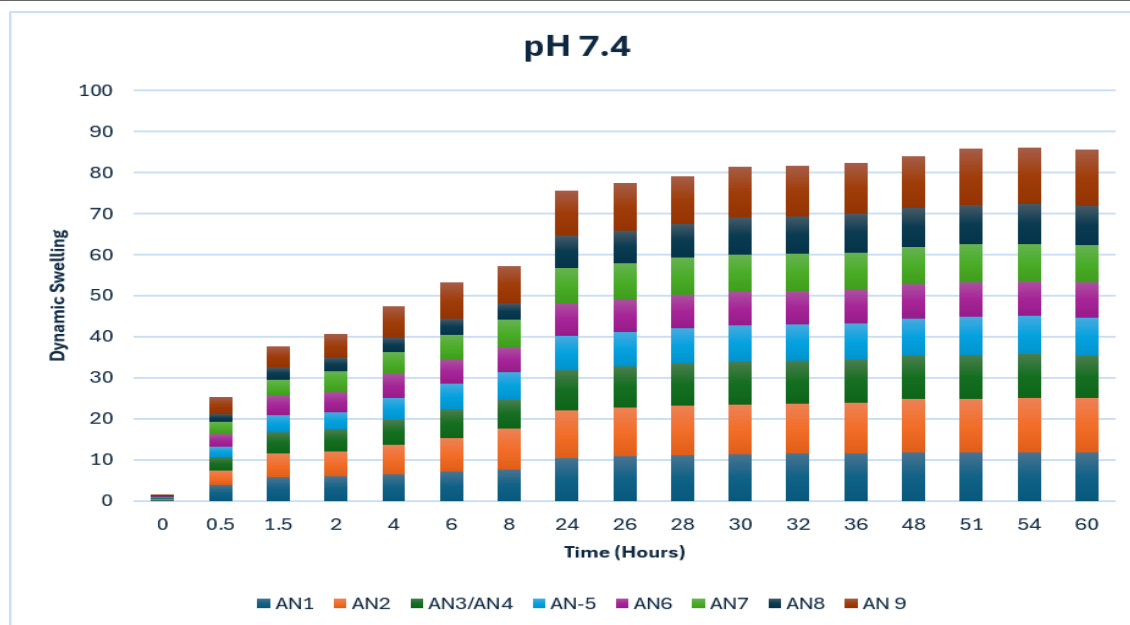


Figure 4 Extent of swelling of AN-1-AN-9 Hydrogel at pH 7.4

In-vitro Drug Release Studies

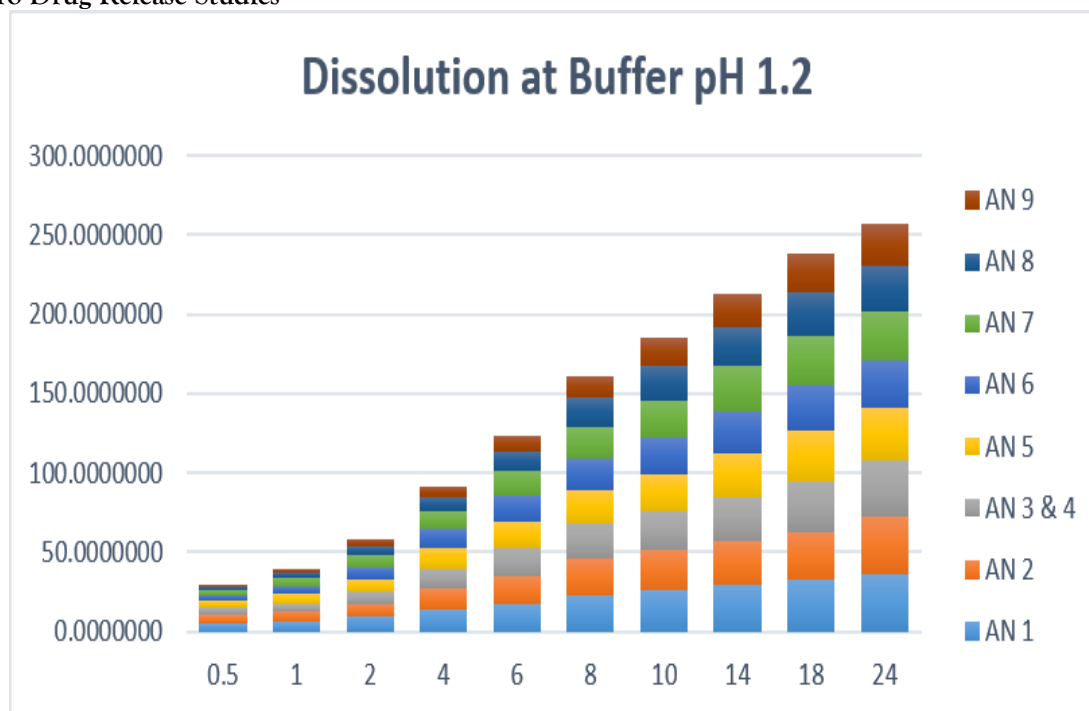


Figure 5 Cumulative In vitro release patterns AN1-AN-9 at pH 1.2

To assess their impact on drug release, a range of CMC-co-poly(methacrylic acid) Hydrogels were prepared with varying amounts of polymers and monomers. CMC-co-poly(methacrylic acid) Hydrogel percent drug release was measured using

USP dissolving apparatus II procedures. After being precisely weighed, the drug-loaded discs were kept in 900 milliliters of phosphate buffer medium at variable pH values (1.2, 6.8, and 7.4) for 24 hours at $37 \pm 0.5^\circ\text{C}$. As seen in Figures 10–

12, the produced Hydrogel with varying concentrations of polymer, monomer, and cross-linker exhibits distinct release patterns.

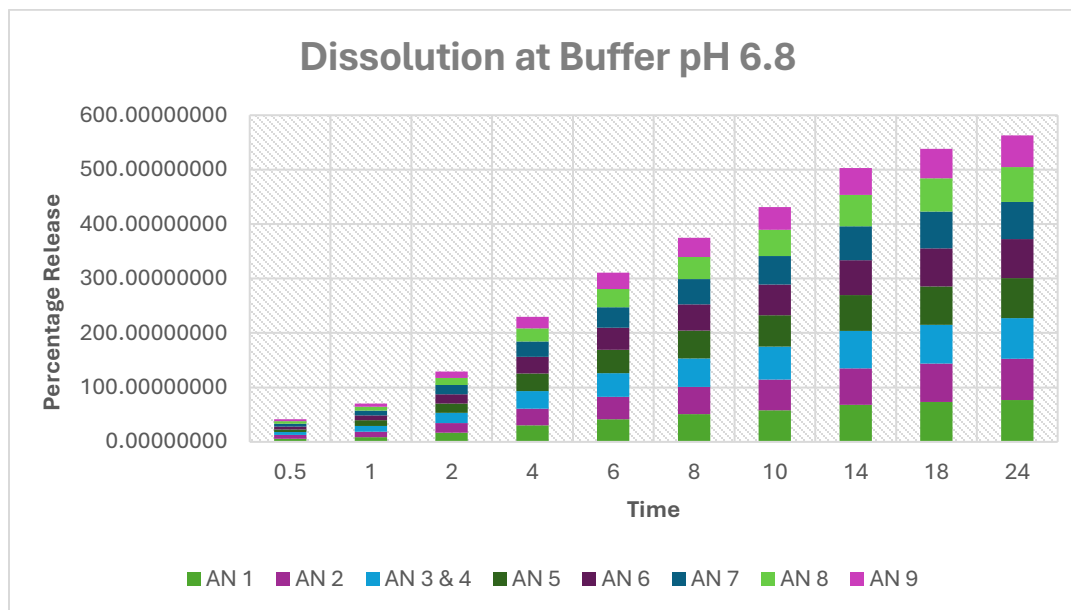


Figure 6 Cumulative In-vitro release pattern of AN-1 to AN-9, at pH 6.8

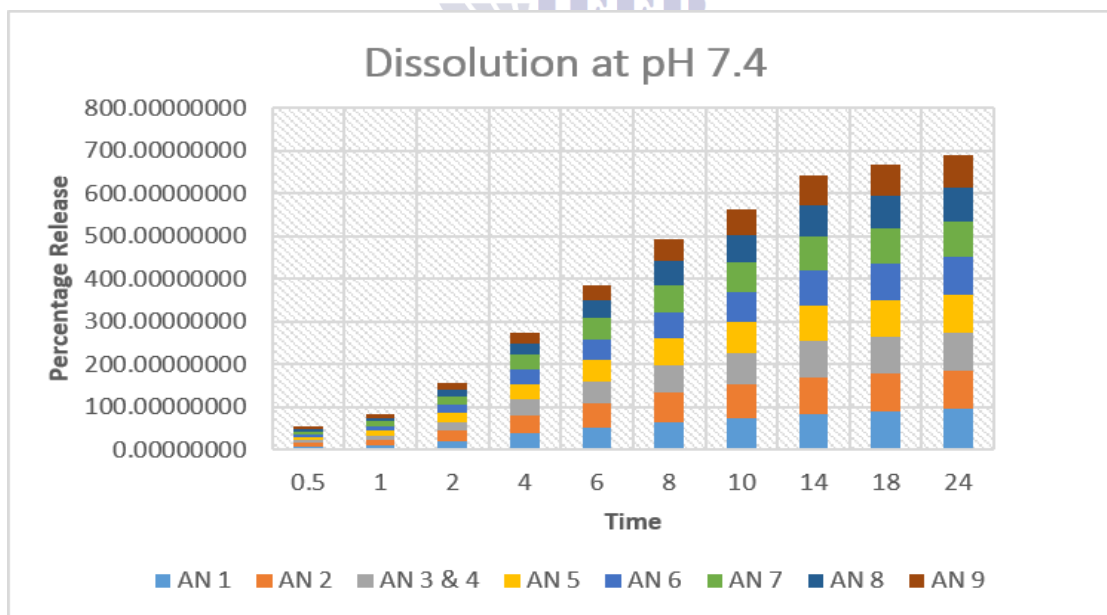


Figure 7 Cumulative In-vitro release pattern of AN-1 to AN-9, at pH 7.4

Kinetic Models of Drug Release

Different release kinetic models were applied to the data obtained from dissolution tests performed on all formulations from AN-1 to AN-

9, and the pattern of drug release was analyzed by applying various release models, as shown in the Table

Table 2 Drug release kinetic models of CMC-co-poly(methacrylic acid) Hydrogel formulation with changing CMC concentration

Sample Codes	Carboxy Methyl Cellulose	pH	Zero-order Kinetics	First Order kinetics	Higuchi Model	Korsmeyer peppas
			R2	R2	R2	n
AN-1	1g	1.2	0.9218	0.946	0.9876	0.9846
	1g	6.8	0.8736	0.9605	0.9876	0.9805
	1g	7.4	0.8551	0.9965	0.9649	0.9752
AN-2	0.8g	1.2	0.9285	0.9521	0.9858	0.9849
	0.8g	6.8	0.8744	0.9582	0.9745	0.9835
	0.8g	7.4	0.8034	0.9634	0.9367	0.9654
AN-3	0.6g	1.2	0.9113	0.9364	0.9841	0.984
	0.6g	6.8	0.8469	0.9363	0.9641	0.9831
	0.6g	7.4	0.8351	0.9554	0.9528	0.9725

Table 3 Drug release kinetic models of CMC-co-poly (methacrylic acid) Hydrogel formulation with changing MAA concentration

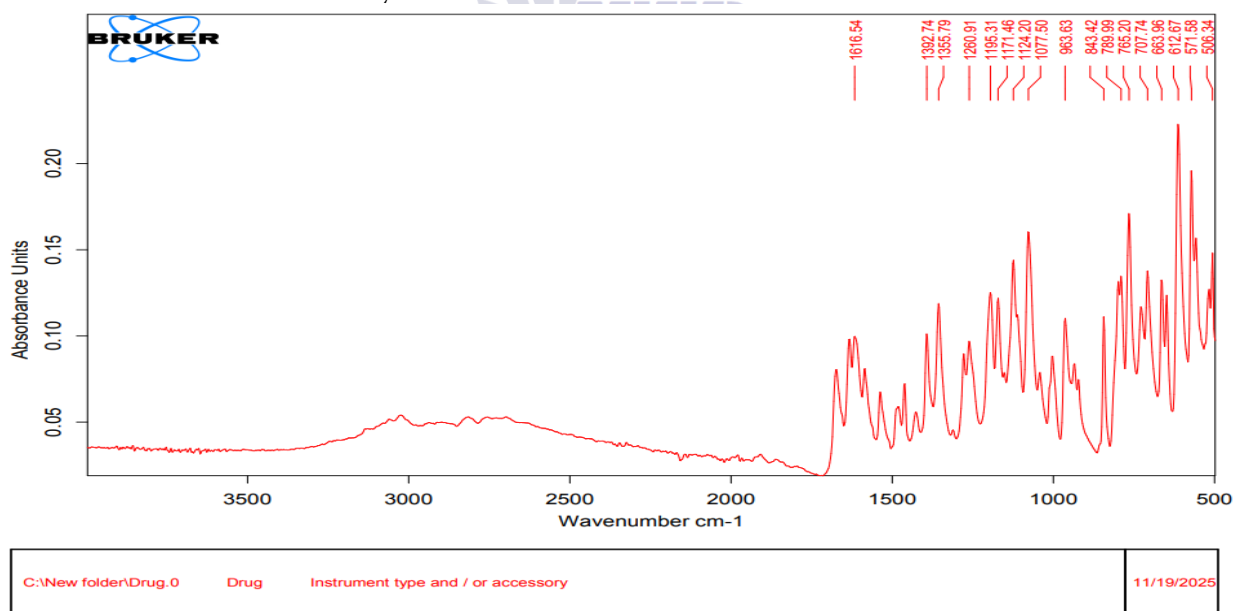
Sample Codes	MAA Contents (/100g)	pH	Zero-order Kinetics	First Order kinetics	Higuchi Model	Korsmeyer peppas
			R2	R2	R2	n
AN-4	4mL	1.2	0.8319	0.9424	0.9511	0.984
	4mL	6.8	0.8442	0.9349	0.9619	0.9717
	4mL	7.4	0.8351	0.9554	0.9528	0.9725
AN-5	5mL	1.2	0.9192	0.941	0.9881	0.9913
	5mL	6.8	0.8421	0.9313	0.9616	0.9313
	5mL	7.4	0.8423	0.96	0.9566	0.9769
AN-6	6mL	1.2	0.8933	0.914	0.9799	0.9916
	6mL	6.8	0.86	0.9391	0.9685	0.9771
	6mL	7.4	0.8319	0.9424	0.9511	0.9728

Table 4 Drug release kinetic models of CMC-co-poly (methacrylic acid) Hydrogel formulation with changing MBA concentration

Sample Codes	MBA Contents (/100g)	pH	Zero-order Kinetics	First Order kinetics	Higuchi Model	Korsmeyer peppas
			R2	R2	R2	n
AN-7	0.010	1.2	0.8588	0.9317	0.9557	0.9909
	0.010	6.8	0.8663	0.934	0.9711	0.9797
	0.010	7.4	0.8367	0.9411	0.9541	0.9754
AN-8	0.012	1.2	0.9089	0.9251	0.9684	0.9836
	0.012	6.8	0.8804	0.9398	0.9748	0.9831
	0.012	7.4	0.8465	0.9306	0.9528	0.9781
AN-9	0.014	1.2	0.9297	0.9425	0.9785	0.9868
	0.014	6.8	0.9049	0.9567	0.9841	0.9813
	0.014	7.4	0.8588	0.9317	0.9557	0.979

Invitro characterization

Fourier Transform Infrared Analysis



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Figure 8: Fourier Transform Infrared analysis of Sulfasalazine

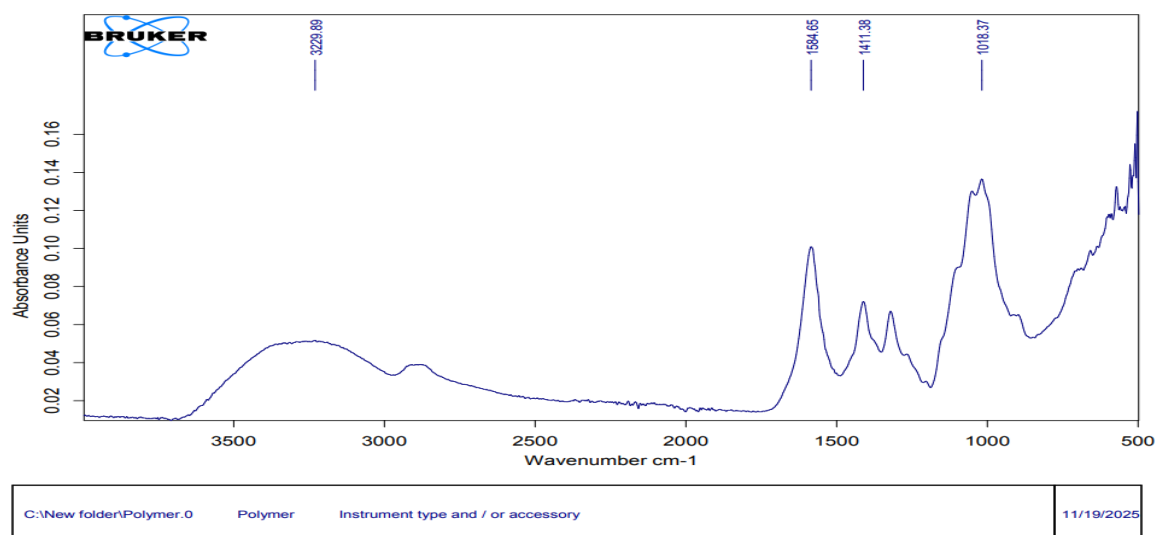


Figure 9: Fourier Transform Infrared analysis of Polymer

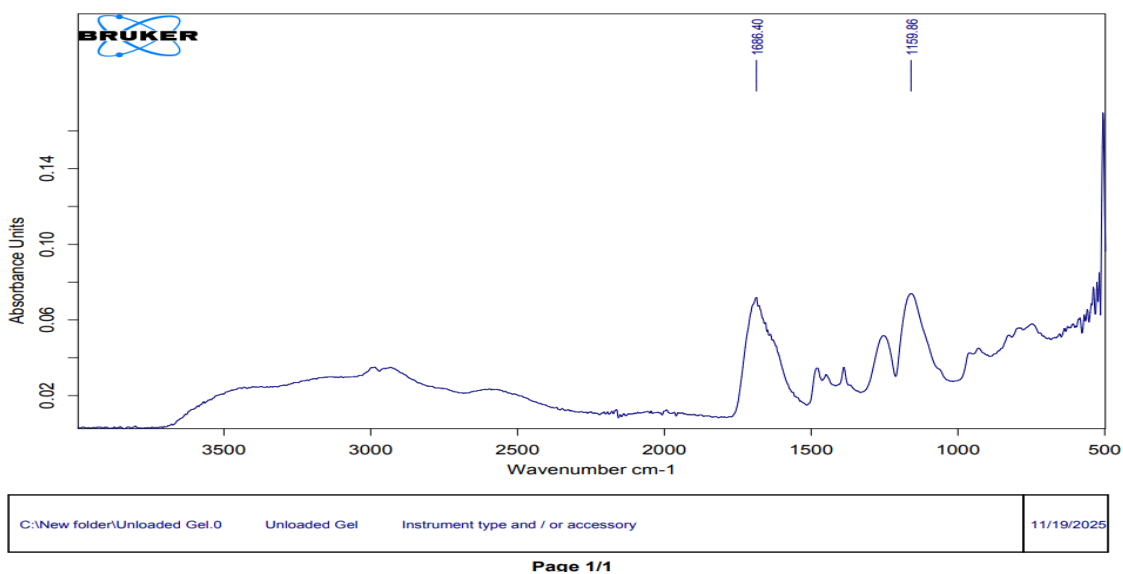
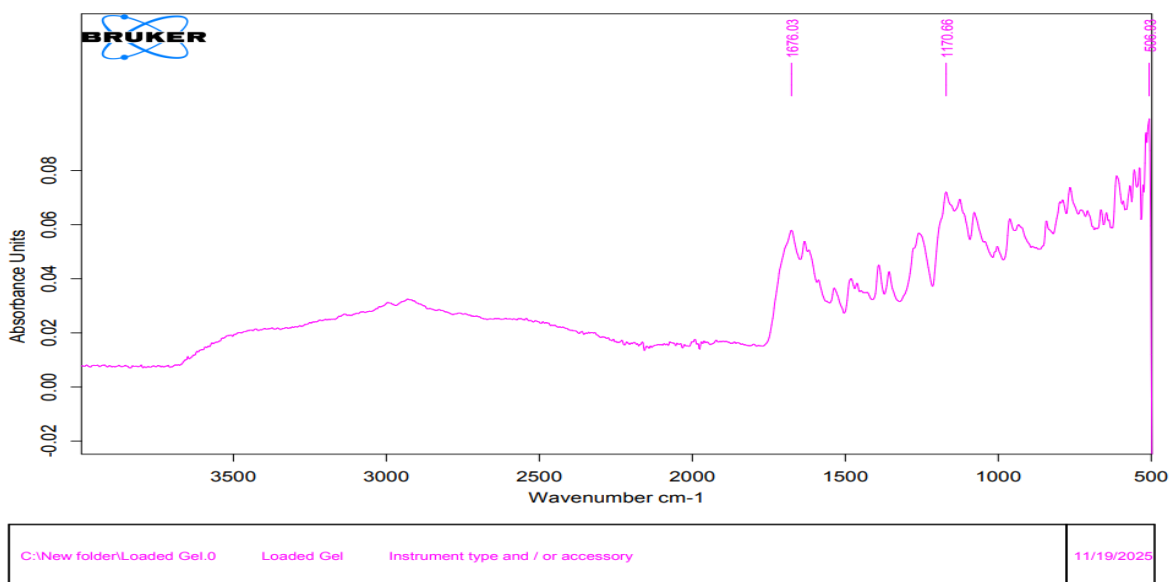


Figure 10: Fourier Transform Infrared analysis of CMC-co-poly MAA Microgel



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Figure 11: Fourier Transform Infrared analysis of Sulfasalazine loaded CMC-co-poly MAA Microgel

FTIR analysis of the pure substances—CMC, methacrylic acid (MAA), CMC-co-poly(MAA) microgel, Sulfasalazine, and Sulfasalazine-loaded CMC-co-poly(MAA) microgel—were analyzed to investigate the functional groups and confirm chemical interactions within the microgel matrix. For CMC, prominent peaks were observed at 3229.89 cm^{-1} , corresponding to -OH stretching due to hydrogen-bonded hydroxyl groups, while peaks at 1584.65 cm^{-1} and 1411.38 cm^{-1} indicate C-C stretching within the polysaccharide backbone. The band at 1018.37 cm^{-1} corresponds to C-O stretching vibrations of the ether and carboxymethyl groups, confirming the polymer's chemical structure. (Dilaver & Yurdakoc, 2016). The CMC-co-poly (MAA) microgel exhibited new peaks at 1686.40 cm^{-1} and 1159.86 cm^{-1} , corresponding to C=C stretching and C-O-C vibrations, respectively. The appearance of these peaks, along with the slight shift relative to the individual polymer and monomer analyses, confirms successful copolymerization and crosslinking between CMC and methacrylic acid. The free-radical polymerization likely resulted in

the formation of a three-dimensional polymeric network. (Hameed et al., 2020; Liu et al., 2018).

The FTIR spectrum of Sulfasalazine showed characteristic peaks at 1616.54 , 1392.74 , 1355.79 , 1260.91 , 1195.31 , 1171.46 , 1124.20 , 1077.50 , 963.63 , 843.42 , 789.99 , 765.20 , 707.74 , 663.96 , 612.67 , 571.58 , 506.34 cm^{-1} , representing functional groups such as -NH , -SO_2 , -COOH , and aromatic C-H bending modes, consistent with previously reported Sulfasalazine analysis. (Cao et al., 2021)

In the Sulfasalazine-loaded CMC-co-poly (MAA) microgel, peaks at 1676.03 cm^{-1} , 1170.66 cm^{-1} , and 506.93 cm^{-1} indicate that the primary functional groups of the drug remain intact after encapsulation. A slight shift in the C=C and C-O-C stretching peaks suggests interaction between the drug molecules and the polymer network, likely through hydrogen bonding or van der Waals interactions, without any chemical degradation of Sulfasalazine. This confirms successful drug loading while maintaining the chemical integrity of both the polymeric microgel and the encapsulated drug.

Thermogravimetric Analysis/Differential Scanning Electrometry

Sample: Sample C
Size: 0.8230 mg
Method: DSC Heatflow

DSC-TGA

File: C:\...New folder\Sample C.001
Run Date: 15-Jul-2003 22:14
Instrument: SDT Q600 V8.3 Build 101

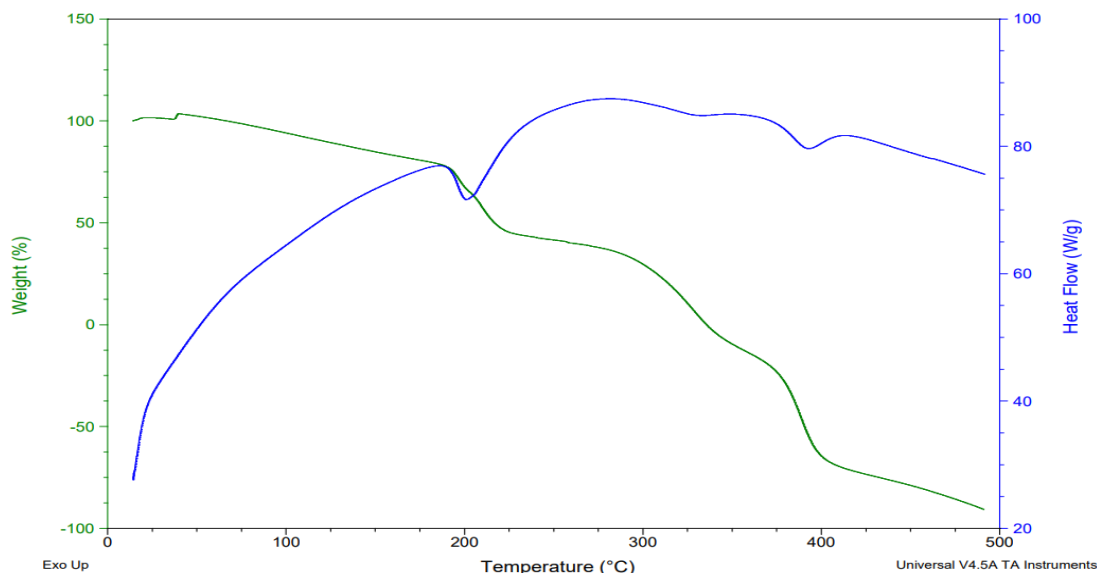


Figure 12 Polymer

Sample: Methacrylic Acid
Size: 13.2560 mg
Method: DSC Heatflow

DSC-TGA

File: C:\...Methacrylic Acid.001
Run Date: 07-Jun-2004 23:30
Instrument: SDT Q600 V8.3 Build 101

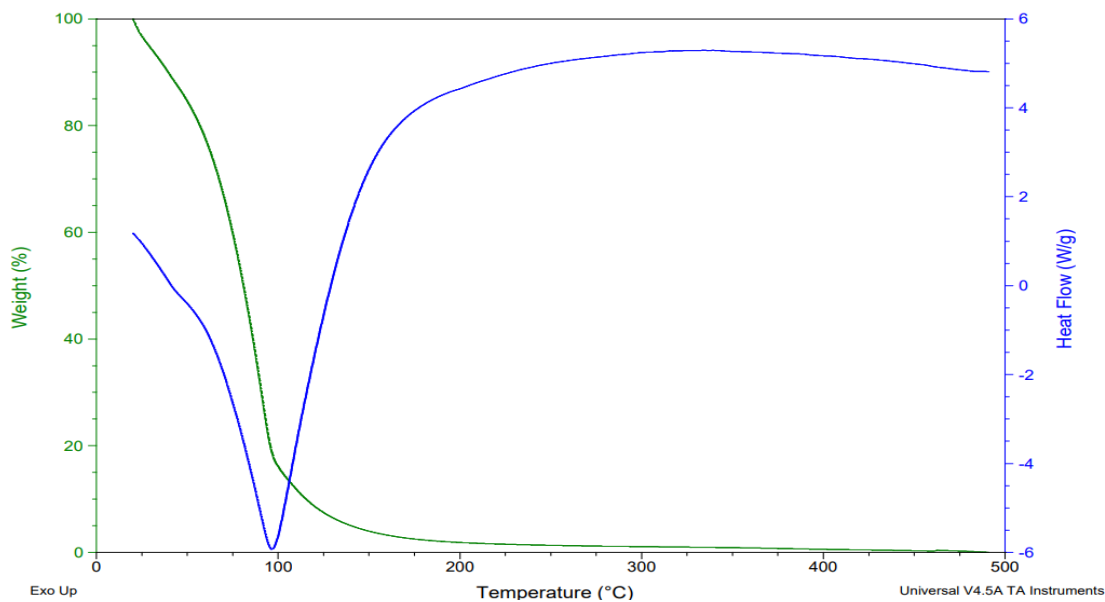


Figure 13 Methacrylic acid

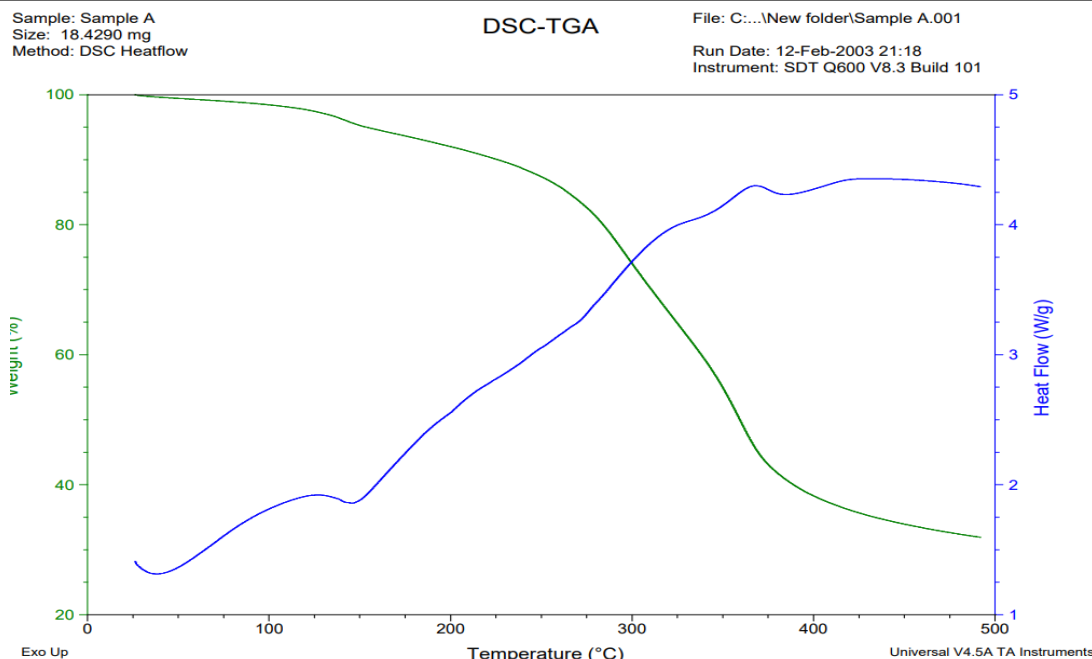


Figure 14 CMC-co-poly MAA Microgel

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were conducted on pure carboxymethyl cellulose (CMC), methacrylic acid-derived polymer constituents, and the synthesized CMC-co-poly (methacrylic acid) microgel to assess their thermal robustness and transitions. In hydrophilic polysaccharides such as CMC, the initial weight loss observed in TGA at relatively low temperatures is typically attributed to the release of physically adsorbed and bound water molecules, due to the high affinity of the carboxymethyl groups for moisture. Thermograms of CMC-based systems have shown this early water loss prior to substantial polymer decomposition, consistent with previous thermal analyses of CMC Hydrogels. (Tuan Mohamood et al., 2021)

The major degradation step for CMC generally occurs at higher temperatures (above ~250–300 °C) and involves the breakdown of the cellulose backbone, including cleavage of glycosidic linkages and decarboxylation of substituted side chains, reflecting the polysaccharide network's intrinsic thermal decomposition behavior. (Tuan Mohamood et al., 2021)

Methacrylic acid monomers are typically not analyzed alone by TGA/DSC in thermal studies, but the thermal behavior of poly(methacrylic acid) and its Hydrogels has been documented. For example, in poly(methacrylic acid) Hydrogels synthesized for drug delivery, DSC measurements revealed transitions corresponding to polymer relaxation and decomposition processes, while TGA provided degradation profiles showing thermally induced weight-loss steps characteristic of methacrylic acid-derived polymer networks. (García et al., 2004)

When comparing copolymers containing CMC with methacrylic acid-derived networks, the TGA curves of CMC-derived microgels typically show a shift to higher degradation temperatures than those of the pure components, indicating enhanced thermal stability. This improved resistance to thermal breakdown is due to the formation of a crosslinked polymer network where strong interchain interactions and the incorporation of methacrylic acid segments increase the energy required to disrupt the structure. (Omer et al., 2023)

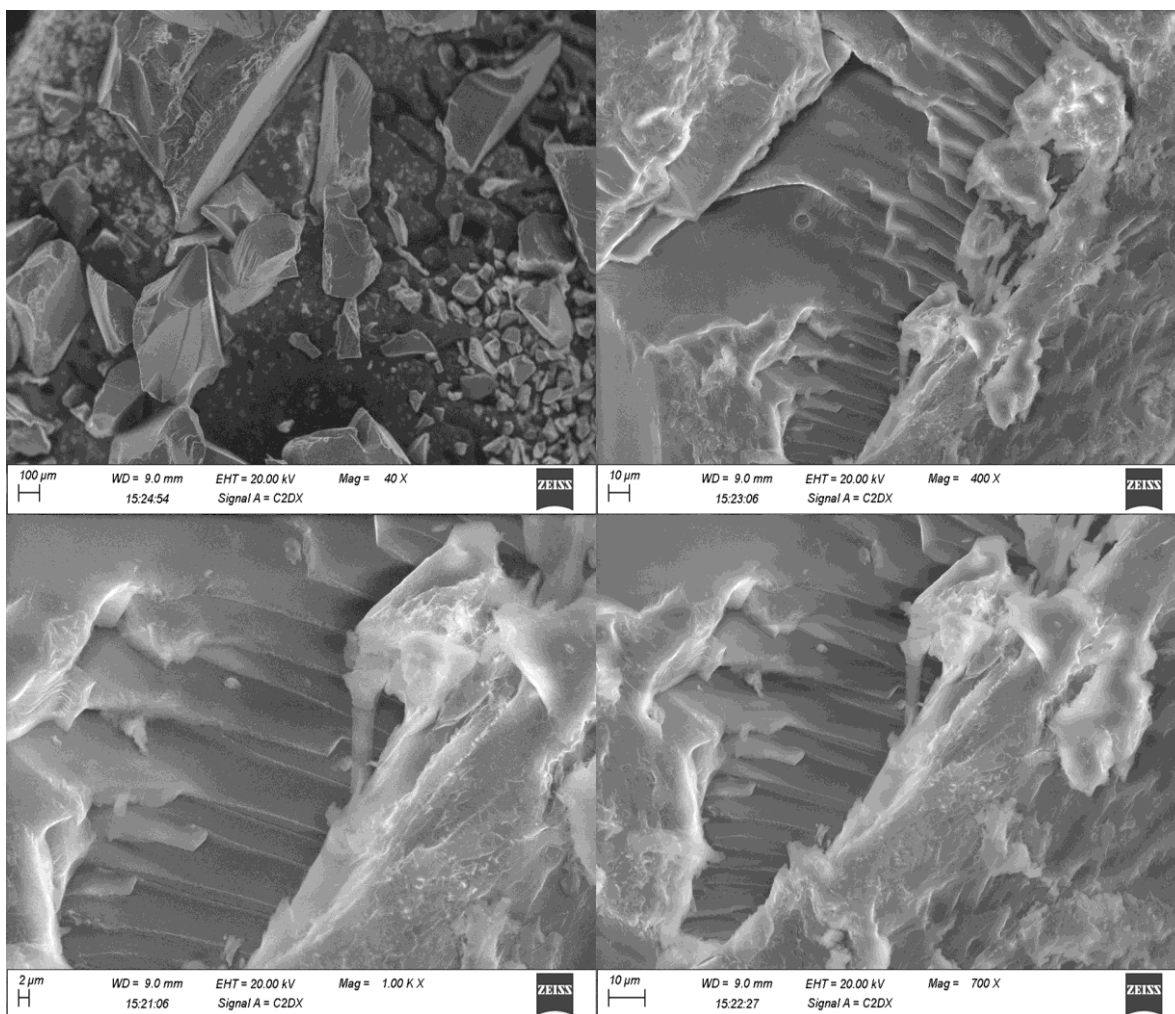
DSC analysis complements TGA results by showing characteristic endothermic peaks associated with moisture loss and polymer

transitions. In copolymer systems, shifts in thermal transitions toward higher temperatures than those of individual homopolymers reflect the increased rigidity and reduced molecular mobility resulting from successful copolymerization and crosslinking. These thermal analytical results confirm that the CMC-co-poly(methacrylic acid) microgel exhibits superior thermal robustness compared to its constituent components,

supporting its structural integrity at elevated temperatures relevant to processing and application. (Omer et al., 2023)

Scanning Electron Microscopy

SEM analysis of the optimized CMC-co-poly (methacrylic acid) Hydrogel's surface morphology is displayed in Figure



Scanning electron microscopy (SEM) was employed to investigate the surface morphology and microstructural features of the optimized CMC-co-poly (methacrylic acid) microgels, as well as those loaded with Sulfasalazine. SEM provides spatial information on the surface texture, pore structure, and morphology that can influence swelling, drug loading, and release behavior. In

many CMC-based Hydrogel systems, SEM images reveal a porous, interconnected network characteristic of highly swollen, freeze-dried polymeric gels. This open, porous structure arises from the extensive crosslinked network formed during polymerization, which creates voids and channels throughout the Hydrogel matrix. (Aswathy et al., 2022)

The intact CMC-co-poly (methacrylic acid) microgel typically exhibits a continuous, porous surface with well-defined pores at different magnifications. Such morphologies result from significant crosslinking between CMC and methacrylic acid monomer units, which disrupts the original polymer chain orientation and leads to a three-dimensional network with enhanced surface area. This porous morphology is beneficial for water absorption, swelling, and drug diffusion, as it provides a larger interface for interaction with the surrounding medium. (Dewi et al., 2024)

Upon loading Sulfasalazine into the CMC-co-poly(methacrylic acid) microgel, SEM images typically show that the porous network remains intact, with slight changes in pore size and surface texture. The presence of the drug within the network may partially fill pores or smooth surface irregularities, indicating successful drug incorporation. This observation aligns with previous SEM studies of drug-loaded CMC

Hydrogel systems, in which morphological features differ from those of unloaded Hydrogels due to the presence of encapsulated molecules within the polymer matrix. (Aswathy et al., 2022; Dewi et al., 2024)

Overall, the SEM analysis indicates that both the unloaded and drug-loaded CMC-co-poly(methacrylic acid) microgels possess porous, interconnected structures, which are essential for efficient swelling and drug release. The observed morphology supports the formation of a stable and robust polymeric network that can accommodate and release Sulfasalazine in a controlled manner.

X-ray diffraction (XRD)

Crystalline and amorphous characteristics of CMC-co-poly(methacrylic acid), pure drug, and drug-loaded CAP-co-poly(methacrylic acid) were analyzed through a diffractometer. Results are shown in Figure

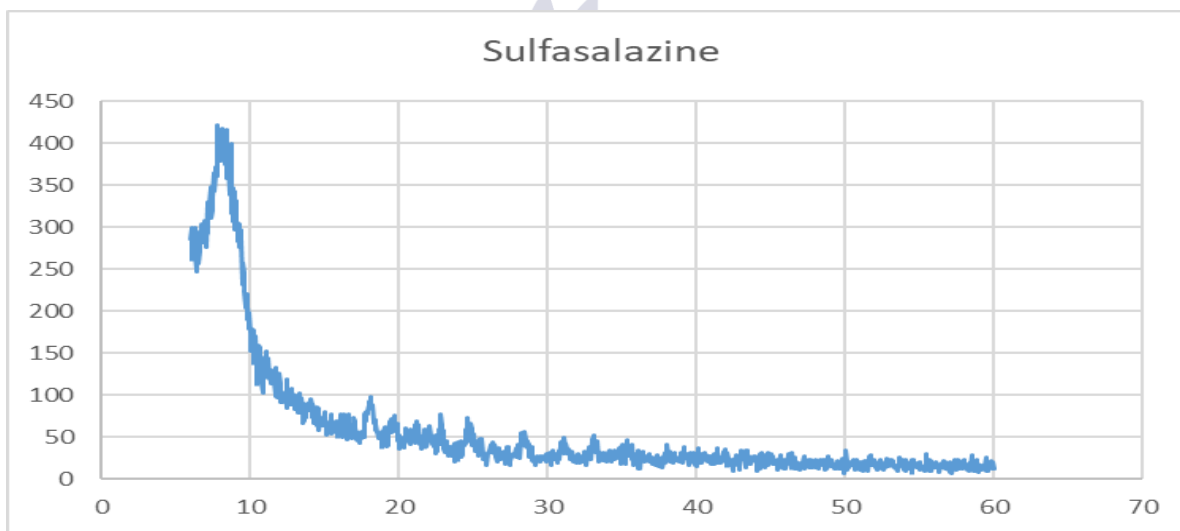


Figure 15 XRD spectrum of Sulfasalazine

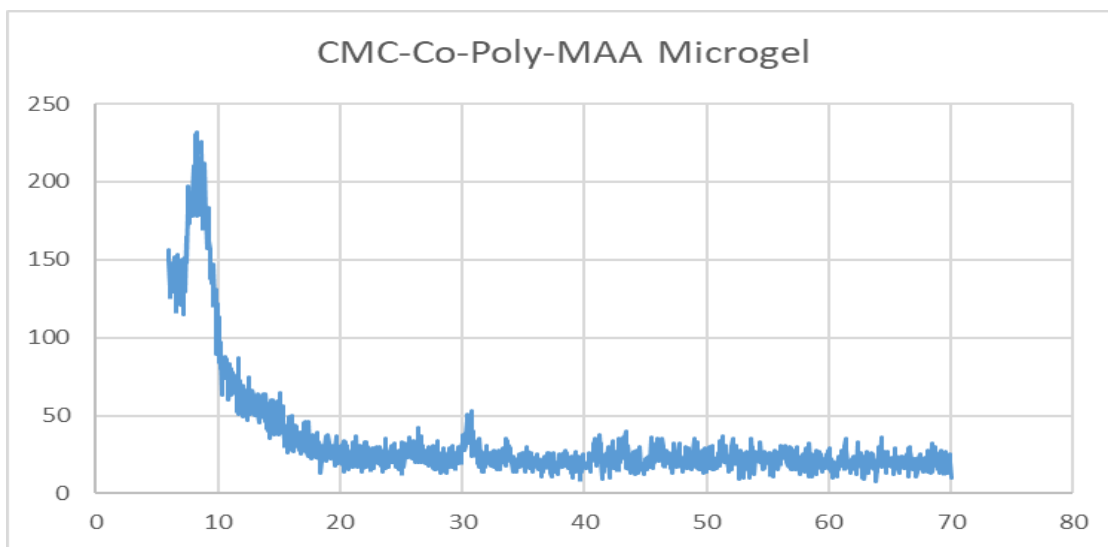


Figure 16 XRD spectrum of CMC-co-Poly-MAA Microgel

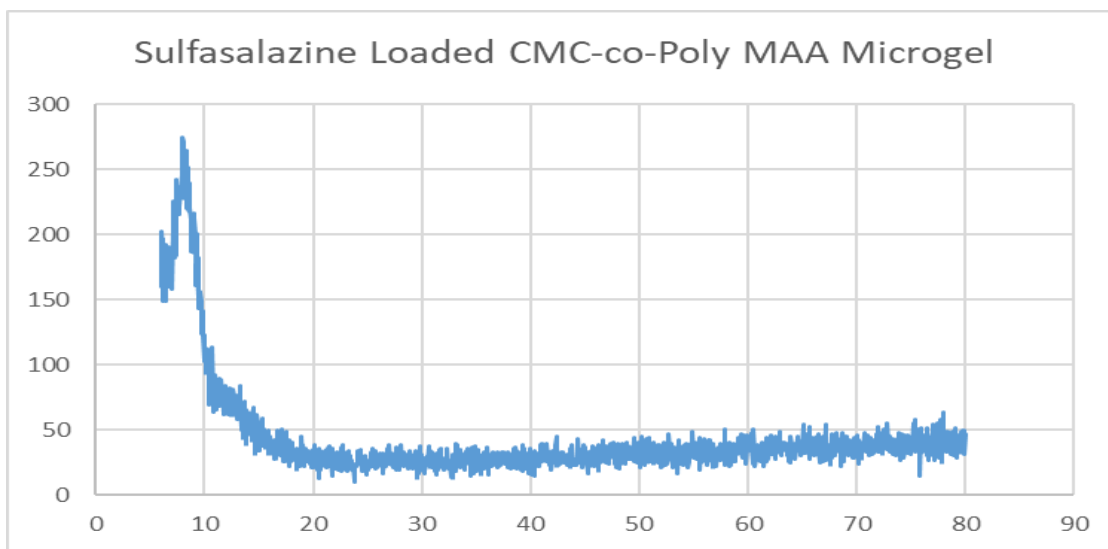


Figure 17 XRD spectrum of Sulfasalazine Loaded CMC-co-Poly MAA Microgel

X-ray diffraction (XRD) analysis was conducted on pure Sulfasalazine, CMC-co-poly (methacrylic acid) microgel, and Sulfasalazine-loaded CMC-co-poly (methacrylic acid) microgel to investigate their crystallinity and structural characteristics. The XRD pattern of the pure Sulfasalazine drug typically exhibits distinct, sharp diffraction peaks, which are characteristic of its crystalline nature and confirm long-range periodic atomic arrangement in the solid state. Powder X-ray diffraction studies of sulfasalazine have shown well-defined diffraction patterns corresponding to

its polymorphic crystal structures, demonstrating that the drug exists in a crystalline form prior to formulation into delivery systems. (Wu & Su, 2018)

In contrast, the diffractogram of the unloaded CMC-co-poly(methacrylic acid) microgel reveals broad halos and the absence of sharp peaks, confirming its predominantly amorphous structure resulting from a randomly cross-linked polymer network. This lack of well-defined crystalline peaks is typical of many Hydrogel systems, where the formation of an interconnected

polymer matrix during copolymerization disrupts regular crystalline domains, leading to a more amorphous profile. (Pourmadadi et al., 2023; Suhail et al., 2022)

Upon loading Sulfasalazine into the CMC-co-poly (methacrylic acid) microgel, the XRD pattern typically demonstrates a reduction in intensity of the drug's characteristic diffraction peaks or a broadening of these peaks, reflecting a decrease in drug crystallinity within the Hydrogel network. This change suggests that Sulfasalazine molecules are partially dispersed at the molecular level within the polymer matrix, leading to reduced long-range order and indicating successful drug encapsulation. Such partial amorphization or reduction in drug crystallinity upon inclusion in polymeric Hydrogels is commonly observed in drug-loaded polymer systems and can enhance dissolution behavior by increasing the drug's molecular dispersion within the carrier network. (Pourmadadi et al., 2023; Suhail et al., 2022)

Overall, the XRD analysis supports the conclusion that pure Sulfasalazine remains highly crystalline, the CMC-copoly(methacrylic acid) microgel is largely amorphous, and the drug-loaded microgel exhibits diminished drug crystalline peaks, consistent with drug incorporation and dispersion within the Hydrogel matrix.

Porosity Measurement

The porosity of a microgel is directly influenced by the number of pores within its structure. Porosity of Hydrogel is directly proportional to the concentration of both CMC and MAA, but is inversely proportional to MBA concentration. It is observed that the porosity of the microgel increases as the CMC concentration increases from 0.1% to 0.3% W/W. The porosity of microgel formulations was found to be influenced by the viscosity of the polymer solution (REF). The removal of bubbles from the formulation decreases with increasing viscosity of the polymer solution, and the residual bubbles are responsible for forming pores within the microgel structure. (Zia et al., 2020). As a result of polymer-monomer crosslinking, increasing MBA concentration decreased porosity. Because of this significant entanglement, the occupied volume decreases.

(Zia et al., 2020). Characterization tests showed that while an increase in crosslinker concentration is advantageous for mechanical stability, a decrease in porosity may reduce the rate of drug release via diffusion through these capillary channels. (Chavda & Patel, 2011)

Because there is less MBA in the AN-7 formulation, the volume of pores is at its maximum; in the AN-9 formulation, however, the volume of pores in Hydrogels is reduced due to the insertion of a higher cross-linker within the polymer structure. When AN-7, AN-8, and AN-9 formulations were compared, the cross-linker concentration increased gradually, while porosity decreased.

Swelling Index

Swelling studies of microgels have been conducted at pH 1.2, 6.8, and 7.4 to verify their swelling behavior at different pH levels. The results from the studies show that the microgel's swelling increased as pH increased. A swelling investigation was conducted on three Hydrogel formulations: AN-1, AN-2, and AN-3. As the concentration of cellulose acetate phthalate was increased from 0.1% w/w to 0.3% w/w, the swelling behavior increased. The swelling index was studied at different pH levels at different time intervals.

A higher polymer content leads to less crosslinking, increasing porosity and allowing higher solvent levels in the formulation, thereby increasing swelling.

Because CMC (polymer) comprises hydroxyl (-OH) and carboxyl (-COOH) hydrophilic groups, it imparts hydrophilicity to the formulation, increasing its ability to absorb water and swell. Additionally, the presence of more ionizable moieties (acetyl) at higher CAP concentrations increases the likelihood of electrostatic repulsion, leading to expansion of the polymeric network.

CMC-co-poly (methacrylic acid) Hydrogel was subjected to swelling tests at different pH levels with a rise in monomer content of 10% w/w in AN-4, 20% w/w in AN-5, and 30% w/w in AN-6 formulations. A decrease in edema was observed as the MAA concentration increased. Less swelling was observed in formulations A-4 and A-5, which contained higher monomer (MBA)

concentrations. Increasing the monomer concentration lowers the swelling index and raises the viscosity of the formulation. (Zia et al., 2020). CMC-co-poly(methacrylic acid) Hydrogel was subjected to swelling tests across a range of cross-linker concentrations. created Hydrogel AN-7, AN-8, and AN-9 with varying MBA concentrations, utilized as a cross-linker.

High cross-linker concentrations cause the microgels to swell less because their structures are denser and have less water-accessible volume. Because it directly influences the degree of swelling and, consequently, the viscoelastic properties of the Hydrogel, the concentration of the crosslinking agent in the Hydrogel network is a crucial parameter to study. The impact of three distinct crosslinking agent concentrations, 1, 2, and 3 mol% relative to the monomer, was examined in this study.

In-Vitro Drug Release Studies

As indicated by 3 to 19 and Figure 3-12 to 3-22, the % drug release in the CMC-co-poly(methacrylic acid) Hydrogels with varied CAP, MAA, and MBA concentrations had distinct release patterns at pH 1.2, 6.8, and 7.4. As seen in Figure 3-20, the percentage of medication release at pH 1.2 ranges from 25.63 to 36.88. AN-2 exhibited a maximum release of 36.88 at pH 1.2, while AN-9 displayed a release of 36.88.

Compared to pH 1.2, the percentage release at pH 6.8 is substantially larger. At pH 6.8, the release ranges from 58.49 to 77.02. According to Figure 3-21, AN-9 had the highest release of 77.02 percent, whereas AN-1 had a release of 58.49 percent. However, comparing the release behavior at pH 7.4 with that at pH 1.2 and 6.8 reveals the greatest release at pH 7.4. As seen in Figure 3-22, the AN-1 formulation had the highest release of 94.62 at pH 7.4, while the AN-9 formulation had the lowest release of 75.63%.

Sulfasalazine release was markedly lower at pH 1.2 than at pH 6.8 or 7.4. After 24 hours of dissolution, the maximum release at pH 1.2 was 36.88%, compared with 77.02% and 94.62% at pH 6.8 and 7.4, respectively, indicating enhanced release at higher pH values.

Sol-gel Analysis

Sol-gel analysis was used to ascertain the amount of unreacted polymer or monomer in the microgel. Sol-gel analysis was used to quantify the fraction of monomer or polymer remaining uncrosslinked within the hydrogel network. To assess the impact of various Hydrogels compositions, CMC-co-poly (methacrylic acid) Hydrogel formulations were examined. The fraction of gel decreased as the amount of carboxy Methyl Cellulose in the hydrogel formulation. This is because a high polymer concentration reduces the extent of crosslinking, thereby increasing the Hydrogel formulation's solution fraction. Conversely, increasing the concentrations of the monomer and crosslinker accelerated gelation. At higher concentrations, the fraction of the material existing as gel becomes predominant over the solution phase, due to enhanced crosslinking and polymer chain entanglement.

Water uptake analysis

The pore size and volume in the microgel preparations are critical factors that influence the water-absorption capacity of the developed system. Highly porous microgel formulations with numerous pores and a high capacity to hold water are produced by increasing the polymer concentration. An increase in polymer concentration from 0.1 to 0.3% was found to increase water absorption capacity due to decreased crosslinking, while a rise in monomer content from 10 to 30% boosts water absorption due to an increased interconnected pore structure. However, in the case of the MBA, crosslinking and tangling reduced the microgel formulation's water absorption capacity as the concentration of each component increased.

Conclusion

The preparation and characterization of the pH-sensitive microgel for the gastroprotective administration of Sulfasalazine are the objectives of this study. To make a pH-sensitive microgel, CMC, MAA, and APS were used via free-radical polymerization. It was then crushed into a powder with consistent particle size and favorable flow

characteristics. The model medication was filled with Sulfasalazine. It can be concluded that the microgel formulations developed have a high safety index, as validated by toxicological investigations. They are also useful for regulating the drug's release rate when administered orally for gastroprotective purposes. Along with the toxicological assessment of the produced Hydrogels, sol-gel, water absorption, apparent density, porosity, swelling index, and drug release were measured. The highest swelling and release behavior were observed at pH 7.4, demonstrating the pH-responsive behavior. Swelling and release were carried out at pH 1.2, pH 6.8, and pH 7.4. At pH 1.2, CMC-co-poly (methacrylic acid) swelled very little at the release rate.

The studies conducted to analyze microgels and manufactured products indicate gastroprotective drug delivery and controlled drug release from CMC-co-poly(methacrylic acid) Hydrogels and pH-responsive matrix tablets designed for targeted Sulfasalazine delivery, a gastric irritant.

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