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Development and Evaluation of pH-Sensitive Polyethylene Glycol Hydrogels Containing Aloe Barbadensis for Sustained Drug Release in Ulcerative Colitis Treatment"

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Abstract

The present study explores the development and evaluation of pH-sensitive polyethylene glycol (PEG) hydrogels loaded with Aloe Barbadensis for controlled drug release, particularly for localized treatments like ulcerative colitis. Aloe Barbadensis, a popular medicinal plant, is utilized as the therapeutic agent due to its known healing properties. Various PEG-based hydrogels were synthesized through different combinations of gelatin (Monosan), monomers, and cross-linkers to assess their impact on hydrogel properties. The gel content percentage and gel formation time were key parameters measured during the hydrogel preparation. Results showed that PEG-1 to PEG-3 formulations, which had increasing concentrations of gelatin, exhibited lower gel content percentages, with values between 70% and 80%. In contrast, formulations PEG-4 to PEG-6, with higher monomer content, demonstrated significantly higher gel yields, ranging from 80% to 90%. The time required for complete gel formation was shortest in formulations with higher monomer and cross-linker concentrations, reaching completion within 2–3 hours. In vitro drug release studies, conducted under pH 1.2 and pH 7.4 conditions, revealed that Aloe Barbadensis release was highly pH-dependent. At pH 1.2, the release was minimal, showing around 20% drug release, while at pH 7.4, the cumulative release reached approximately 89% within 48 hours. This data confirms that Aloe Barbadensis-loaded PEG hydrogels exhibit a pH-

responsive drug delivery system, with controlled and sustained release, making them a promising option for localized topical applications in conditions like ulcerative colitis.

Keywords: Aloe Barbadensis, Hydrogel, Polyethylene Glycol, Ulcerative Colitis, Controlled Drug Release,

Introduction

In recent years, the development of targeted drug delivery systems has gained significant attention, particularly for treating diseases affecting the intestinal region, such as irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, and colorectal cancer. These conditions often require localized drug delivery to ensure therapeutic efficacy while minimizing systemic side effects. Colon Targeted Drug Delivery Systems (CDDS) have emerged as a critical tool to deliver drugs effectively to the colon, a region characterized by a high pH environment, which prevents premature drug release in the stomach [3]. The colon's unique features, including its limited proteolytic activity and long residence time (up to five days) compared to the small intestine, make it an ideal target for pharmaceutical intervention [5].

Various strategies have been employed to enhance colon-specific drug delivery, including the use of prodrugs [6,7], pH-responsive polymer coatings [8,9], and timed-release formulations [10]. The pH gradient across the gastrointestinal tract is particularly useful for pH-sensitive drug delivery systems, which release the active pharmaceutical ingredients (APIs) in a controlled manner depending on the local pH. Over the past few years, pH-dependent polymers such as chondroitin sulfate (CS), polyethylene glycol (PEG), and acrylic acid (AA) derivatives have been increasingly used due to their ability to solvate in water, providing an effective mechanism for drug release [12].

Hydrogels, which are three-dimensional, cross-linked polymeric networks, have become a cornerstone in drug delivery applications. These hydrogels, composed of natural and synthetic polymers, exhibit high water retention and can swell without dissolving in physiological conditions, making them particularly well-suited for controlled drug release. Additionally, these materials can be engineered to be biodegradable or dissolvable under specific environmental conditions, such as changes in pH or temperature, providing further versatility in biomedical applications [11-15].

Despite their high biocompatibility, hydrogels must be carefully designed to optimize mechanical stability, swelling capacity, and biofunctional properties. The present study investigates the synthesis of pH-sensitive hydrogels using polyethylene glycol (PEG) combined with natural polymers like Aloe Barbadensis to provide a sustained, localized release of therapeutic agents. By examining various cross-linking techniques and polymer ratios, this research aims to enhance the design of drug delivery systems for colon-specific applications, with particular emphasis on treating inflammatory bowel diseases (IBD) like ulcerative colitis. Through this approach, we aim to advance the field of targeted drug delivery by developing a robust platform for controlled drug release tailored to the needs of specific diseases.

Materials & Methods:

Polyethylene Glycol (PEG), Gelatin, Eudragit, Formaldehyde, Aloe Barbadensis extract, Methacrylic Acid (MAA), N, N'-Methylenebisacrylamide (MBA), Hydrochloric acid (HCl), phosphate buffer solutions, solvents (Water + Ethanol), FTIR Spectrophotometer, UV-Vis Spectrophotometer, Dissolution apparatus-II (USP type II Paddle method, 900 mL vessel), Vacuum oven, weighing balance, Rotary evaporator, cross-linking apparatus, Swelling studies setup, reaction vessels, and stirrers.

Method:

Preparation:

The procedure began by filling three beakers with 50 mL of distilled water each. To each beaker, 2.5 g (plate#12), 2 g (plate#7), and 1.5 g (plate#11) of Eudragit were added, and the solutions were mixed with magnetic stirrers to ensure uniformity. In parallel, three other beakers with 50 mL of distilled water received gelatin in varying amounts: 9 g, 8 g, and 7 g. The gelatin in water was mixed using a stirrer to form a gel solution. For the preparation of the gelatin combinations, Gel A and B (9 g total) were mixed, and then 1.5 g, 2 g, and 2.5 g of the Eudragit mixtures were added, resulting in Mixtures A, B, and C, respectively. Afterward, formaldehyde drops (10, 20, and 15) were added to each mixture, followed by the incorporation of 1 g of Aloe Vera using magnetic stirrers. The prepared mixtures were then poured into test tubes and allowed to set at room temperature for 24 hours. After setting, the hydrogels were cut into cubes and subjected to stability and purity characterization.

Characterization

FT-IR Analysis: The FT-IR spectra of pure gelatin, Eudragit, Aloe Barbadensis plant extract solution (with formaldehyde), as well as drug-unloaded and drug-loaded hydrogel discs, were recorded. The hydrogel samples were crushed and analyzed using ATR-FTIR (Bruker, Germany) in the range of 4000–600 cm^{-1} to investigate the molecular interactions and confirm the incorporation of the therapeutic agent into the hydrogel network.

Gel%, Yield%, and Gel Time Analysis:

The Gel%, Yield%, and Gel time were measured to assess the extent of reactant organic polymerization during the hydrogel formulation process. The dry hydrogels were incubated in water for seven days, after which the Gel% and Yield% were determined, along with the swelling values (%) to evaluate the hydrogel's ability to retain water and its overall performance during the swelling process. These parameters provided insights into the efficiency of crosslinking and the hydrogel's structural integrity [18].

Hydrogels Swelling

To study swelling for pH-sensitive Hyd r ogel disks, they were dried, and then immersed in either pH 1. 2 HCl or phosphate buffer (pH = 7. 4) solution for 24 h under 37 °C temperature conditions. During this period of time that the swelling degree Q, which is the weight of water inside the hydrogels per unit of g dry gel mass per mass [28], was calculated.

Drug Release Study

Drug release studies were conducted at both low and high pH to assess the pH-dependent delivery of Aloe from the PEG hydrogel system. Swollen hydrogel discs containing Aloe were placed in 900 mL of pH 1.2 and pH 7.4 solutions, and evaluated using the USP Dissolution Apparatus-II, with stirring at 37 ± 0.5°C. The released Aloe was quantified using a UV-visible spectrophotometer at λmax 205 nm to determine the amount of drug released over time [19].

Kinetic Study of Aloe Barbadensis Release in Deionized Water

To study swelling for pH-sensitive Hydrogel disks, they were dried, and then immersed in either pH 1. 2 HCl or phosphate buffer (pH = 7. 4) solution for 24 h under 37 °C temperature conditions. During this period of time that the swelling degree Q, which is the weight of water inside the hydrogels per unit of g dry gel mass per mass [28], was calculated.

Zero-Order Release

The release of the substance in a disk has nothing to do with drug concentration--that's plain old zero-order release all the time Then the equation for zero-order release becomes: Ft = Fo + Kot Where F is fraction of medication released at time 't' (zero-order release); K0= apparent speed constant required for Zero order and Fo is Initial amount of drug loaded into hydrogel disc.

First-Order Release

The first-order release has a better performance, that under equilibrium conditions for boxbebads and bridge linked formulations can be written as:

[Ft = Fo + K_1t]

Where:

K1 - first order release constant rate which are relationship of drug retention is linearly proportional to the retained amount in the dosage form/matrix, and provided once sink condition performed by medium.

Higuchi model

The Higuchi model, based on Fick's Law, describes the amount of medication delivered over time as the square root of time multiplied by a constant. Where the constant, K2, is related to the diffusion and release of the drug or active ingredient.

Korsmeyer-Peppas kinetic model

The Korsmeyer-Peppas kinetic model analyzes drug discharge from implanted drug delivery mechanisms as the fraction of drug released over time raised to a release exponent. The magnitude of n provides insight into the process taking place: If n is less than or equal to 0.45, diffusion alone governs release. Should n fall between 0.45 and 0.89, both diffusion and degradation synergistically control release kinetics. When n is greater than or equal to 0.89, degradation predominates in determining the rate and extent of drug deployment from the delivery system.

RESULTS

FTIR Analysis

FTIR spectral analysis of Eudragit, gelatin, formaldehyde, and Aloe Barbadensis (ALOE) revealed absorption peaks at 3439 cm^{-1} (intermolecular hydrogen-bonded -OH stretching) and 3282 cm-1 (-NH stretching in secondary amides, specifically Gelatin amide A), which correlated with an increase in gelatin content. A specific absorption peak at approximately 1383 nm, not observed in FTIR spectra, suggests the presence of multiple N-H bond groups at the interface. When Eudragit RS-100 was analyzed in the IR spectrum, additional peaks were detected due to interactions between its carbonyl group and adjacent moieties. The carboxylic ester region at 1736 cm^{-1} was associated with CO stretches from both the free acid and ester forms, producing a seven-point peak. The stretching vibration peak at 3283–3466 cm^{-1} and 1637 cm^{-1} in the FTIR spectrum is attributed to amino groups in alcohol, phenol, and amines, which may be present in the Aloe Vera extract used during the synthesis of

nanoparticles (NP) as shown figure **1**.

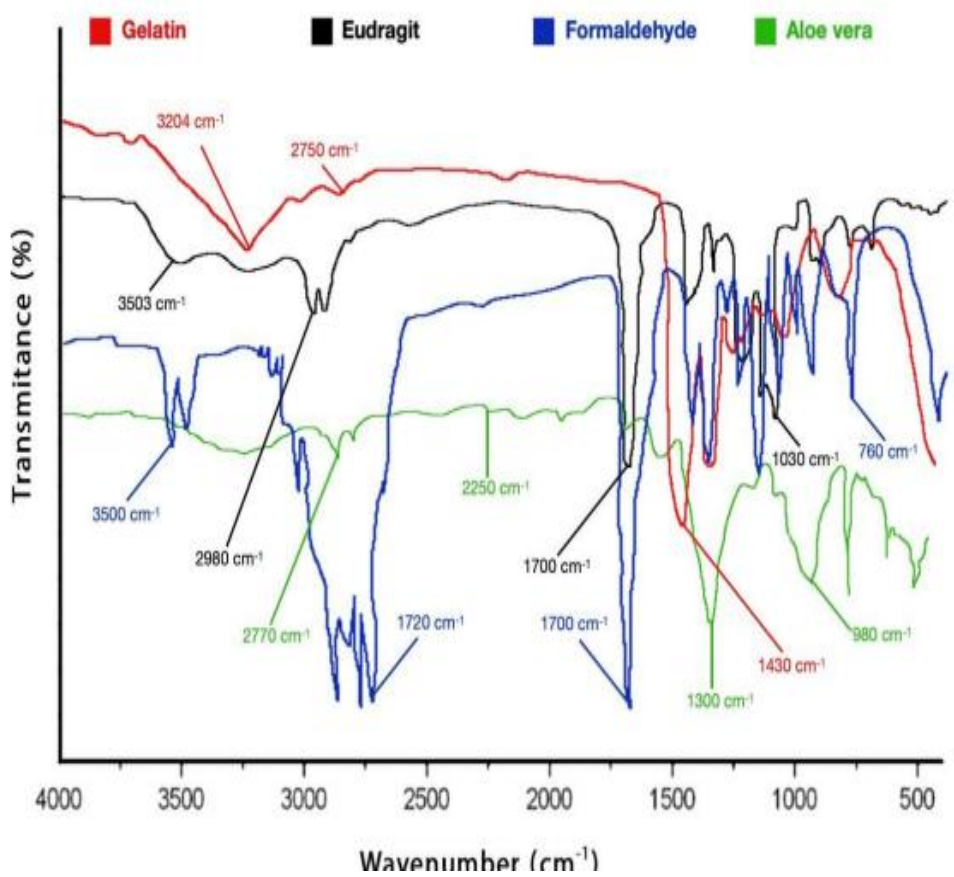

Figure 1. FTIR Spectrum, Gelatin, Eudragit, Formaldehyde and Aloe vera

Influence on the Gel%, Yield% Gelling Time of Devolved Hydrogel

Figure 3 illustrates the gel content (%) and yield (%) of PEG hydrogels as a function of polymer, monomer, and cross-linker concentrations, as shown in panel (a). Additionally, panel (b) presents the gel time corresponding to each variable. The study evaluates the influence of these variables on the hydrogel properties, with all factors carefully adjusted in the model to isolate their individual effects. This analysis provides insight into how the concentration of each component—polymer, monomer, and cross-linker—affects both the gel formation and yield, as well as the time required for complete gelation.

Polymer Content: An increase in the gelatin content led to lower gel% values for a series of polymeric hydrogels (characterized by PEG-1 to PEG-3). However, the gelatin yield% increased as the gelatin content rose, indicating that the initial concentration of gelatin significantly influenced the crosslinking density of the hydrogels. This demonstrates the critical role of gelatin concentration in both the gel content and the efficiency of the crosslinking process. Additionally, when the monomer content was increased (PEG-4 to PEG-6), both yield% and gel% values were higher across all formulations, further emphasizing the importance of monomer concentration in hydrogel formation [21-24].

Gel Time: The higher concentration of active primary radicals in SDCS22 resulted in a decreased average gel time, as more initial free radicals of the C=C chain with N=O onotomer were formed. This led to a faster reaction rate and earlier monomer combination compared to the control group, as shown in Figures 2. Regarding cross-linker content, formulations with higher cross-linker concentrations (PEG-7 to PEG-9)

demonstrated a decrease in gel time as the percentage of cross-linker increased from 20% to 30%. Additionally, both yield% and gel% improved with higher cross-linker content, highlighting the role of cross-linker concentration in accelerating gel formation and enhancing hydrogel properties. An increase in cross-linker concentration resulted in a rapid decrease in gel time and an improvement in yield%.

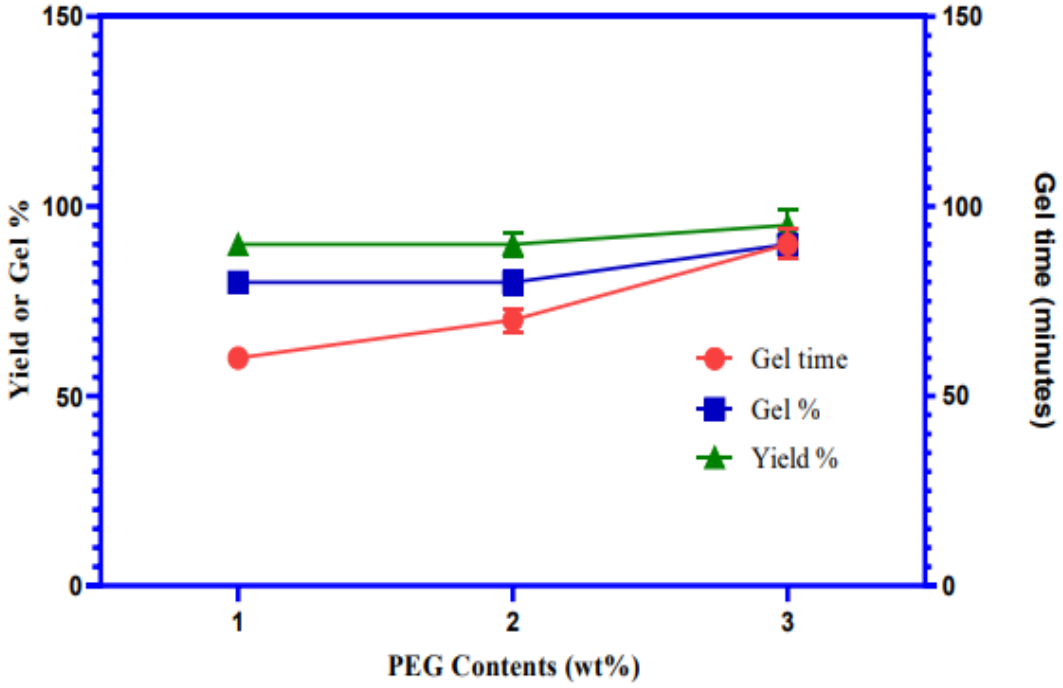

Figure 2. Effect of PEG concentrations

Swelling and Deswelling of Hydrogels in Phosphate Buffer Solution

Swelling behavior of the hydrogels was studied in phosphate buffer media at pH 1.2 and pH 7.4. The swelling of the hydrogels was analyzed through graphs over different time periods. The swelling behavior was found to be medium-specific, with the rate of swelling varying depending on the conditions. The formulations were adjusted by changing the concentration of the polymer, the type of monomer, and the concentration of cross-linkers. Three series of formulations were prepared to investigate the influence of polymer (PEG) content on dynamic swelling, Qt, and equilibrium swelling. The PEG series from PEG-1 to PEG-3 showed an increase in polymer concentration, PEG-4 to PEG-6 focused on a stepwise increase in monomer concentration (Gelatin), and PEG-7 to PEG-9 studied the evolution of cross-linker concentration (ditertbutylcarbamate, MBA). The results demonstrated that the hydrogels exhibited pH-dependent swelling behavior, likely due to the ionization of functional groups in the polymeric system. The influence of an increased polymer-to-polymer (Gelatin) ratio, from PEG-1 to PEG-3 formulations, was tested for its effect on swelling behavior. Gelatin, being highly hydrophilic and containing numerous functional groups such as OH (hydroxyl), SO3- (sulfonic), and COOH (carboxyl) groups, contributed to the pH-responsive nature of the hydrogel. As pH levels increased above 4, sulfonate and carboxylate groups were deprotonated, enhancing the charge and causing these groups to repel each other. This repulsion induced significant swelling and disruption of the hydrogel's structural continuity. The increase in swelling was attributed to ionization and electrostatic repulsion,

particularly influenced by the incremental gelatin ratio.[45]

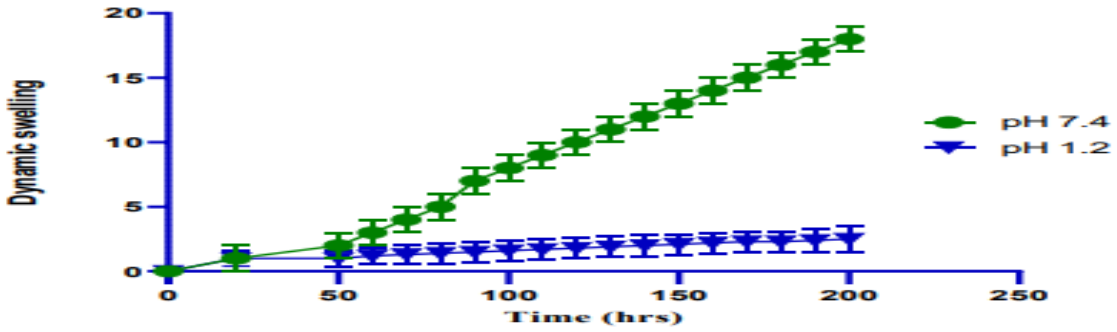

Figure 4.3 Effect of different pH mediums on dynamic swelling

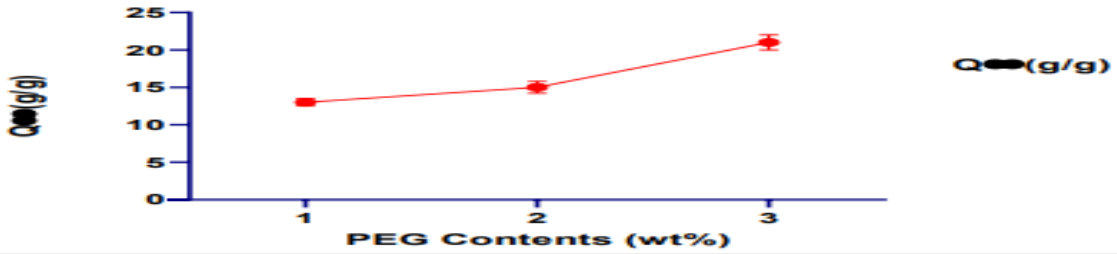

Figure 3. Effect of PEG concentration on drug release

Drug Entrapment

Hydrogels demonstrate effective drug encapsulation due to their network structures, which swell to accommodate the drug, making it a key factor influencing water uptake within the system. Drug loading was significantly affected by the entrapment capacity, which increased as the pH of the medium rose. This behavior is attributed to the ionization of carboxylic, hydroxyl, and sulfonate groups present on the PEG chains. As the pH increased, the deprotonation of the hydroxyl and carboxyl groups was enhanced, leading to electrostatic repulsion between the negatively charged groups along the polymer chain. This repulsion promoted greater water absorption by the hydrogel, facilitating the encapsulation of a higher volume of drug within the polymeric network. Consequently, the higher the polymer content, the more swelling and drug entrapment were observed in the hydrogels, indicating a direct relationship between polymer concentration, water uptake, and drug loading in the system.

Aloe Barbadensis Release Profile

Figure 3 presents the dispersion profiles of Aloe Barbadensis from PEG hydrogels, showing the drug release behavior over time under different pH conditions. In the dissolution medium, the drastic changes in pH significantly impacted the drug release from the hydrogels, as illustrated by the profiles. The pH-sensitive swelling behavior of the hydrogels was evident, with a low degree of swelling observed in acidic conditions (pH 1.2). However, the swelling was much more pronounced in alkaline conditions, where the hydrogel mass increased by approximately five times between its dry weight and final equilibrium weight after 48 hours of incubation at pH 7.4.

At lower pH (1.2), the hydrogels exhibited reduced swelling due to the protonation of carboxylic acid groups, which enhanced hydrogen bond strength and reduced electrostatic repulsion between the COOH groups. This resulted in a lower swelling rate and reduced release of Aloe. In contrast, at pH 7.4, the deprotonation of carboxylic groups led to a greater negative charge, reducing hydrogen bonding and

causing the hydrogel to swell more significantly. This facilitated a higher release of Aloe from the polymeric system. In vitro release studies in phosphate buffer at pH 7.4 demonstrated that the release followed zero-order and first-order kinetics, as per various mathematical models that correspond to diffusion from the drug-polymeric composite gels. The results confirmed controlled drug delivery, particularly under higher pH conditions, with significant potential for targeted drug delivery devices in the small intestine within 24 hours.

Moreover, the release of Aloe from the hydrogels was influenced by the concentration of reactants. Higher polymer concentrations led to greater deprotonation of carboxylic and sulfonic groups, which in turn increased the drug release percentage. Hydrogels with higher concentrations of monomer (MAA) and cross-linker (MBA) exhibited slower drug release rates, likely due to the increased proportion of unionized carboxylic and sulfonic groups that reduced diffusive erosion. The initial release of Aloe at pH 1.2 was approximately 20%, but under alkaline conditions (pH 7.4), the cumulative release reached nearly 89%, simulating the small intestine environment. The radiometric results also aligned with the percentage Q-values, confirming the release behavior, similar to studies by Oprea et al., who reported drug release values of 83% in chitosan (CS) and cellulose formulations [25].

Release Profiles and Kinetic Models of Aloe Barbadensis

Moreover, the release kinetics of Aloe Barbadensis from all PEG hydrogels were evaluated via different kinetic models including zero-order kinetically (ZOK), first order momentum and Higuchi model as well as Korsmeyer–Peppas equation. The releases were non-conforming to zero-order kinetics, thereby denoting that the mechanism of drug release from these hydrogels was diffusion controlled in all cases. The Coefficient of correlation stand higher among all different comparison indicated the consistency in releasing drug into receptor compartment and decreased concentration at release site were found which declared that Drug release was controlled by diffusion, reveal one order kinetic model. Different formulations (PEG-1– PEG 5 – PEG-9) were shown possible to be release from Higuchi model with higher R^2 values, range between is from 0.9194 and 0.9775 The diffusion exponent (n) between 0.592-0.721 shows that all of the formulations comply with Korsemeyer-peppas requirements [20]. This suggested that the drug release mechanism was non-Fickian type which described a super Case-II transport, and can be expressed by Korsmeyer et al. (1983) (21). Drug diffusion in the hydrated matrix and polymer relaxation together were main mechanism of this combination. Similar kinetic models were also applied by Amrutkar and Gattani to the formulations based on chondroitin sulphate [11]. Their results revealed a different model as the best fit compared to ours where the first-order kinetics were followed by Korsmeyer–Peppas [26].

Table 1 Release kinetic modeling of Aloe loaded

Formulation	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)	n
PEG-1	79.55%	96.82%	92.75%	96.42%	0.721
PEG-2	70.02%	98.83%	92.77%	91.94%	0.639
PEG-3	83.10%	99.23%	91.94%	97.75%	0.634
PEG-4	87.75%	99.66%	97.71%	92.75%	0.592
PEG-5	76.25%	97.06%	97.75%	92.77%	0.567
PEG-6	77.13%	91.26%	96.71%	96.17%	0.511
PEG-7	84.15%	96.00%	93.56%	95.67%	0.691
PEG-8	88.10%	97.39%	95.67%	97.71%	0.697
PEG-9	73.21%	97.96%	96.42%	93.56%	0.691

Discussion

In the present study, we provide a comprehensive investigation of pH-sensitive polyethylene glycol (PEG) hydrogels, examining their chemical composition, physical properties, and drug release behavior for the first time. FT-IR analysis revealed the characteristic peaks of Gelatin, Eudragit RS 100, Formaldehyde, and Aloe Barbadensis, which are responsible for various functional groups in these drug compounds. These findings are crucial for understanding the cross-modal interactions within the hydrogel system. The study also highlighted the complex relationship between gel properties and the concentrations of polymer, monomer, and cross-linker. Specifically, an increase in gelatin content resulted in both higher gel content and yield, underscoring the integral role gelatin plays in determining the crosslinking density of the hydrogels. This finding aligns with previous studies that suggest the concentration of gelatin is a critical factor influencing the mechanical and structural properties of hydrogels.

In contrast, altering the concentrations of monomer and cross-linker produced opposing effects on the hydrogel properties. Higher initial monomer content, for instance, accelerated the reaction rate, but it also led to longer gelation times, indicating that the reaction kinetics is sensitive to the monomer concentration. Previous research has similarly demonstrated that increasing the cross-linker concentration improves gelation efficiency, although the rate of gel formation may still vary depending on the polymer's composition. These insights are essential for optimizing the formulation of hydrogels with desirable mechanical properties for drug delivery systems.

The swelling studies conducted under different pH conditions revealed that the hydrogel network is responsive to pH, with ionization of functional groups influencing swelling behavior. Gelatin, being hydrophilic, exhibited a higher degree of swelling at pH values above neutral. This suggests that PEG-based hydrogels with gelatin can be effectively used in controlled drug release systems that need to swell in response to different physiological conditions, such as those found in the gastrointestinal tract. The swelling behavior was found to be concentration-dependent, further highlighting the role of polymer concentration in determining the swelling capacity and, consequently, the drug release profile. Increased swelling resulted in greater drug entrapment, reinforcing the relationship between swelling and drug loading capacity in hydrogels[25].

Aloe Barbadensis demonstrated a pH-dependent drug release profile, providing site-specific delivery under varying pH conditions. This pH-responsive behavior is particularly beneficial for applications targeting the colon, where pH changes dramatically from acidic in the stomach to neutral/alkaline in the intestines. Drug release kinetics were analyzed using several models, including zero-order, first-order, and Higuchi models, with the results suggesting a complex interplay of factors influencing the drug release mechanism. The data points to a diffusion-controlled release mechanism, wherein drug diffusion through an acrylate-based matrix, combined with relaxation steps, governs the overall release rate. This pH-sensitive release profile makes the Aloe Barbadensis-loaded PEG hydrogels a promising candidate for site-specific drug delivery applications, particularly for targeting localized treatment areas such as the colon, where controlled and sustained release is crucial.

Conclusion

The chemical cross-linking of Gelatin and Eudragit significantly improved their individual performances, leading to the development of a pH-sensitive polymer network. This cross-linking enhanced the mechanical properties of the polymeric system, achieving a balance between limited water uptake at low pH levels and

effective ion influx at high pH values. The pH-responsive nature of the hydrogel was tailored to promote drug release, particularly in alkaline conditions. This design enabled the hydrogels to respond dynamically to changes in pH, ensuring efficient drug delivery in target areas such as the intestines. The controlled release profile of Aloe-loaded hydrogels exhibited similar release kinetics to Hydrogel Ib, which contained both nano- and microparticles. This suggests that the incorporation of Aloe Barbadensis into the pH-sensitive hydrogel matrix results in a consistent and sustained drug release, further supporting the potential of these hydrogels for targeted drug delivery applications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

All the authors equally contributed to this manuscript.

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