

Article

Structural, Swelling, and In Vitro Digestion Behavior of DEGDA-Crosslinked Semi-IPN Dextran/Inulin Hydrogels

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Abstract

In this study, semi-interpenetrating polymer network (semi-IPN) hydrogels based on methacrylated dextran and native inulin were designed as biodegradable carriers for the colon-specific delivery of uracil as a model antitumor compound. The hydrogels were synthesized via free-radical polymerization, using diethylene glycol diacrylate (DEGDA) as a crosslinking agent at varying concentrations (5, 7.5, and 10 wt%), and their structural, thermal, and biological properties were systematically evaluated. Fourier transform infrared spectroscopy (FTIR) confirmed successful crosslinking and physical incorporation of uracil through hydrogen bonding. Concurrently, differential scanning calorimetry (DSC) revealed an increase in glass transition temperature (T_g) with increasing crosslinking density (149, 153, and 156 °C, respectively). Swelling studies demonstrated relaxation-controlled, first-order swelling kinetics under physiological conditions (pH 7.4, 37 °C) and high gel fraction values (84.75, 91.34, and 94.90%, respectively), indicating stable network formation. SEM analysis revealed that the hydrogel morphology strongly depended on crosslinking density and drug incorporation, with increasing crosslinker content leading to a more compact and wrinkled structure. Uracil loading further modified the microstructure, promoting the formation of discrete crystalline domains within the semi-IPN hydrogels, indicative of physical drug entrapment. All formulations exhibited high encapsulation efficiencies (>86%), which increased with increasing crosslinker content, consistent with the observed gel fraction values. Simulated in vitro gastrointestinal digestion showed negligible drug release under gastric conditions and controlled release in the intestinal phase, primarily governed by crosslinking density. Antimicrobial assessment against *Escherichia coli* and *Staphylococcus epidermidis*, used as an initial or indirect indicator of cytotoxic potential, revealed no inhibitory activity, suggesting low biological reactivity at the screening level. Overall, the results indicate that DEGDA-crosslinked dextran/inulin semi-interpenetrating (semi-IPN) hydrogels represent promising carriers for colon-targeted antitumor drug delivery.

Keywords: dextran; inulin; semi-interpenetrating biopolymer hydrogel; biodegradation in intestinal fluid



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1. Introduction

According to GLOBOCAN 2022 data, colorectal cancer ranks third in incidence worldwide, following breast and lung cancer, and second in terms of cancer-related mortality [1]. Chemotherapy remains a cornerstone of colorectal cancer treatment. However, due to the non-selective nature of most anticancer drugs, which exhibit comparable affinity toward both healthy and malignant cells, severe systemic side effects and limited patient tolerance are frequently observed. This limitation is particularly critical in patients over the age of 55, who represent the predominant demographic affected by this disease [1]. To minimize adverse effects and maximize the therapeutic concentration of the drug at the tumor site, the development of suitable drug carriers plays a crucial role. These systems are primarily designed to encapsulate the active compound and enable controlled and site-specific release through different mechanisms, largely dictated by the structural and physicochemical design of the carrier. Nanoparticle-based systems can facilitate cellular internalization, thereby increasing drug accumulation within tumor cells. In addition, certain carriers can be engineered to preferentially accumulate in cancer tissue through passive or active targeting mechanisms [2]. Considerable research effort has been devoted to designing micelles, coating systems, conjugates, complexes, microparticles, and nanoparticles for drug encapsulation and controlled delivery. However, such approaches are often complex, time-consuming, and require advanced expertise and substantial investment [3]. In addition, some of them are limited to one group of drugs. To overcome these limitations, readily synthesized hydrogels capable of entrapping high amounts of drug have emerged as promising materials for controlled drug delivery. Based on their composition, particularly the presence of ionizable functional groups, hydrogels can release the active compound in response to specific pH values characteristic of tumor tissue. Nevertheless, pH-triggered release alone is not sufficiently reliable, given the high variability in pH across different segments of the digestive tract and the inability to achieve quantitatively controlled release at the target site [4].

In light of these limitations, hydrogel systems designed to degrade specifically in the colorectal region offer a more efficient strategy for targeted drug delivery. For effective colon-targeted drug delivery, active compounds must reach the colorectal region intact [4–6], which can be achieved by formulating hydrogels from biopolymers that remain resistant to degradation in the upper gastrointestinal tract but are selectively degraded in the intestinal phase by enzymes present in the colonic microflora. Dextran and inulin, both generally recognized as safe (GRAS), are excellent candidates for developing colon-targeted delivery systems. They can form matrices that resist enzymatic degradation under gastric conditions, enabling drug release in the intestinal environment through biodegradation mediated by colorectal microbiota enzymes. Dextran is a microbial-derived polysaccharide synthesized by *Leuconostoc mesenteroides* composed primarily of α -(1→6)-linked D-glucopyranosyl units with varying degrees of α -(1→3) branching, widely used in biomedical and pharmaceutical applications due to its excellent water solubility, biocompatibility, and film-forming ability [7]. Inulin is a naturally occurring fructan consisting mainly of β -(2→1)-linked fructofuranosyl units terminated by a glucose residue, commonly extracted from plants such as chicory and Jerusalem artichoke, and is valued for its biodegradability, prebiotic activity, and suitability as a matrix for encapsulation and controlled-release systems [8]. The 1,6- α -D-glucosidic linkages in dextran are susceptible to hydrolysis by the action of dextranase enzymes [7]. In the human colon, these enzymes are predominantly produced by anaerobic Gram-negative bacteria of the genus *Bacteroides* [9], which represent the dominant members of the anaerobic intestinal microbiota, constituting approximately 30% of the total cultured microflora [10]. At physiological pH (7.0–7.5), the main effect of enzyme activity is reflected in the rapid release of D-glucose, where the

degradation is mainly limited to the outer parts of the molecule. The specific activity of dextranase has been determined in the mucous membrane of the human intestine: in the small intestine, it is related to intracellular enzymes of mammalian cells, whereas in the large intestine, the dominant activity is related to the surface of the cell membrane of bacteria of the genus *Bacteroides* or to the enzymes that these bacteria secrete into the external environment [11]. Among polysaccharides degradable by intestinal microflora, inulin has recently attracted considerable attention due to its potential in targeted drug delivery to the large intestine and numerous beneficial physiological effects [8]. Inulin is a natural fructan, a complex biopolymer composed of β -(2 $\rightarrow$ 1)-linked fructose units, and ranks among the most abundant carbohydrates in nature after starch. This biopolymer is a dietary prebiotic fiber and the most abundant polysaccharide that occurs in nature after starch [12]. As a dietary prebiotic fiber, inulin is resistant to hydrolysis by gastric and small intestinal enzymes, thus reaching the colon intact, where it is fermented by inulinases and inulin-lyases produced by *Bifidobacteria*—Gram-positive bacteria that are natural inhabitants of the large intestine [13]. Since 1995, the potential of dextran- and inulin-based hydrogels for the colon-targeted delivery of active compounds has been demonstrated in numerous studies. Hovgaard and Brøndsted synthesized carriers based on aliphatic diisocyanate-crosslinked dextran, which exhibited biodegradability in a human colonic fermentation model, confirming the potential of dextran derivatives for targeted drug delivery in the distal parts of the gastrointestinal tract [14]. In a related approach, Kim et al. reported the development of hydrogels composed of glycidyl methacrylate-modified dextran and poly(acrylic acid), synthesized via UV-initiated polymerization for colon-specific drug delivery applications [15]. In numerous subsequent studies, researchers have highlighted inulin hydrogels as effective carriers for the controlled and targeted release of antitumor drugs and bioactive substances in the colon. In order to produce an inulin hydrogel with low swelling capacity and high stability in acidic environments, Van den Mooter et al. modified inulin with methacrylic anhydride, after which they derivatized it with succinic acid and crosslinked it with UV radiation [16]. In another study, hydrogels were obtained via esterification of inulin with pyromellitic dianhydride at room temperature in dimethylformamide (DMF) [17]. In the study by Maris et al., hydrogels were synthesized by copolymerizing methacrylated inulin (IN-MA) with bis(methacryloylamino)azobenzene (BMAAB), an aromatic azo agent, and with 2-hydroxyethyl methacrylate (HEMA) or methacrylic acid (MA), thereby yielding pH- and enzyme-sensitive systems suitable for targeted drug delivery to the colon [18].

Building upon our previous investigations, in the present study, we introduce a structure-driven hydrogel design strategy in which the gel architecture is deliberately engineered to control digestion stability and drug release performance. In our earlier work, we demonstrated that inulin incorporation suppresses hydrogel degradation under simulated gastric conditions when synthesized in aqueous media [19]; in a subsequent study, we identified diethylene glycol diacrylate (DEGDA) as an optimal crosslinking agent for dextran-based hydrogels prepared in dimethyl sulfoxide, owing to its ability to generate hydrogels with well-defined and homogeneous morphologies [20]. Nevertheless, the architectural integration of inulin-mediated gastric protection with DEGDA-controlled network formation within a single hydrogel system has not previously been explored. In the present work, we for the first time design and systematically evaluate semi-interpenetrating (semi-IPN) hydrogels composed of methacrylated dextran forming the primary crosslinked network and native (non-methacrylated) inulin interpenetrating the matrix, with DEGDA acting as a key architectural regulator of network density and morphology. This semi-IPN hydrogel configuration establishes direct structure–function relationships, whereby the network architecture governs (i) resistance to acidic gastric conditions, (ii) swelling and erosion behavior during digestion, and (iii) the encapsulation efficiency and controlled

release kinetics of uracil as a model antitumor agent. As in our previous studies, uracil was selected as a safe model compound for 5-fluorouracil (5-FU) to investigate hydrogel structure–property relationships and release behavior. The novelty of this study lies in the architecture-centered integration of biopolymer composition and crosslinking chemistry, which enables rational control of hydrogel structure to improve gastric stability and achieve predictable intestinal drug release. By directly linking gel architecture with functional performance, this work advances dextran–inulin hydrogels from empirical formulations toward mechanistically guided gel design for oral drug delivery, specifically in gelatin capsules filled with xerogel granules.

2. Results and Discussion

2.1. Results of Infrared Spectroscopy with Fourier Transform (FTIR) Analysis

The FTIR spectra of xerogels Dex-DEGDA 5 (S5), Dex-DEGDA 7.5 (S7.5), and Dex-DEGDA 10 (S10) are presented in Figure 1 and show no significant differences among samples of identical composition containing different amounts of crosslinking agent. A broad band centered at $3310\text{--}3312\text{ cm}^{-1}$ corresponds to overlapping O–H stretching vibrations originating from dextran, inulin, and residual hydroxyl groups within the network. Two peaks in the $2900\text{--}2850\text{ cm}^{-1}$ region are attributed to C–H stretching of CH_2 groups originating from methacrylated dextran, inulin (Figure S1, Supporting Information), and DEGDA (Figure S2, Supporting Information). The weak bands observed at 2158 and 2027 cm^{-1} in the FTIR spectrum of neat DEGDA—assigned to overtone/combination bands associated with the acrylate C=C system—are not present in the hydrogel spectra, confirming the consumption of vinyl groups during crosslinking. The band at 1719 cm^{-1} corresponds to the ester carbonyl stretching vibration of methacrylated dextran and DEGDA. It becomes more pronounced in xerogels with higher DEGDA content, consistent with its characteristic presence in the DEGDA spectrum (Figure S2, Supporting Information). The peak at $1652\text{--}1650\text{ cm}^{-1}$ is attributed to the bending vibration of absorbed/bound water. Peaks in the $1435\text{--}1335\text{ cm}^{-1}$ range correspond to CH_2 and CH_3 bending modes. The band at $1250\text{--}1150\text{ cm}^{-1}$ originates from asymmetric C–O–C stretching vibrations of ester and ether groups, while the peak at $1155\text{--}1151\text{ cm}^{-1}$ corresponds specifically to C–O–C asymmetric stretching. The band at $1113\text{--}1107\text{ cm}^{-1}$ is assigned to C–C–O stretching coupled with O–H bending vibrations. A peak at 1012 cm^{-1} corresponds to asymmetric C–O–C stretching of glycosidic linkages in dextran and inulin coupled with C–O stretching of the secondary OH group. The peak at 951 cm^{-1} , visible in all spectra, corresponds to vibrations of the pyranose ring and C–O–C (glycosidic) stretching. The band observed at about 680 cm^{-1} is assigned to out-of-plane bending and skeletal vibrations of the polysaccharide ring (C–O and C–C deformation modes of the glucopyranose units).

In Figure 2, the FTIR spectra of the neat S5 xerogel and the uracil-loaded S5 xerogel are compared. Upon uracil loading, the band corresponding to the O–H stretching vibrations originating from dextran, inulin, and residual hydroxyl groups becomes slightly broader and shifted toward lower wavenumbers, suggesting the formation of additional hydrogen bonds between the hydroxyl groups of the biopolymers and the carbonyl and amide functionalities of uracil. In the FTIR spectrum of uracil-loaded hydrogel, two weak peaks appear at 2158 and 2027 cm^{-1} , likely arising from the combination of C=O stretching and N–H in-plane bending (scissoring). Overall, the observed band shifts and intensity variations confirm successful uracil encapsulation, governed by hydrogen bonding. This mode of incorporation is consistent with the high encapsulation efficiency and suggests that uracil is physically entrapped within the hydrogel matrix without disrupting the crosslinked network architecture.

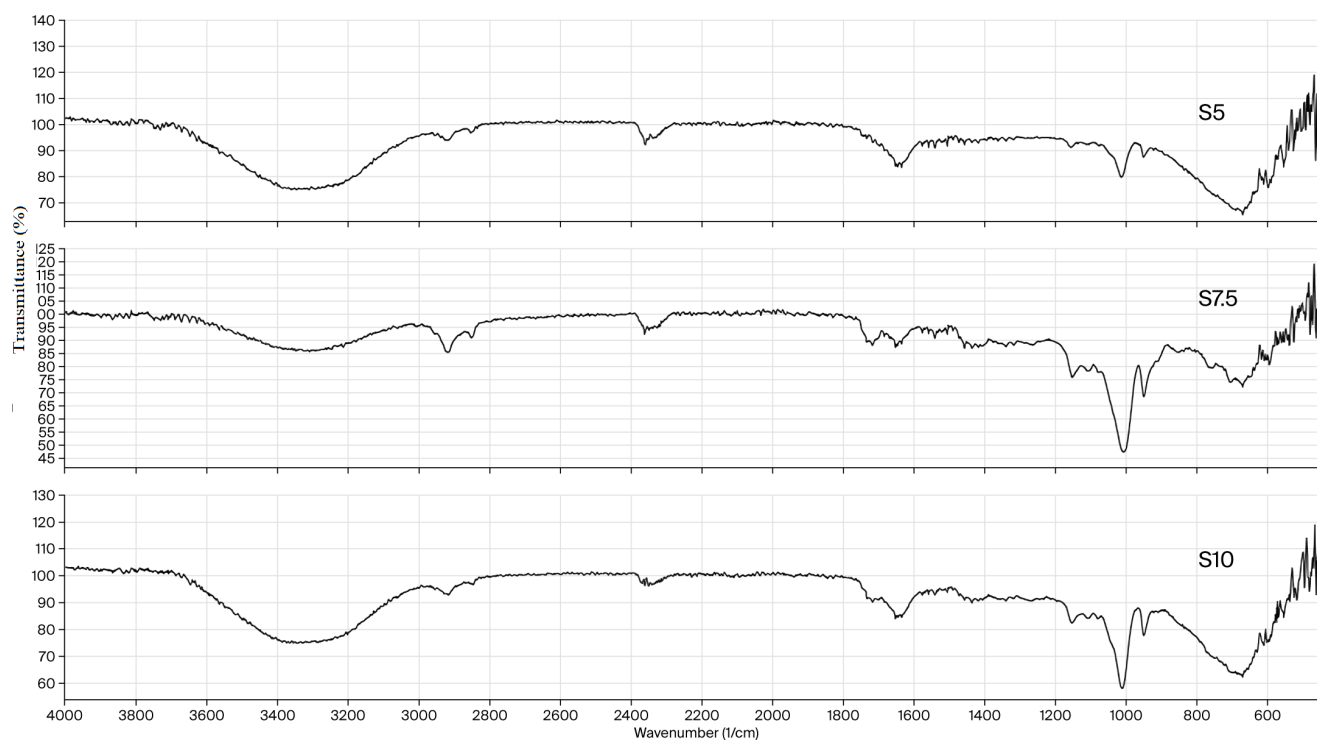


Figure 1. FTIR spectra of semi-IPN dextran/inulin hydrogels.

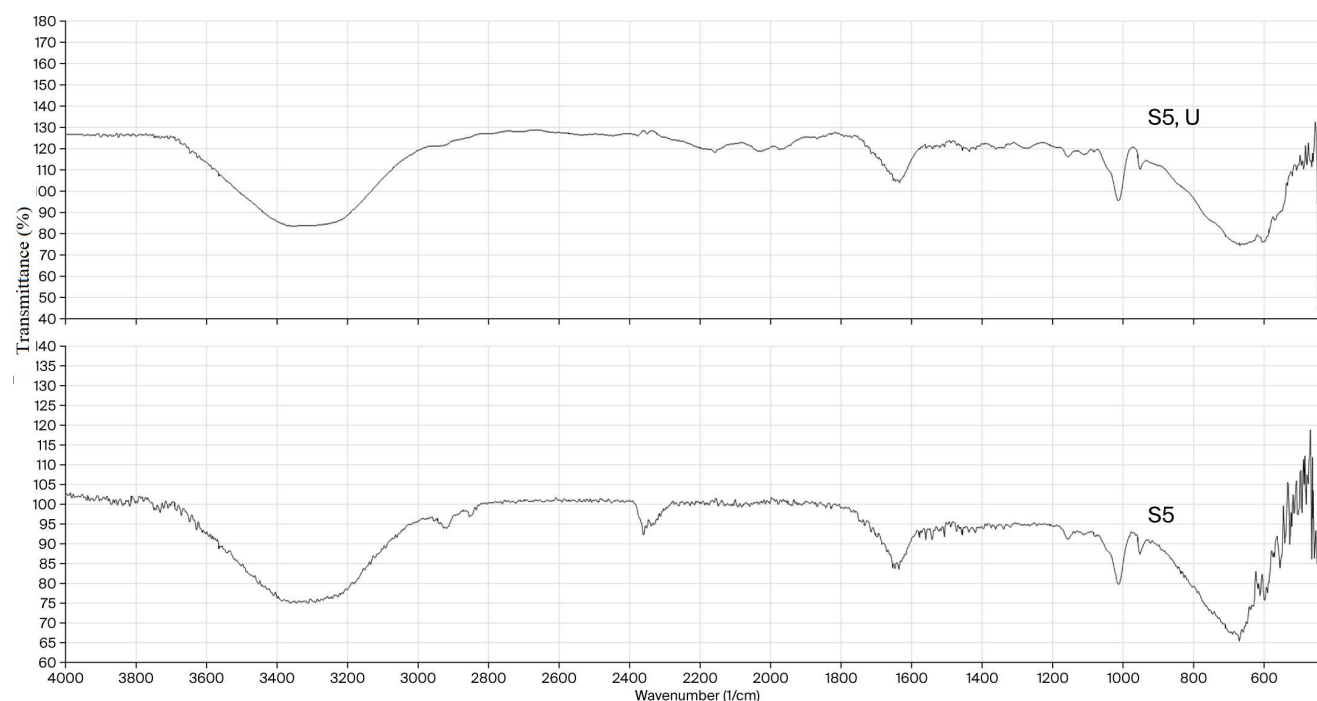


Figure 2. FTIR spectra of the neat semi-IPN dextran/inulin hydrogel (S5) and uracil-loaded semi-IPN dextran/inulin hydrogel (S5, U).

2.2. Results of DSC Analysis

The glass transition temperature (T_g) increases with increasing crosslinking agent content (Figure 3), reflecting a direct correlation between the amount of DEGDA in the hydrogel formulation and the resulting crosslinking density [21]. DEGDA acts as a multifunctional crosslinking agent, and its higher concentration promotes a greater number of covalent junction points between dextran chains, resulting in the formation of a more

rigid xerogel structure. Accordingly, the xerogel containing the lowest DEGDA content (S5) exhibits the lowest T_g value (149 °C). A progressive increase in crosslinker concentration, and thus crosslinking density, results in higher T_g values, reaching 153 °C and 156 °C for xerogels S7.5 and S10, respectively. Thermal degradation of the xerogels occurs in the temperature range of 190–202 °C. Given that the T_g values of all xerogels are substantially higher than the temperature of the swelling medium, polymer chain mobility is highly restricted under swelling conditions. As a result, polymer chain relaxation proceeds more slowly than solvent diffusion within the hydrogel network, indicating that the swelling behavior is relaxation-controlled and follows a non-Fickian mechanism [22].

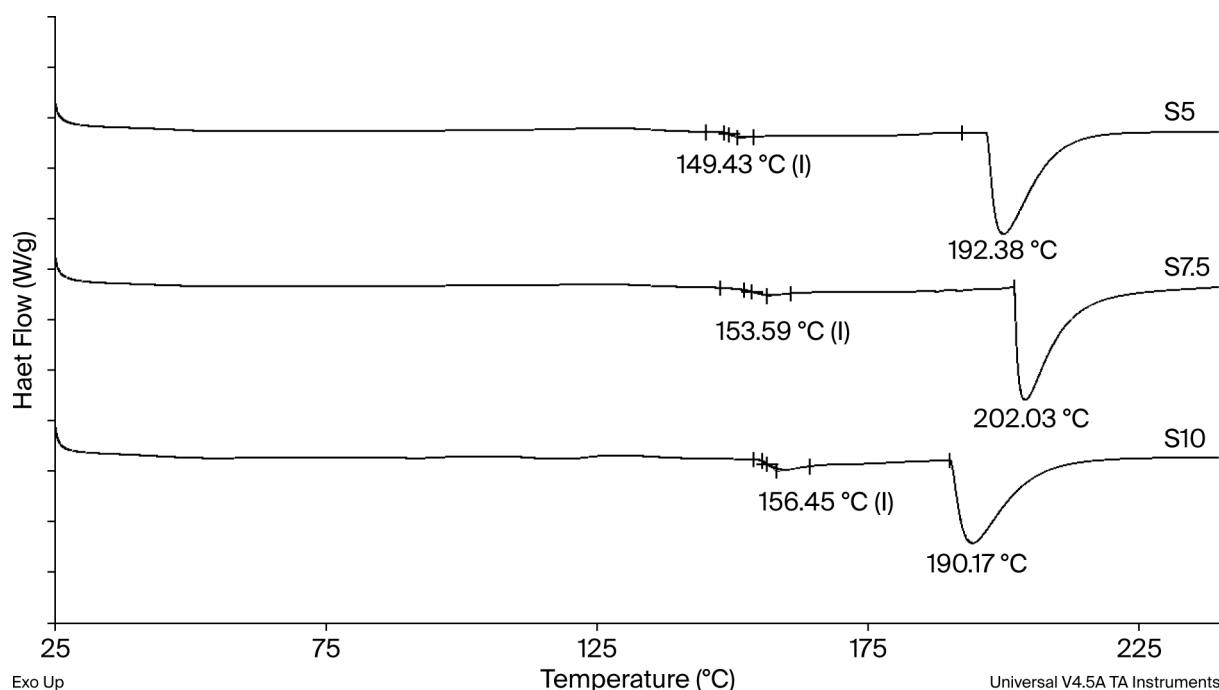


Figure 3. DSC thermograms for the neat semi-INP dextran/inulin hydrogel.

2.3. Results of Scanning Electron Microscopy (SEM) Analysis

Figure 4 presents SEM micrographs of neat dextran/inulin semi-interpenetrating hydrogels prepared with different amounts of DEGDA, recorded at increasing magnifications. The S5 sample (Figure 4(1a–1c)) exhibits a highly porous and heterogeneous morphology, characterized by large, irregularly shaped pores. This pronounced porosity is attributed to solvent (DMSO) evaporation during hydrogel formation, which promotes pore generation. With increasing DEGDA content, a progressive reduction in pore size is observed, accompanied by the formation of a denser and more compact polymer matrix. Samples S7.5 (Figure 4 S7.5 (2a–2c)) and S10 (3a–3c) show a markedly reduced porosity and a more consolidated internal structure, indicating a higher crosslinking density. At higher magnifications, these samples display a wrinkled and folded surface morphology, suggesting restricted polymer chain mobility and enhanced network rigidity due to increased crosslinking. That is in coherence with the results of DSC analysis. Furthermore, the presence of neat inulin within the hydrogel matrix significantly influences the overall morphology. In comparison with the hydrogel reported in our previous study [20], which did not contain inulin, the incorporation of inulin is clearly seen to influence the surface morphology, leading to a lower pore size and more wrinkled appearance, and less regular structural features [23].

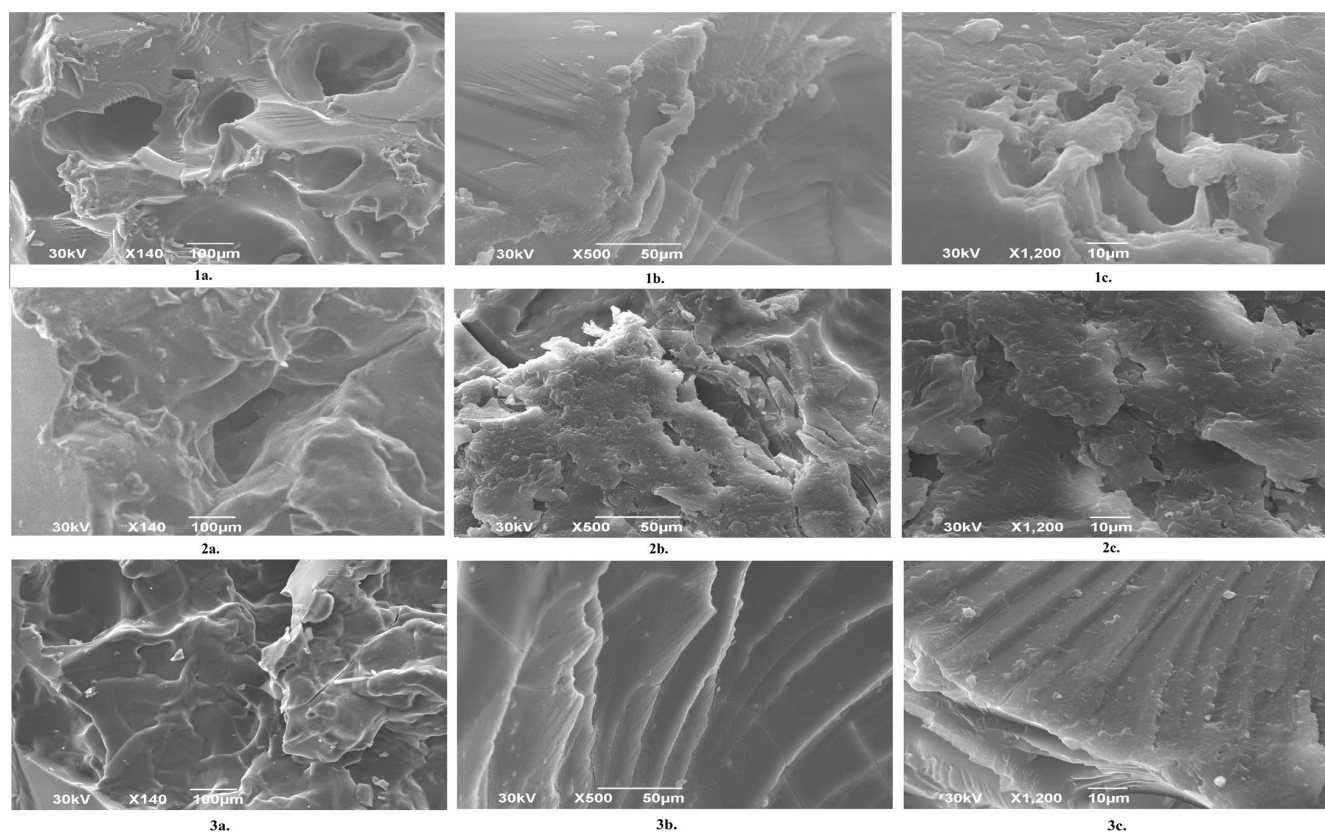


Figure 4. SEM images of semi-INP hydrogels at different magnifications (140, 500, and 1200 $\times$): S5 (1a–1c); S7.5 (2a–2c); S10 (3a–3c).

Figure 5 shows SEM micrographs of semi-interpenetrating dextran/inulin hydrogels loaded with uracil, recorded at magnifications of 140 $\times$, 500 $\times$, and 1200 $\times$. In comparison to the neat hydrogels, the incorporation of uracil induces pronounced morphological changes across all samples. The hydrogel matrix displays irregular domains and partially collapsed regions, which can be attributed to the partial occupation of free volume within the network by uracil molecules. At intermediate magnification (Figure 5(1b–3b)), distinct particulate and crystalline entities are observed, confirming the presence of uracil either embedded within or deposited on the hydrogel surface. At higher magnification (Figure 5(1c–3c)), well-defined crystalline structures with angular and plate-like morphologies become clearly visible, which are characteristic of recrystallized uracil. These crystalline features are distributed across the hydrogel surface, indicating that uracil is predominantly physically entrapped within the semi-interpenetrating polymer network (semi-IPN). An increase in the amount of crosslinking agent leads to a higher crosslink density within the hydrogel network, which reduces chain mobility and decreases the available free volume. As a consequence, the polymer matrix becomes less capable of accommodating uracil molecules in a molecularly dispersed state. During crosslinking, the restricted diffusion of uracil promotes local supersaturation, favoring nucleation and growth of crystalline domains [24]. The denser network thus facilitates uracil aggregation and recrystallization, resulting in a higher number and larger size of crystalline domains observable by SEM. Overall, SEM observations confirm the successful incorporation of uracil into the semi-interpenetrating hydrogel system and demonstrate that drug loading markedly influences surface morphology, structural compactness, and microstructural arrangement.

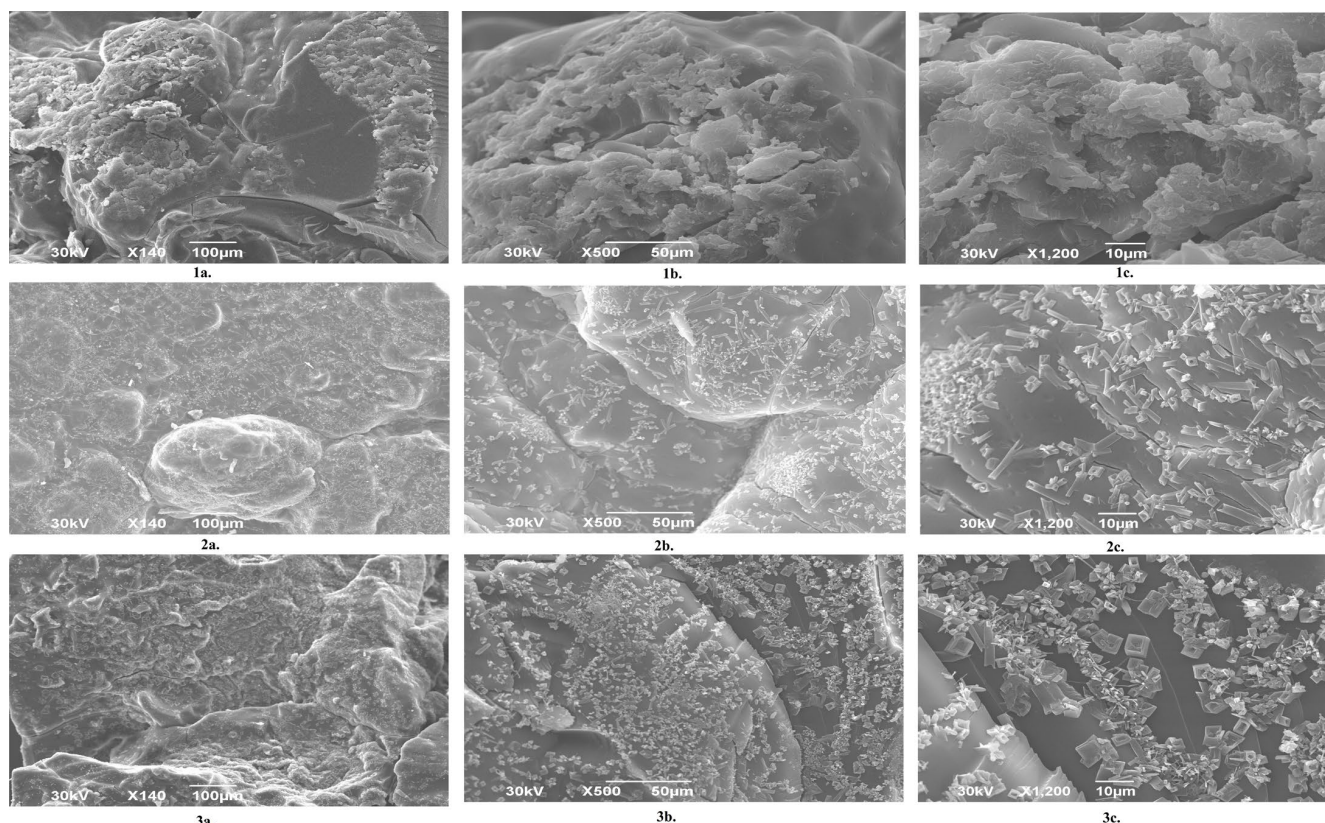


Figure 5. SEM images of uracil-loaded semi-INP hydrogels at different magnifications (140, 500, and 1200 $\times$): S5 (1a–1c); S7.5 (2a–2c); S10 (3a–3c).

2.4. Results of Swelling Properties Analysis

The swelling ratio versus time is presented in Figure 6. The equilibrium swelling ratio (ESR) is strongly governed by the network architecture, which is dictated by both crosslinking density and polymer composition. As the DEGDA content decreases, the number of covalent crosslinks within the dextran network is reduced, resulting in a lower network density, larger mesh size, and increased polymer chain mobility. These structural changes facilitate enhanced water penetration and retention within the hydrogel matrix, leading to higher ESR values [21]. Accordingly, the S5, S7.5, and S10 hydrogels exhibit ESR values of 1680%, 1491%, and 1277%, respectively, clearly demonstrating the inverse relationship between crosslinking density and swelling capacity. In comparison with the swelling behavior of the dextran-based hydrogel prepared with 10 wt% DEGDA reported in our previous study [20], the semi-interpenetrating hydrogel of comparable composition (S10) displays a similar swelling profile. This observation indicates that swelling is predominantly governed by the chemically crosslinked dextran framework, while the physically entrapped inulin chains do not significantly compromise the structural integrity of the network. Nevertheless, the incorporation of inulin enhances the overall hydrophilicity of the system due to the presence of multiple hydroxyl groups capable of forming hydrogen bonds with water molecules [25]. At pH 7.4, hydrogel S10 exhibits a slightly lower ESR value compared to the similar one at pH 6, which can be attributed to differences in biopolymer–biopolymer and biopolymer–buffer interactions. At the higher pH, partial screening of hydrophilic functional groups and the formation of a more compact network structure likely reduce the osmotic driving force for water diffusion into the hydrogel [26]. Overall, the prepared hydrogels exhibit relatively high ESR values (>1200%), which are significantly higher than those reported for glycidyl methacrylate–dextran and poly(acrylic acid)–based hydrogels investigated as carriers for colon-targeted drug delivery [15]. Swelling measurements

were performed in triplicate, and the results of the statistical analysis are provided in the Supplementary Materials (Table S1).

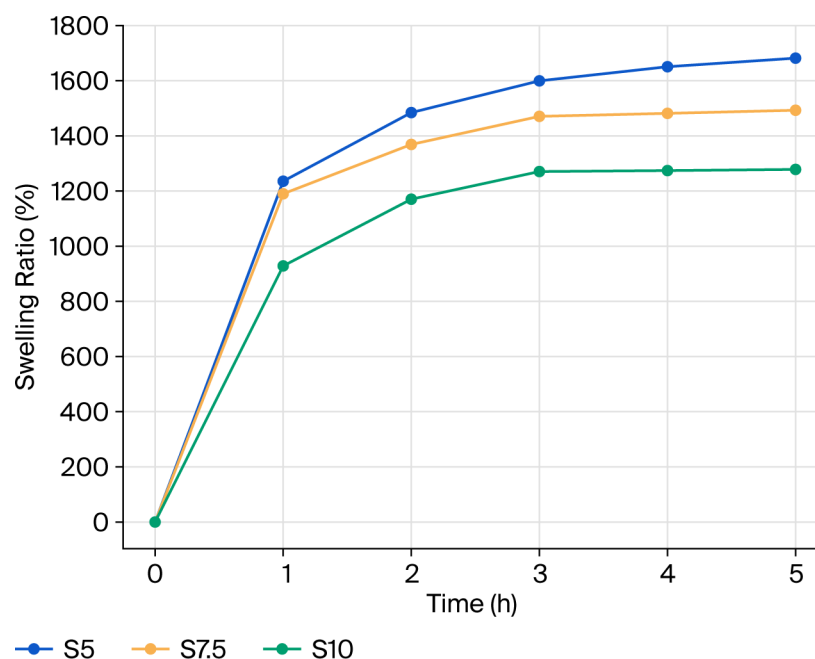


Figure 6. Swelling ratio versus time for the prepared semi-IPN hydrogels.

To evaluate whether the swelling behavior of the prepared hydrogels follows first-order kinetics, the values of $\ln [S_e / (S_e - S)]$ calculated using Equation (4) were plotted as a function of time (Figure S3, Supplementary Materials). The first-order swelling rate constants (Table 1) were determined as the absolute values of the slopes of the corresponding linear regressions [27]. For all investigated samples, a linear relationship was obtained at pH 7.4 and a temperature of 37 °C, indicating good agreement with the first-order kinetic model and confirming that the swelling process of the hydrogels can be adequately described by first-order kinetics under the applied conditions. The linearity of the plots was further confirmed by high coefficients of determination ($R^2 = 0.97$ – 0.99 , Table 1), indicating an excellent agreement between the experimental swelling data and the first-order kinetic model for all hydrogel samples at pH 7.4 and 37 °C. The obtained values demonstrate a strong correlation between the experimental results and the applied kinetic model, thereby confirming the reliability and applicability of the first-order approach for describing the swelling behavior of the prepared hydrogels.

Table 1. Estimated first-order kinetic constant (K_1), coefficients of determination (R^2), gel fraction (Gf), and encapsulation efficiency (EE).

Hydrogels	K_1 , pH 7.4, 37 °C	R^2	Gf (%)	EE (%)
S5	0.97	0.99	84.75 ^a ± 1.12	86.13 ± 0.88 ^a
S7.5	1.24	0.98	91.34 ^b ± 1.42	89.67 ± 1.15 ^b
S10	1.55	0.97	94.90 ^c ± 0.60	93.12 ± 0.77 ^c

Values are expressed as the mean ± standard deviation. Different superscript letters within the same column denote statistically significant differences ($p < 0.05$).

2.5. Results of Gel Fraction (Gf) Determination

The gel fraction (Gf) increased with increasing content of the crosslinking agent, reflecting the corresponding increase in crosslinking density within the hydrogel network (Table 1). For all investigated samples, the Gf values exceeded 84%, indicating a high

degree of network formation. Notably, hydrogel S10, which contained the highest amount of crosslinking agent, exhibited the highest G_f value, confirming the formation of a densely crosslinked and stable hydrogel structure. Measurements were performed in triplicate, and the statistical analysis results are provided in the Supplementary Materials (Table S2).

2.6. Results of Encapsulation Efficiency (EE) Determination

Encapsulation efficiency (EE) values increase with increasing crosslinking agent content (Table 1). Accordingly, the hydrogel synthesized with 10 wt% DEGDA (S10) exhibits the highest EE, which can be attributed to its highest crosslinking density. Nevertheless, all samples show relatively high EE values (>86%), indicating efficient encapsulation across the entire series and confirming that the applied synthesis and loading procedure is well-suited for the incorporation of the active compound, even at lower degrees of crosslinking. Measurements were performed in triplicate, and the statistical analysis results are provided in the Supplementary Materials (Table S3).

2.7. Results of Simulated In Vitro Gastrointestinal Digestion (GID)

The results of the in vitro digestion process, expressed as the amount of released uracil, are presented in Table 2. The observed release behavior can be directly linked to differences in network architecture arising from variations in DEGDA content. Higher DEGDA concentrations result in a more densely cross-linked network with a smaller mesh size and reduced chain mobility. These structural features limit solvent penetration and solute diffusion [27], leading to lower uracil release in both the gastric and intestinal phases, as observed for sample S10. In comparison with our previous study [20], this value is very close to that obtained for a dextran-based hydrogel synthesized with the same DEGDA content but without the addition of inulin. In contrast, hydrogels synthesized with lower DEGDA contents exhibited detectable uracil release already in the gastric phase, which is most likely a consequence of reduced entrapping efficiency associated with a lower crosslinking density. Furthermore, the release behavior in the intestinal phase was inversely related to the crosslinking density, with higher DEGDA contents leading to decreased uracil release. The presence of inulin within the semi-IPN hydrogels does not introduce additional covalent crosslinks but contributes primarily through physical entanglement with the dextran network. Under identical crosslinking conditions, this leads to only minor changes in mesh size and diffusional pathways, which explains why uracil release from S10 remains comparable to that of the corresponding dextran-only hydrogel investigated in our previous work [20].

Table 2. Amounts of uracil released from the prepared hydrogels as a result of enzymatic biodegradation during the gastric and intestinal phases.

Uracil-Loaded Hydrogels	Gastric Phase Release, $\mu\text{g/mL}$	Intestinal Phase Release, $\mu\text{g/mL}$	Gastric Phase Release, %	Intestinal Phase Release, %	Total Released Amount of Drug, %
S5, U	6.17 ± 0.22^a	91.82 ± 3.78^a	4.93 ± 0.21^a	78.79 ± 2.97^a	$83.73^a \pm 3.02^a$
S7.5, U	4.50 ± 0.19^b	65.91 ± 2.63^b	3.60 ± 0.15^b	52.73 ± 2.11^b	56.33 ± 2.62^b
S10, U	0.00^c	$57.24^c \pm 2.86^c$	0.00^c	45.79 ± 2.29^c	45.79 ± 2.29^c

Values are expressed as the mean $\pm$ standard deviation. Different superscript letters within the same column denote statistically significant differences ($p < 0.05$). The total releasable amount was $125 \mu\text{g/mL}$, calculated based on a loading of 20 mg per g of dry carrier and 0.25 g of dry material.

Considering the erosive (biodegradative) drug release, the Korsmeyer-Peppas model has been applied for the description of release kinetics of prepared hydrogels (Figure S4a,b, Supplementary Materials). The kinetic constant (k), release exponent (n), and coefficients of determination (R^2) are summarized in Table 3. These values of n , above 1.00, indicate a super case-II transport mechanism, confirming a biodegradative

release mechanism governed mainly by polymer relaxation and structural breakdown. Active compound release occurs as the hydrogel matrix gradually degrades, with polymer chain cleavage and network erosion promoting faster release. This behavior is typical of biodegradable hydrogels, where water absorption first causes swelling and is followed by hydrolytic or enzymatic bond cleavage, leading to a progressive loss of network integrity. The magnitude of the kinetic constant k reflects the intrinsic release rate of the system. Values on the order of 10^{-2} indicate a relatively faster release, consistent with a degradable hydrogel matrix in which polymer relaxation and erosion significantly contribute to drug liberation. In contrast, k values on the order of 10^{-3} suggest a more moderate release rate, which can be attributed to higher crosslink density and a more compact network structure, where degradation-controlled release becomes prominent over time [28]. The high coefficients of determination ($R^2 = 0.94$ and 0.97 ; Table 3) demonstrate excellent agreement between the experimental release data and the Korsmeyer–Peppas model, confirming its suitability for describing the biodegradative release behavior of the studied hydrogel systems.

Table 3. Korsmeyer–Peppas parameters for semi-IPN hydrogels.

Uracil-Loaded Samples	n	k	R^2
S5	2.98	1.1×10^{-2}	0.94
S7.5	2.61	8.6×10^{-3}	0.97

2.8. Results of Antimicrobial Assessment

In accordance with the principles of ISO 10993 [29] for the biological evaluation of materials, antimicrobial activity testing may be applied as an initial screening tool to assess the potential biological reactivity of newly developed hydrogels. Although the primary purpose of the developed hydrogels is not antibacterial action, the disk diffusion assay enables the detection of low-molecular-weight or diffusible species originating from residual monomers and cross-linking agents that may adversely affect cellular viability. Therefore, antibacterial testing is relevant as a preliminary indicator of possible nonspecific biological reactivity that could also be detrimental to mammalian cells and thus warrants further cytocompatibility assessment. Considering these aspects, *Escherichia coli* ATCC 8739 (Gram-negative) and *Staphylococcus epidermidis* ATCC 12228 (Gram-positive) were selected as model microorganisms for preliminary biological screening because bacteria are generally more sensitive to physicochemical stress and toxic leachables than mammalian cells. This increased susceptibility arises from fundamental differences between prokaryotic and eukaryotic cells. Bacteria possess relatively simple membrane systems and rigid peptidoglycan-based cell walls, and they lack advanced detoxification, repair, and stress-response pathways, making them more vulnerable to oxidative damage, osmotic stress, and membrane-active species. In contrast, mammalian cells have tightly regulated plasma membranes, efficient antioxidant defenses, and multiple repair mechanisms that enhance tolerance to moderate chemical and physical insults. Therefore, antimicrobial testing serves as a sensitive preliminary indicator of the possible release of biologically active or cytotoxic components from the hydrogel matrix. Pronounced antibacterial effects may suggest the presence of diffusible species that could also pose a risk to mammalian cells and thus justify further cytocompatibility evaluation, whereas the absence of inhibition zones indicates low nonspecific biological reactivity [30].

The disk diffusion assay provides information on the release of low-molecular-weight or diffusible components from the hydrogel matrix that are capable of interfering with cellular integrity or metabolic activity. Since such effects may arise from non-selective mechanisms that could also affect mammalian cells, pronounced antibacterial activity may

indicate a potential risk of cytotoxicity. Antimicrobial activity was assessed by measuring the diameter of the inhibition zone, and the results are summarized in Table 4 and presented in Figure 7. The lack of antimicrobial activity in the hydrogel samples strongly indicates that they are unlikely to exhibit cytotoxic effects toward mammalian cells [20]. Therefore, antimicrobial measurements can be considered a complementary and preliminary approach that may partially substitute cytotoxicity testing at the early stage of material development, particularly for comparative screening of formulations. This strategy enables prioritization of samples for further biological evaluation and reduces unnecessary use of mammalian cell-based assays.

Table 4. Inhibitory activity of hydrogel formulations against *Escherichia coli* ATCC 8739 and *Staphylococcus epidermidis* ATCC 12228.

Sample Number	Inhibition Zone (mm)	
	<i>Escherichia coli</i> ATCC 8739	<i>Staphylococcus epidermidis</i> ATCC 12228
Ampicillin 10 mcg	10	15
S5	-	-
S7.5	-	-
S10	-	-

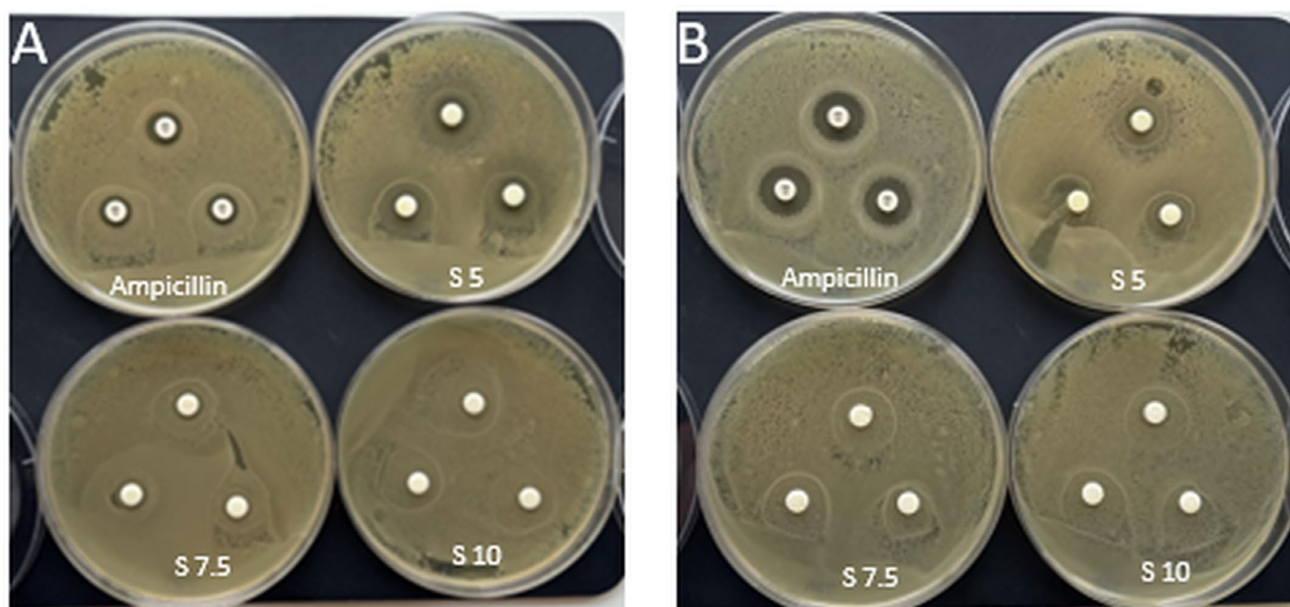


Figure 7. Antimicrobial activity of hydrogel samples against *Escherichia coli* ATCC 8739 (A) and *Staphylococcus epidermidis* ATCC 12228 (B).

3. Conclusions

Semi-interpenetrating biodegradable (semi-IPN) hydrogels based on methacrylated dextran and native inulin were successfully synthesized using three different amounts of diethylene glycol diacrylate (DEGDA) as a crosslinking agent. The prepared hydrogels were systematically evaluated as potential carriers for colon-targeted drug delivery. DSC analysis confirmed efficient crosslinking and the formation of stable hydrogel networks, with increasing crosslinking density resulting in higher glass transition temperatures, gel fraction values, and encapsulation efficiencies. SEM analysis revealed that hydrogel morphology is strongly influenced by crosslinking density and drug incorporation. Increasing DEGDA content produced a denser, more wrinkled network with reduced porosity, in agreement with DSC results. Inulin incorporation further decreased pore size and structural regularity. Uracil loading led to matrix densification and the formation of

crystalline domains, indicating physical entrapment. The hydrogels exhibited controlled, relaxation-driven swelling behavior under physiological conditions (pH 7.4, 37 °C) and demonstrated high stability during simulated gastric digestion. SEM analysis demonstrated that both crosslinking density and uracil incorporation play a decisive role in defining the microstructural organization of dextran/inulin semi-interpenetrating hydrogels. Uracil release during in vitro gastrointestinal digestion was strongly governed by crosslinking density, with more densely crosslinked systems effectively preventing premature drug release and enabling controlled delivery in the intestinal phase. The lack of antimicrobial activity against both Gram-positive and Gram-negative bacteria suggests minimal release of biologically aggressive species, supporting the suitability of these materials for further biological evaluation.

Looking ahead, these results provide a solid foundation for advancing dextran/inulin semi-IPN hydrogels toward more comprehensive biological validation. The focus of future studies will be on advancing the in vitro gastrointestinal model by incorporating inulinase, in addition to performing standardized in vitro cytotoxicity testing in accordance with ISO 10993 guidelines. Further investigations will include evaluation of antitumor efficacy using relevant colorectal cancer cell lines and a detailed assessment of degradation behavior in the presence of colonic enzymes and microbiota. In addition, extending this hydrogel platform to encapsulate clinically relevant chemotherapeutic agents and evaluating its in vivo performance will be essential steps toward potential translational and clinical applications. In comparison with our previous studies, the incorporation of inulin was shown to reduce premature dissolution under gastric conditions, highlighting its beneficial role in improving site-specific delivery. These findings support the strategic combination of inulin with dextran-based hydrogels, particularly when an optimal amount of crosslinking agent, such as DEGDA or azo-based one, is employed to balance structural stability and controlled biodegradation.

4. Materials and Methods

4.1. Materials

Dextran from *Leuconostoc* ($M_w \approx 40,000$ g/mol, CAS 9004-54-0), inulin from chicory ($M_w \approx 500\text{--}3600$ g/mol, CAS 9005-80-5; free glucose < 0.05% and free fructose < 0.05% determined by enzymatic assay; fructose-to-glucose ratio $\geq 20:1$), glycidyl methacrylate, diethylene glycol diacrylate (DEGDA), initiator azobisisobutyronitrile (AIBN), NaCl, NaHCO₃, KCl, KH₂PO₄, MgCl₂·6H₂O, (NH₄)₂CO₃, CaCl₂·2H₂O, Pefabloc®, dextranase, pepsin, bile salts, pancreatin, and uracil (analytical grade) were all obtained from Sigma-Aldrich (St. Louis, MO, USA). Dimethyl sulfoxide (DMSO) was obtained from Merck KGaA (Darmstadt, Germany). 4-Dimethylaminopyridine (4-DMAP) was purchased from Thermo Fisher Scientific Inc. (Waltham, MA, USA), and acetone and 96% ethanol were supplied by Zorka (Šabac, Serbia).

4.2. Preparation of Hydrogels

Semi-IPN hydrogels were synthesized through a two-step procedure. In the first step, dextran was modified following the method described in our previous studies [19,20] to obtain dextran–methacrylate (Dex–MA). In the second step, Dex–MA and inulin were dissolved in DMSO at 50 °C in a relative mass ratio of 90:10, with a total polymer concentration of 20 wt%. After complete dissolution, di(ethylene glycol) diacrylate (DEGDA) was added as a crosslinker in varying amounts (5, 7.5, and 10 wt% relative to the total Dex–MA mass). The samples prepared with 5, 7.5, and 10 wt% of DEGDA were labeled as S5, S7.5, and S10. The temperature was then increased to 80 °C, and 0.09 g of AIBN, dissolved in 1 mL of DMSO, was introduced as a free-radical initiator. The polymerization reaction

proceeded for 20 min, after which the system reached the gel point, yielding the crosslinked hydrogel network (Figure 8). The degree of dextran methacrylation was reported in our previous study as approximately 1.2 hydroxyl groups per repeating unit modified with glycidyl methacrylate [19].



Figure 8. Hydrogels with a rising amount of crosslinking agent DEGDA from left to right (S5, S7.5, S10).

Drug-loaded hydrogels were prepared via in situ incorporation of uracil through the addition of 0.02 g of uracil to a DMSO solution containing methacrylated dextran and inulin, before the addition of AIBN. Uracil was selected as a model compound because of its structural similarity to the anticancer drug 5-fluorouracil and its well-established safety profile. As an endogenous pyrimidine base, uracil possesses well-defined physicochemical characteristics, including low molecular weight, a heterocyclic structure, and strong hydrogen-bonding capability, which make it structurally comparable to 5-fluorouracil. This similarity enables reliable interpretation of diffusion behavior and interactions between the model compound and the polymer matrix. Unlike 5-fluorouracil, which is highly cytotoxic, uracil is non-toxic and safe to handle, allowing systematic investigation of polymer network architecture, swelling behavior, and controlled release mechanisms without biological risk management. Consequently, the use of uracil provides fundamental insight into release kinetics and matrix–guest interactions while ensuring experimental safety and simplified regulatory handling. This approach, as demonstrated in our previous studies, enables effective evaluation of the drug delivery system under conditions that realistically reflect the behavior of 5-fluorouracil, while avoiding the risks and regulatory constraints associated with cytotoxic chemotherapeutic agents [19,20]. The prepared hydrogels were dried in a dryer at 50 °C until a constant mass was achieved.

4.3. Infrared Spectroscopy with Fourier Transform (FTIR) Analysis

FTIR analysis of the samples was conducted using a Shimadzu IRTracer-100 Fourier Transform Infrared Spectrometer (Kyoto, Japan) equipped with MIRacle 10 ATR-FTIR with a ZnSe crystal. The analysis was performed over a wavelength range of 4000 to 400 cm^{-1} , averaging 40 scans at a spectral resolution of 4 cm^{-1} . Data were processed with LabSolutions IR software (version 2.21, Shimadzu, Japan).

4.4. DSC Analysis

To investigate the influence of the crosslinking agent content on the xerogel glass transition temperature (T_g), differential scanning calorimetry (DSC) measurements were performed using TA Instruments Q20 equipment (New Castle, DE, USA). Samples were

heated from 25 to 250 °C at a heating rate of 10 °C/min under a nitrogen atmosphere. The T_g values were determined from the midpoint of the heat-capacity step (ΔC_p), with a standard uncertainty of $u(T) = 0.5$ °C.

4.5. SEM Analysis

The microstructural features of the neat and uracil-loaded hydrogels were examined using a JEOL JSM-6390 scanning electron microscope (JEOL Ltd., Tokyo, Japan). Before SEM observation, the samples were coated with a thin conductive layer using a BALTEC SCD 005 sputter coater (BAL-TEC GmbH, Lübeck, Germany). Micrographs were acquired at magnifications of 140×, 500×, and 1200×.

4.6. Analysis of Swelling Properties

The swelling properties of colon-targeted hydrogel carriers synthesized using dextran, inulin, and DEGDA were reported in our previous study. In this study, we aimed to investigate the swelling capacity of the prepared hydrogels at physiological pH 7.4, at 37 °C, in order to simulate intestinal conditions, under which enzymatic activity is most pronounced. At this pH range, enzymes involved in polysaccharide degradation exhibit high activity, which leads to the cleavage of glycosidic bonds and the rapid release of D-glucose. Monitoring the swelling behavior under these conditions, therefore, provides relevant insight into the structural stability and water uptake of the hydrogel network in an environment that closely mimics *in vivo* intestinal conditions. The swelling ratio (SR) was determined using Equation (1):

$$SR (\%) = \frac{W_t - W_i}{W_i} \cdot 100\% \quad (1)$$

where W_t is the weight of the gel after swelling for a given time (1, 2, 3, 4, or 5 h), and W_i is the initial weight of the dry gel (xerogel).

The swelling kinetics were evaluated under the assumption that the swelling process follows first-order kinetics, as described by Equation (2) [21,22]:

$$\frac{dS}{dt} = K_1 \cdot (S_e - S) \quad (2)$$

In this equation, S represents the swelling ratio at time t , S_e denotes the equilibrium swelling ratio, and K_1 (h^{-1}) is the first-order kinetic constant. Integration of Equation (3) using the initial conditions $t = 0$ to t and $S = 0$ to S yields Equation (3):

$$\ln \frac{S_e - S}{S_e} = -K_1 \cdot t \quad (3)$$

4.7. Gel Fraction Determination

Gel fraction, used as an indicator of the crosslinking degree achieved with different amounts of crosslinking agent, was determined using Equation (4):

$$Gf = \frac{W_{ERS}}{W_i} \cdot 100\% \quad (4)$$

where W_{ERS} denotes the mass of the gel after reaching equilibrium swelling and subsequent drying to constant weight, and W_i represents the initial mass of the xerogel before immersion in the buffer.

4.8. Determination of Encapsulation Efficiency

For the determination of encapsulation efficiency, the method described by Erceg et al. [19] was applied. Encapsulation efficiency (EE) of the hydrogels was determined using Equation (5):

$$EE (\%) = \frac{w_t}{w_i} \cdot 100\% \quad (5)$$

where w_t represents the total amount of uracil incorporated into the xerogel, and w_i represents the initial amount of uracil incorporated during hydrogel synthesis (0.2 g per gram of dry xerogel). The total uracil content was evaluated using a two-step extraction and quantification procedure. First, xerogel samples were submerged in DMSO for 12 h to enable complete uracil release, after which the suspensions were centrifuged and filtered to eliminate insoluble material. Subsequently, uracil concentrations in the collected supernatants were measured via UV–Vis spectrophotometry using an Agilent BioTek EPOCH 2 (Santa Clara, CA, USA). A calibration curve prepared from uracil standards dissolved in DMSO was used to ensure accurate determination. All analyses were conducted in triplicate, and the obtained data are presented in Table S3.

4.9. Simulated In Vitro Gastrointestinal Digestion (GID)

A standardized static in vitro digestion model was applied following the protocol reported by Kostić et al. (2021) [31], with minor modifications introduced in the intestinal digestion stage. Because the hydrogel formulations are intended to be administered as hard gelatin capsules filled with xerogel granules, the oral phase of digestion was excluded from the experimental design. In this dosage form, the material is swallowed directly and does not undergo retention, disintegration, or interaction with saliva in the oral cavity before gastric release; therefore, inclusion of the oral phase was considered irrelevant. The procedure employed was described in our previous papers [19,20]. Three experimental groups were prepared in triplicate. Digestion was initiated with the gastric phase, with 0.25 g of xerogel (corresponding to 2.5 g of the rehydrated material) encapsulated in gelatin capsules (26.1 mm). The compositions of SGF and SIF were prepared based on the INFOGEST protocol [32] described in our previous studies [19,20].

Uracil quantification via UV–Vis spectrophotometry was carried out following a method modified from Khajehsharifi and Soleimanzadegan (2013) [33], in combination with procedures established in our earlier studies [19,20]. Spectral measurements were performed using an Agilent BioTek EPOCH 2 photodiode array UV–Vis spectrophotometer (Agilent BioTek Instruments, Winooski, VT, USA) controlled by Gen5™ Microplate Reader and Imager Software (version 3.13), and fitted with a quartz cuvette of 1 cm optical path length. Sample preparation involved dispersing approximately 25 mg of material in 25 mL of distilled water, followed by sonication for 5 min to achieve complete dispersion. The resulting suspension was subsequently diluted to obtain a stock solution with a concentration of 100 mg/mL.

For the description of releasing kinetics, the Korsmeyer-Peppas exponential model was used based on the following Equation (6) [28,34]:

$$\frac{M_t}{M_\infty} = k \cdot t^n \quad (6)$$

where M_t/M_∞ is the fractional drug release at time t , k is a kinetic constant incorporating the structural and geometric characteristics of the drug delivery system, and n is the release exponent. The value of n indicates the dominant release mechanism: $n = 0.5$ corresponds to Fickian diffusion, $0.5 < n < 1.00$ to anomalous (non-Fickian) transport, and $n > 1.0$ to super case-II transport, which is associated with polymer relaxation and/or erosion-controlled

release. The data were linearized according to Equation (7) using experimental points collected within the 1–4 h time interval:

$$\log \frac{M_t}{M_\infty} = \log k + n \cdot \log t \quad (7)$$

4.10. Antimicrobial Assessment

In accordance with our previous study [20], the antibacterial properties of the neat hydrogels were evaluated against *Escherichia coli* ATCC 8739 (Gram-negative) and *Staphylococcus epidermidis* ATCC 12228 (Gram-positive), which are frequently associated with bacterial infections. Lyophilized reference cultures were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and maintained in the culture collection of the Institute of Food Technology, University of Novi Sad. Stock cultures were preserved at $-80\text{ }^{\circ}\text{C}$ in Trypto–Casein Soy Broth (TSB; Biokar BK046 HA, Beauvais, France) supplemented with 15% (*v/v*) glycerol. Before analysis, bacterial strains were revived by streaking onto tryptic soy agar (TSA; Oxoid CM0131, Hampshire, UK) and incubated for 24 h at $37\text{ }^{\circ}\text{C}$. For antimicrobial testing, freshly grown colonies were transferred into phosphate-buffered saline (PBS; Oxoid, Hampshire, UK; pH 7.3), and the cell density was adjusted to correspond to a 0.5 McFarland standard. The suspensions were subsequently diluted in TSB to obtain a final concentration of 1×10^6 CFU/mL. Antibacterial activity of the three dextran-based samples was determined using the disk diffusion assay, following the protocol described by Šuput et al. (2024) [35] with minor modifications. Ampicillin (Bioanalyse, Ankara, Turkey) was included as a positive control to verify bacterial susceptibility. Briefly, 100 μL of the standardized bacterial suspension (1×10^6 CFU/mL) was uniformly spread onto TSA plates. Sterile paper disks (approximately 6 mm in diameter) were then placed on the agar surface and loaded with 10 μL of dextran-based sample stock solutions (256,000 $\mu\text{g/mL}$). The plates were incubated at $37\text{ }^{\circ}\text{C}$ for 24 h, after which antibacterial efficacy was evaluated by measuring the diameter of the inhibition zones surrounding each disk. Results were expressed as mean inhibition zone diameters (mm), and all experiments were performed in triplicate for each bacterial strain.

Antimicrobial activity measurements can serve as an initial or indirect indicator of cytotoxic potential, particularly in the early-stage biological evaluation of hydrogel materials. The disk diffusion assay reflects the ability of compounds released from the hydrogel matrix to diffuse into the surrounding medium and disrupt cellular integrity. Since both bacterial and mammalian cells rely on membrane integrity and metabolic function for survival, pronounced antibacterial effects—particularly against Gram-positive and Gram-negative strains—may suggest non-selective cytotoxic mechanisms, such as membrane disruption or oxidative stress induction.

4.11. Statistical Analysis

All measurements were performed in triplicate and are reported as mean values $\pm$ standard deviation. Statistical analysis of the experimental data was conducted using Microsoft Excel 2010. Mean values, standard deviations, and ranges for the swelling ratio, gel fraction, color parameters, and plateau elastic modulus were calculated in Microsoft Excel 2010, in addition to the determination of the standard errors of the intercept and slope of the linearly fitted curves.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/gels12020103/s1>. Figure S1. FTIR spectrum of neat inulin; Figure S2. FTIR spectrum of DEGDA; Figure S3. Plot of $\ln [Se/(Se-S)]$ versus time according to Equation pH 7.4 (37 °C temperature); Figure S4. Plot of $\log [Mt/M\infty]$ versus $\log (t)$ according to Equation (7); Table S1. Statistical analysis of the ESR values; Table S2. Statistical analysis of the gel fraction (Gf); Table S3. Statistical analysis of the encapsulation efficiency (EE).

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Abbreviations

The following abbreviations are used in this manuscript:

DMF	Dimethylformamide
BMAAM	Bis(methacryloylamino)azobenzene
HEMA	2-hydroxyethyl methacrylate
MA	Methacrylic acid
DMSO	Dimethyl sulfoxide
4-DMAP	4-Dimethylaminopyridine
AIBN	Azobisisobutyronitrile
DEGDA	Diethylene glycol diacrylate
Dex-MA	Dextran-methacrylate

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