Harnessing chemical functionality of xylan hemicellulose towards bio-based pH/magnetic dual-responsive nanocomposite hydrogel for drug delivery

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Abstract

This study reports for the first time an innovative pH/magnetic dual-responsive hemicellulose-based nanocomposite hydrogel with a nearly 100% bio-based and biodegradable compositions. We synthesized pure Fe$_3$O$_4$ magnetic nanoparticles (Fe$_3$O$_4$ MNPs) using co-precipitation, then engineering xylan hemicellulose (XH), acrylic acid (AA), polyethylene glycol diacrylate (PEGDA), and Fe$_3$O$_4$ MNPs to synthesize the pH/magnetic dual-responsive hydrogel (Fe$_3$O$_4$@XH-Gel), through free radical graft polymerization on natural XH with in-situ doping Fe$_3$O$_4$ MNPs initiated by the ammonium persulfate/tetramethylethylenediamine (APS/TMEDA) redox system. Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance ($^1$H-NMR), X-ray diffractometry (XRD), scanning electron microscopy and energy dispersive spectrometer (SEM-EDS), Brunauer-Emmett-Teller (BET), dynamic light scattering (DLS), swelling gravimetric analysis, vibrating sample magnetometer (VSM) were employed to analyze the hydrogel's chemical structures, surface morphologies, pH-responsive behaviors, and magnetic responsiveness characteristics. The results indicate that the Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel exhibited excellent dual responsiveness to pH and magnetism. Furthermore, an emphasis was placed on the in-depth analysis of the pH response mechanism and drug release control. Finally, we utilized this cutting-edge hydrogel to investigate the controlled-release behavior of two model drugs, *Acetylsalicylic acid* and *Theophylline*, within the simulated gastrointestinal tract. The Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel demonstrated exceptional controlled release attributes, positioning it as a potential carrier for targeted drug delivery, particularly to the gastrointestinal conditions.

1. Introduction

In recent years, there has been a surge of research dedicated to the exploration of hydrogels—an intriguing class of hydrophilic polymers characterized by their three-dimensional crosslinked network structure, achieved through diverse chemical and physical methodologies[1–4]. Of particular interest is their remarkable capacity for water absorption and swelling[5, 6]. Hydrogels, owing to their hydrophilicity, soft tissue stiffness mimicry, high metabolite permeability, antioxidation, and environmental sensitivity, have found diverse applications[7, 8]. A captivating attribute is their adaptability to incorporate various functionalities into crosslinked networks, resulting in “smart” or “intelligent” hydrogels[9, 10]. These intelligent hydrogels exhibit diverse responses to external conditions like temperature[11], pH value[12], salinity[13], electric fields[14], magnetic fields[15], and chemical environments[16]. Smart hydrogels have plenty of applications in industries, agriculture, and biomedical fields, such as wastewater treatment[17], drug release[18], contact lenses[19], tissue engineering[20], and wound healing[21, 22].

Among the hydrophilic polymers used in hydrogel formation, polysaccharides, due to their economic, biocompatible, nontoxic, and biodegradable nature, offer distinct advantages over synthetic polymers[23, 24]. Xylan hemicellulose (XH), a major component in plant cell walls and second most naturally available polysaccharide after cellulose, particularly in hardwood and herbaceous plants, constitutes approximately 20–35% of biomass[25, 26]. Its abundance in forestry, agriculture, pulp, and paper industries by-products makes it advantageous for preparing biomass-derived hydrogels for biomedical applications[27–29]. For
instance, Peng F. et al. developed a novel hemicellulose hydrogel for skincare by crosslinking dialdehyde xylan and incorporating glycerol and nicotinamide, which exhibited promising properties including improved texture, antibacterial efficacy, and favorable cytocompatibility[25]. Bian J. et al designed a conductive xylan hemicellulose hydrogel (CHH) by incorporating carboxyl terminated aniline pentamer into the hydrophilic xylan-rich hemicellulose networks with epichlorohydrin. The CHH showed tunable conductivity and swelling behavior, which can be used to transmit bioelectrical signals and improve the cellular activity in living organism[30]. Si C. et al synthesized a temperature/pH dual sensitive hemicellulose-based hydrogels from eucalyptus APMP waste liquor by incorporating acrylic acid and acrylamide as monomers, N, N-methylene bis acrylamide as a cross-linking agent[31]. Nevertheless, the crosslinkers and monomers employed in the preparation of these hydrogels were non-biomass-derived and non-degradable, potentially compromising the ability of hydrogels to dissolve and be absorbed, and raising concerns about cellular toxicity in biomedical applications. Furthermore, achieving effective controlled release and precise treatment at the root of the disease remains challenging for these biomedical hydrogels[32, 33].

AA emerges as a pivotal monomer, accessible as a biomass-derived constituent through a single-step conversion via lactate dehydration[34–36]. PEGDA, derived from polyethylene glycol, stands as a pivotal biocompatible polymer with eco-friendly attributes and degradable characteristics[37]. Due to the wealth of reactive hydroxyl functional groups within the XH molecular structure, these sites can be harnessed for chemical reactions[38, 39]. By incorporating bio-based AA and PEGDA through a free radical graft polymerization process, a three-dimensional hemicellulose hydrogel can be created with a nearly 100% bio-based and biodegradable compositions[40]. The incorporation of carboxyl groups enables the hemicellulose hydrogel to respond to external stimuli such as pH values and salinity, making it suitable for drug release platforms. Given the diverse pH variations in various regions of the human body, including the gastrointestinal tract, vagina, and blood vessels, the entirely biomass-derived pH-responsive hemicellulose hydrogel emerges as an optimal drug carrier for drug-controlled release applications in nature[41]. Besides that, the introduction of inorganic particles into the hemicellulose hydrogel networks can not only improve the hydrogel’s mechanical properties, but also impart new functionalities[42–44]. For example, the introduction of Fe$_3$O$_4$ magnetic nanoparticles (MNPs) into the hemicellulose hydrogel can realize multi-magnetic responsiveness[45]. In addition to visualizing the hydrogel carriers through magnetic resonance imaging, it is also possible to use Fe$_3$O$_4$ MNPs to provide alternating magnetic fields, enabling localized heating of the target area and remote release of encapsulated medicines/drugs[46]. In summary, encapsulating these Fe$_3$O$_4$ MNPs into a biomass-based hemicellulose hydrogel can protect biological tissues from direct contact with inorganic particles, resulting in a multifunctional drug-loaded hydrogel platform with both polymer matrix and magnetic nanoparticle characteristics.

Building upon the aforementioned concept, this study centers on harnessing the chemical functionality inherent in natural biomass—specifically, XH as the primary material, PEGDA as the biodegradable crosslinker, and incorporating the advantages of AA and Fe$_3$O$_4$ MNPs to engineer an innovative bio-based pH/magnetic dual-responsive hemicellulose nanocomposite hydrogel, named as Fe$_3$O$_4$@XH-Gel. Initially, Fe$_3$O$_4$ MNPs were prepared using a co-precipitation method, with characterization through XRD, BET, and DLS analyses. Subsequently, a bio-based pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel nanocomposite
hydrogel, was successfully crafted by free radical graft polymerization on natural XH, incorporating in-situ doping of Fe$_3$O$_4$ MNPs. The chemical structures, crystalline characteristics, surface morphologies, pH and magnetic responsiveness of the newly developed Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel were concisely characterized using FTIR, $^1$H-NMR, XRD, SEM-EDS, swelling gravimetric analysis, and VSM, respectively. Furthermore, the impacts of crosslinker PEGDA concentrations and AA/XH weight ratios on the hydrogel’s swelling properties were scrutinized. Finally, *in vitro* drug release studies with Acetylsalicylic acid and Theophylline as model drugs were conducted, revealing the outstanding pH sensitivity and magnetic responsiveness of the designed hemicellulose hydrogels, presenting them as promising candidates for targeted drug delivery, particularly in the gastrointestinal tract.

2. Experimental procedure

2.1 Materials

XH from Birch wood chips (Betula pendula) was prepared by pressurized hot-water extraction and stored as a solution with concentration of 10 wt.% for further use. AA, PEGDA, APS, TMEDA, phosphoric acid, acetylsalicylic acid, theophylline, ferric chloride hexahydrate, and ferrous chloride tetrahydrate, all of analytical purity, were sourced from Aladdin. Sodium dihydrogen phosphate and disodium hydrogen phosphate, both analytically pure, were acquired from Shanghai Titan Technology Co., Ltd.

2.2 Methods

2.2.1 XH extraction and characterization

The native XH dispersion underwent precipitation using an industrial-grade ethanol solution at a 2:8 (v/v) water-ethanol ratio. A glass fiber filter was employed for vacuum filtration, and the resulting filter cake was redissolved in water. This ethanol precipitation and filtration process was iterated, with the third filtration stage followed by consecutive washing steps using pure ethanol, acetone, and MTBE. The purified XH filtrate was dried overnight at ambient temperature and further subjected to vacuum desiccation at 40°C for 48 h to eliminate residual MTBE. The purified XH exhibited a number-average molecular weight ($M_n$) of 2.42×10$^3$ g mol$^{-1}$ and a weight-average molecular weight ($M_w$) of 6.29×10$^3$ g mol$^{-1}$, with a polydispersity ($M_w/M_n$) of approximately 2.60, as determined by high-performance size exclusion chromatography (HPSEC). Sugar composition (wt.%) of the XH was determined through gas chromatography (GC), revealing a composition of 90.8% xylose, 4.9% arabinose, and 2.5% glucose. Traces of other sugars, including galactose, mannose, and rhamnose, were detected at levels below 1.8 wt.%. 

2.2.2 Preparation of Fe$_3$O$_4$ MNPs

Fe$_3$O$_4$ MNPs were prepared through a co-precipitation method, based on the following reaction Eq. 1:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \rightarrow Fe_3O_4 + 4H_2O$$
The specific procedure involved dissolving 2.1 g FeCl$_2$ • 4H$_2$O and 5.8 g FeCl$_3$ • 6H$_2$O in 100 mL of deionized water at 50 °C under a N$_2$ atmosphere, forming a Fe$^{2+}$/Fe$^{3+}$ mixed solution. While continuously stirring, 20 mL of ammonia solution was added dropwise to the Fe$^{2+}$/Fe$^{3+}$ mixed solution. After a reaction time of 0.5 h, a black suspension was obtained. The resulting black suspension underwent repeated washing with deionized water until achieving a neutral pH value. Separation was facilitated using an external magnetic field, and the synthesized Fe$_3$O$_4$ MNPs were stored in an environment at around 4 °C. This co-precipitation method yielded Fe$_3$O$_4$ MNPs with desirable magnetic property, demonstrating the effectiveness of this approach in nanoparticle synthesis.

2.2.3 Synthesis of bio-based pH-response XH-Gel hydrogel

In the synthesis of the XH-Gel hydrogel, 0.5 g of XH was dissolved in 15 mL of deionized water. The solution was stirred for 0.5 h at 50 °C under a N$_2$ atmosphere. Subsequently, 6 g of AA, 25 mg of APS, 50 µL of TMEDA, and 0.1 g of PEGDA were sequentially introduced into the reaction solution. The reaction temperature was then adjusted to 70 °C, and stirring continued for an additional 3 h. The resultant gel-like solid was characterized as XH-Gel. The XH-Gel underwent thorough washing with deionized water until achieving a neutral pH value. This step is pivotal to ensure the elimination of any residual reactants, guaranteeing the desired properties of the targeted hydrogel. Ultimately, the XH-Gel hydrogel was stored at 4 °C for subsequent utilization.

2.2.4 Fabrication of bio-based pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel

A dual-responsive nanocomposite hydrogel, Fe$_3$O$_4$@XH-Gel, was prepared through a one-step in-situ polymerization method. A specified quantity of Fe$_3$O$_4$ MNPs, 0.5 g of XH, and 15 mL of deionized water were combined and reacted. The mixture was stirred for 0.5 h at 50 °C under a N$_2$ atmosphere. Subsequently, a specific amount of AA, 25 mg of APS, 50 µL of TMEDA, and an appropriate volume of PEGDA were sequentially introduced into the reaction solution. The reaction temperature was adjusted to 70 °C, and stirring continued for an additional 3 h, yielding a black gel-like solid identified as Fe$_3$O$_4$@XH-Gel. The detailed synthesis formulation is provided in Table 1. The resulting hydrogel underwent thorough washing with deionized water until reaching a neutral pH value. Separation was facilitated using an external magnetic field, and the final products were stored at 4 °C for subsequent use.
Table 1
Designations of bio-based pH/magnetic dual-responsive Fe₃O₄@XH-Gel nanocomposite hydrogels under various reaction conditions

<table>
<thead>
<tr>
<th>Samples</th>
<th>Reaction conditions</th>
<th>AA/XH (g/g)</th>
<th>PEGDA (g)</th>
<th>Fe₃O₄ (wt.%)</th>
<th>Sₑq</th>
</tr>
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<tbody>
<tr>
<td>Fe₃O₄@XH-Gel-1</td>
<td>12</td>
<td>0.05</td>
<td>10</td>
<td>52.4</td>
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</tr>
<tr>
<td>Fe₃O₄@XH-Gel-2</td>
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<td>0.1</td>
<td>10</td>
<td>207.8</td>
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</tr>
<tr>
<td>Fe₃O₄@XH-Gel-3</td>
<td>12</td>
<td>0.2</td>
<td>10</td>
<td>122.2</td>
<td></td>
</tr>
<tr>
<td>Fe₃O₄@XH-Gel-4</td>
<td>12</td>
<td>0.3</td>
<td>10</td>
<td>115.4</td>
<td></td>
</tr>
<tr>
<td>Fe₃O₄@XH-Gel-5</td>
<td>12</td>
<td>0.4</td>
<td>10</td>
<td>84.6</td>
<td></td>
</tr>
<tr>
<td>Fe₃O₄@XH-Gel-6</td>
<td>2</td>
<td>0.1</td>
<td>10</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Fe₃O₄@XH-Gel-7</td>
<td>4</td>
<td>0.1</td>
<td>10</td>
<td>146.9</td>
<td></td>
</tr>
<tr>
<td>Fe₃O₄@XH-Gel-8</td>
<td>8</td>
<td>0.1</td>
<td>10</td>
<td>151.4</td>
<td></td>
</tr>
<tr>
<td>Fe₃O₄@XH-Gel-9</td>
<td>16</td>
<td>0.1</td>
<td>10</td>
<td>132.4</td>
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<tr>
<td>Fe₃O₄@XH-Gel-10</td>
<td>12</td>
<td>0.1</td>
<td>5</td>
<td>282.5</td>
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<tr>
<td>Fe₃O₄@XH-Gel-11</td>
<td>12</td>
<td>0.1</td>
<td>15</td>
<td>126.3</td>
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<tr>
<td>Fe₃O₄@XH-Gel-12</td>
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<td>0.1</td>
<td>20</td>
<td>40.6</td>
<td></td>
</tr>
</tbody>
</table>

2.3 Characterizations

2.3.1 HPSEC for molecular weight analysis

Molecular weight characteristics (Mₙ, Mₘ, and PDI) of pure XH were determined by HPSEC in online combination with a multi-angle laser light scattering (MALLS) detector and a refractive index (RI) detector using NaNO₃ in the water with a concentration of 0.1 mol/L as the eluent. A two-column system, a Jordi Gel Glucose Mixed-bed guard column (10×50 mm, I.D.×L) and a Jordi Gel GBR Mixed-bed column (10×250 mm, I.D.×L) was used. Dissolved samples (5 mg mL⁻¹) were filtered through a 0.45 µm Nylon syringe filter. The HPSEC/MALLS/RI system was operated under the following conditions: 60°C column temperature; 0.5 mL min⁻¹ flow rate. Data evaluation used ASTRA software, version 7.3.2.

2.3.2 GC for sugar content analysis

The sugar compositions of native XH were determined by GC. 3 mg of XH sample was subjected to 2 mL of 2 M HCl in anhydrous methanol and put in 105°C oven for 3 h. The excess HCl was neutralized by adding 150 µL pyridine. The internal standard of 0.1 mg mL⁻¹ resorcinol in methanol was added to the sample. The
sample was dried by nitrogen flow at 50°C and further dried in a vacuum desiccator at 40°C for 30 min. The sample was dissolved in 150 µL pyridine, and 150 µL hexamethyldisilane and 80 µL trimethylchlorosilane were added. The silylated sample was left overnight for GC analysis. The analyses were carried out using HP-1 column (Hewlett Packard) by the carrier gas of 0.8 mL min\(^{-1}\) \(\text{H}_2\) and with the following column temperature program: 100°C; 4°C min\(^{-1}\); 180°C; 12°C min\(^{-1}\); 290°C (5 min). The results were analyzed using the program of TotalChrom Navigator.

### 2.3.3 FTIR analysis

FTIR spectra of XH, Fe\(_3\)O\(_4\), and Fe\(_3\)O\(_4\)@XH-Gel were acquired using a Thermo Scientific Nicolet 6700 Fourier transform infrared spectrometer. Prior to measurement, samples underwent vacuum drying at 50°C until reaching a constant weight, were ground into powder, and subsequently pressed into KBr pellets with 1% sample content. Spectra were recorded in the 500–4000 cm\(^{-1}\) range at a resolution of 4 cm\(^{-1}\), with a scanning frequency of 32 scans per minute.

### 2.3.4 \(^1\text{H}-\text{NMR analysis}\)

\(^1\text{H}-\text{NMR}\) spectra of XH and XH-Gel were obtained at room temperature using a Bruker Ascend 400 MHz NMR spectrometer (Germany). The Fe\(_3\)O\(_4\)@XH-Gel, containing Fe\(_3\)O\(_4\) MNPs, proves resistant to dissolution in conventional deuterium-based reagents, rendering the assessment of its nuclear magnetic resonance spectrum properties unfeasible. Tetramethyl silane served as an internal standard, and deuterated dimethyl sulfoxide (DMSO-d6) was utilized as the solvent.

### 2.3.5 XRD analysis

The X-ray patterns of the samples were obtained using a Rigaku diffractometer (Ultima V, 3 kW), with monochromatic graphite CuK\(\alpha\) radiation (\(\lambda = 1.543 \, \text{Å}\)) as the radiation source. The tube voltage was set at 40 kV, tube current at 40 mA, and the emission/anti-scattering slit DS/SS = 1/6 (deg.). The receiving slit was set at 0.6 mm. Sample testing was conducted at room temperature (25 °C), and the diffractometer's 2θ angle was scanned from 10° to 80° at a scan rate of 6° min\(^{-1}\).

### 2.3.6 SEM-EDS analysis

XH-Gel and Fe\(_3\)O\(_4\)@XH-Gel hydrogels, in a state of swollen equilibrium, underwent freeze-drying after surface water removal with filter paper in a nitrogen atmosphere. The cross-sections of the hydrogels were gold-coated and examined for morphology and elemental distribution using a field emission scanning electron microscope (Zeiss GeminiSEM 500, Germany) equipped with an X-ray energy-dispersive spectrometer.

### 2.3.7 DLS analysis

The particle size and distribution of Fe\(_3\)O\(_4\) nanoparticles were assessed using a Brookhaven Instruments BI-200SM goniometer-based dynamic light scattering instrument. Before measurement, appropriate dilution of Fe\(_3\)O\(_4\) MNPs was carried out with ultrapure water.

### 2.3.8 BET surface area analysis
BET surface area and pore size analysis of Fe$_3$O$_4$ MNPs were conducted using a Micromeritics ASAP2460 multi-station surface area and porosity analyzer under a nitrogen atmosphere. Following degassing at 100°C for 4 h, the specific surface area was determined at 77 K with varying relative pressures (P/P$_0$ = 0–1).

### 2.3.9 Swelling properties

The swelling ratio of the Fe$_3$O$_4$@XH-Gel hydrogels was determined through a gravimetric method. All hydrogel samples were dried until a constant weight was achieved, followed by immersion in separate 200 mL glass beakers containing distilled water at room temperature. Once swelling equilibrium was attained, excess water was carefully removed using filter paper. The weight of the swollen hydrogels was measured, and the equilibrium swelling ratio ($S_{eq}$) was calculated using Eq. 2.

$$S_{eq} = \frac{W_{eq} - W_0}{W_0}$$

Here, $W_{eq}$ represents the weight of the swollen hydrogel, and $W_0$ is the initial weight of the vacuum-dried sample.

### 2.3.10 pH-responsive behaviors

The pH responsiveness of Fe$_3$O$_4$@XH-Gel hydrogels was discerned through the examination of their swelling ratios. Individual gel samples were immersed in buffer solutions with varying pH values of 2, 4, 6, 8, and 10, while maintaining a consistent ionic strength of 0.1 mol L$^{-1}$ through precise adjustments of sodium chloride content. Following the swelling and equilibration of the hydrogel, the swelling ability at distinct pH values was quantified, and $S_{eq}$ was computed using Eq. 2. Notably, each set of experiments was meticulously designed with three parallel trials for robust validation and reliability, adhering to rigorous scientific standards.

### 2.3.11 Magnetic response performance

The magnetic characteristics of Fe$_3$O$_4$ MNPs and Fe$_3$O$_4$@XH-Gel were assessed utilizing a LakeShore 7404 vibrating sample magnetometer (VSM) at room temperature (300 K) under a magnetic field spanning from $-20,000$ Oe to $20,000$ Oe.

### 2.3.12 In vitro drug loading and release

Acetylsalicylic acid and theophylline served as model drugs for drug loading and release experiments. The drugs were dissolved in deionized water, and during the hydrogel preparation, the drug solution was introduced to the hydrogel when the reaction system achieved viscosity. The drug content in the dry hydrogel was maintained at 2% (w/w). Drug release studies were conducted in a shaking incubator at $37^\circ$C and 50 rpm. A specified volume of pH = 1.5, 7.4, and 10.0 buffer solutions immersed the hydrogel (0.1 g). UV spectrophotometry was employed to ascertain drug content (acetylsalicylic acid: 294 nm; theophylline: 273 nm). The drug release concentration was computed using calibration standard curves for each pH value.
For acetylsalicylic acid:

pH 1.5: \( y = -0.00297 + 0.49623x \) (\( r = 0.99848 \));

pH 7.4: \( y = 0.000586 + 0.13807x \) (\( r = 0.99978 \));

pH 10.0: \( y = -0.00245 + 0.07408x \) (\( r = 0.99937 \)).

For theophylline:

pH 1.5: \( y = -0.0006216 + 0.03116x \) (\( r = 0.99946 \));

pH 7.4: \( y = -0.0002916 + 0.02728x \) (\( r = 0.99975 \));

pH 10.0: \( y = -0.00205 + 0.02847x \) (\( r = 0.99772 \)).

The cumulative release rate (%) was calculated using Eq. 3.

\[
\text{Cumulative Release} (%) = \frac{W_{dt}}{W_{\infty}} \times 100
\]

Where \( W_{dt} \) represents the weight of the drug released at time \( t \), and \( W_{\infty} \) is the total weight of the drug loaded in the Fe\(_3\)O\(_4@\)XH-Gel hydrogel.

### 3. Results and discussion

#### 3.1 Reaction mechanism

As illustrated in Fig. 1, an oxidation-reduction system, initiated by APS and TMEDA, orchestrates the capture of hydrogen atoms from hydroxyl groups on xylan chains, generating free radicals. These free radicals then serve as reaction sites for the grafting of AA onto the xylan chains. Subsequently, AA is grafted onto the xylan chains using the free radicals as reaction sites. Simultaneously, propelled by the oxidation-reduction initiator, AA undergoes facile free radical polymerization, culminating in the formation of the polymer (PAA). This transformative modification metamorphoses the xylan chains into a PAA-Xylan-PAA shown in Fig. 1(a). Introducing the cross-linker PEGDA further enhances the process, wherein the unsaturated double bonds in PEGDA molecules unfurl and cross-link with the hydroxyl groups on the polymer, sculpting a resilient three-dimensional network structure, demonstrated in Fig. 1(b). Moreover, the inherent unsaturated double bonds in PEGDA facilitate additional cross-linking reactions with PAA, creating a more intricate and compact three-dimensional network structure (Fig. 1(c)). This smaller network permeates within the molecular framework of the hemicellulose hydrogel, augmenting its structural integrity[47, 48].

#### 3.2 Characterization of chemical structures

To validate the successful preparation of the pH/magnetic dual-responsive hydrogel Fe\(_3\)O\(_4@\)XH-Gel, FTIR was utilized to dissect the chemical functional groups within xylan (XH), Fe\(_3\)O\(_4\) MNPs, and Fe\(_3\)O\(_4@\)XH-Gel (Fig. 2(a)). In the FTIR XH spectrum, distinctive absorption peaks at 3444, 2937, 1633, 1253, 1044, and 897
cm\(^{-1}\) align with typical features of xylan\[49, 50\]. The broad peak at 3444 cm\(^{-1}\) represents the -OH stretching vibration of xylan, and in the FTIR spectrum of Fe\(_3\)O\(_4\)@XH-Gel, this peak is noticeably attenuated and narrowed. This implies a reduction in hydrogen bonding within xylan hydroxyl groups, potentially initiating free radical polymerization reactions with monomers. The absorption peak at 2937 cm\(^{-1}\) corresponds to the C-H stretching vibration of alkanes in the xylan structure, while the peak at 1735 cm\(^{-1}\) is attributed to the C = O stretching vibration of acetyl groups, indicating the preservation of acetyl groups during the extraction process. The absorption peak at 1633 cm\(^{-1}\) is associated with water absorbed by xylan due to its numerous hydroxyl groups. The weaker peaks at 1044 and 897 cm\(^{-1}\) indicate the presence of C-O-C glycosidic bonds and β-glycosidic bonds between sugar units, respectively, suggesting that β-glycosidic bonds serve as internal connections in xylan hemicellulose.

In the FTIR spectrum of Fe\(_3\)O\(_4\), the broad peak around 562 cm\(^{-1}\) is attributed to the Fe-O stretching vibration, 1624 cm\(^{-1}\) corresponds to the FeOO\(^-\) stretching vibration, and 3410 cm\(^{-1}\) is associated with the stretching vibration of hydroxyl groups (OH) on the surface of Fe\(_3\)O\(_4\) particles. The absence of characteristic absorption peaks near 700 cm\(^{-1}\) for suboxide bonds confirms the purity of the Fe\(_3\)O\(_4\) MNPs. In the FTIR spectrum of Fe\(_3\)O\(_4\)@XH-Gel, the emergence of the Fe-O stretching vibration peak at 562 cm\(^{-1}\) suggests the successful embedding of Fe\(_3\)O\(_4\) MNPs. Comparing both spectra with that of XH, the C-COOH stretching vibration peak at 846 cm\(^{-1}\) is present, and the characteristic absorption band of XH at 1044 cm\(^{-1}\) is notably weakened, indicating the grafting of AA chains onto the XH backbone. In summary, these findings signify the successful grafting and cross-linking of AA onto XH, resulting in the formation of a hydrogel that encapsulates Fe\(_3\)O\(_4\) MNPs within its internal networks.

XRD analysis was also employed to corroborate the chemical structures of the biomass-based hydrogel Fe\(_3\)O\(_4\)@XH-Gel. Figure 2(b) depicts the XRD spectra of XH, Fe\(_3\)O\(_4\) MNPs, and Fe\(_3\)O\(_4\)@XH-Gel. The prominent diffraction peak at 2θ = 21.5° is characteristic of xylan hemicellulose. In the XRD spectrum of the Fe\(_3\)O\(_4\)@XH-Gel hydrogel, the intensity of the peak at 2θ = 21.5° is markedly reduced, signifying a chemical reaction between XH, monomer AA, and cross-linking agent PEGDA, leading to the disruption of the crystalline structure of XH. Furthermore, the characteristic peaks at 30.0°, 35.4°, 43.0°, 56.8°, and 62.4° in the XRD spectrum of Fe\(_3\)O\(_4\) MNPs align well with the (220), (311), (400), (511), and (440) planes of Fe\(_3\)O\(_4\) [PDF#89–0688], respectively\[51\]. These corresponding diffraction peaks of Fe\(_3\)O\(_4\) are also evident in the XRD spectrum of Fe\(_3\)O\(_4\)@XH-Gel, confirming the successful encapsulation of Fe\(_3\)O\(_4\) MNPs within the targeted bio-based pH/magnetic dual-responsive Fe\(_3\)O\(_4\)@XH-Gel nanocomposite hydrogel\[52\].

The chemical structures of the pH/magnetic dual-responsive bio-based hydrogel Fe\(_3\)O\(_4\)@XH-Gel, featuring the incorporation of Fe\(_3\)O\(_4\) MNPs, remain elusive through \(^1\)H-NMR analysis, owing to the hydrogel's non-dissolvable nature in various deuterated solvents. Figure 2(c) elucidates the \(^1\)H-NMR spectra of XH and XH-Gel hydrogel. In the \(^1\)H-NMR spectrum of XH, δ = 2.5 ppm denotes the DMSO-d6 solvent peak, while δ = 3.35 ppm corresponds to the water peak in the DMSO-d6 solvent. Regarding XH, characteristic chemical shifts at δ = 1.1, 1.24, 1.98, 3.60, and 4.98 ppm are assigned to H-a, H-b, H-c, H-d, and H-e, respectively. In the \(^1\)H-NMR spectrum of XH-Gel hydrogel, the newly emerged peak at δ = 12.22 corresponds to the carboxyl hydrogen...
resonance introduced after the polymerization of AA monomer. The noticeable disappearance or reduction of active hydrogen resonances in the $\delta = 3 \sim 5.5$ ppm range indicates the involvement of active hydrogen atoms on the XH ring in the graft copolymerization reaction. Additionally, the resonance peak of C = C in PEGDA and AA molecular structures, typically appearing at approximately $5.5 \sim 6.5$ ppm (see in Figure S1), was not observed in the XH-Gel $^1$H-NMR spectrum[53–55]. This suggests that the AA monomer and PEGDA crosslinker have completely joined the free radical graft polymerization on the XH and the produced XH-Gel does not contain unreacted AA monomer and PEGDA crosslinker. Therefore, combining the reduction of hydroxyl functional groups and the disappearance of C = C double bonds, these findings substantiate the successful grafting and cross-linking of AA and PEGDA onto XH, culminating in the formation of the XH-Gel hydrogel. These observations align with the results obtained from the FTIR analysis. In summary, the characterization of chemical structures based on the synergistic results of FTIR, XRD and $^1$H-NMR spectra indicates the successful preparation of bio-based pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel.

### 3.3 Surface morphology analysis

The surface morphologies of the freeze-dried pH-responsive XH-Gel and pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel hydrogels were examined through SEM observations. As illustrated in Figs. 3(a) and 3(b) at magnifications of 2k and 20k, respectively, the XH-Gel hydrogel, without loaded Fe$_3$O$_4$ MNPs, showcases a uniform honeycomb-like structure with well-defined pore morphology. In comparison to XH-Gel, Figs. 3(c) and 3(d) exhibit an integrated network structure with larger pores under 2k and 20k magnifications, suggesting a significant alteration in the hydrogel morphology. These large pores not only provide areas for water infiltration but also serve as interaction spaces between external stimuli and hydrophilic groups of graft copolymers, suggesting a high degree of expansion and swelling. The observed phenomenon can be attributed to the in-situ incorporation of Fe$_3$O$_4$ MNPs. On one front, the incorporation of Fe$_3$O$_4$ nanoparticles confers resilient mechanical support to the hydrogel, averting structural collapse and pore closure during freeze-drying, thereby preserving substantial porosity. On the flip side, it imparts exceptional magnetic properties to the hydrogel, which makes it possible for the precise and directionally controlled release under the action of the external magnetic field. As depicted in Fig. 3(d), the pore size of Fe$_3$O$_4$@XH-Gel is approximately 10–20 µm, providing a suitable micro-environment for drug delivery, such as Acetylsalicylic acid and Theophylline[56].

Figures 3(e-h) present the EDS elemental distribution maps of bio-based pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel hydrogel, including SEM photograph and the corresponding cross-sectional distribution of C, O, and Fe elements. The results demonstrate that Fe element originating from Fe$_3$O$_4$ MNPs are evenly distributed within the hydrogel network. When combined with SEM images containing Fe$_3$O$_4$ nanoparticles including Figs. 3(c) and 3(d), no obvious Fe$_3$O$_4$ nanoparticles are observed on the surface of the hydrogel network. This indicates that the Fe$_3$O$_4$ MNPs are effectively encapsulated within the hydrogel polymer matrix and evenly distributed, preventing direct contact with human biological tissues when utilized for biomedical applications. This underscores the dual properties of the designed Fe$_3$O$_4$@XH-Gel ferrogel, incorporating characteristics of both the polymeric matrix and the magnetic nanoparticles.
3.4 Swelling properties

Figure 4(a) depicts the impact of varied cross-linker PEGDA concentrations on the equilibrium swelling ratio \( S_{eq} \) of \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) hydrogels. As the dosage of the cross-linking agent increases, the \( S_{eq} \) of \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) experiences an initial rise followed by a decline. Specifically, the \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) sample exhibits a minimum \( S_{eq} \) of 52.4 and a maximum \( S_{eq} \) of about 207.8. This observed trend is ascribed to the cross-linking density’s influence on the hydrogel’s swelling behavior. The augmentation of PEGDA content introduces more chemical cross-linking points, initially boosting the swelling ratio. However, a further escalation in the cross-linking agent content results in a denser network structure, hindering the entry of water molecules into the gel structure and consequently reducing the hydrogel’s swelling ratio. Hydrogels devoid of cross-linking agents exhibit slow dissolution in the solution medium due to the presence of only hydrogen bond physical cross-linking forces. Subsequent investigations in our research revealed the pivotal role of a moderate cross-linking density in facilitating effective drug release and degradation\[57–59\].

Figure 4(b) delineates the impact of varied AA/XH weight ratios on the \( S_{eq} \) of hemicellulose-based \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) hydrogels. The \( S_{eq} \) of \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) exhibits a notable rise, escalating from 12.9 to around 207.8, with an increase in the AA/XH weight ratio from 4:1 to 12:1. Within this framework, the carboxyl group content in the hydrogel emerges as a pivotal factor influencing the swelling ratio. Within a specific AA/XH ratio range, heightened AA content results in increased ionization of carboxyl groups within the hydrogel, thereby contributing to a higher swelling ratio. Additionally, the presence of hydrogen bonds in XH serves to augment the density of cross-linking points in the hydrogel, effectively suppressing swelling. The intensified ionization of carboxyl groups disrupts these hydrogen bonds, facilitating hydrogel swelling. However, when the AA/XH ratio exceeds 12:1, the \( S_{eq} \) experiences a decline. Upon subjecting hydrogel samples to immersion in deionized water for 48 hours, hydrogels with higher AA concentrations (16:1) manifest more pronounced mass loss, with the \( S_{eq} \) of 132.4. This observation suggests that the elevated AA content promotes the formation of AA homopolymers, reducing the grafting density of the hydrogel and consequently diminishing the swelling ratio. In general, the optimal AA/XH ratio for excellent water absorption is determined to be 12:1, achieving a maximum \( S_{eq} \) of 207.8.

3.5 pH-responsive behaviors

Drawing insights from the experimental results in Fig. 5(a) and 5(b), a substantial shift in the swelling ratio of all hydrogels is observed between pH = 2 and pH = 10 buffer solutions. In particular, varying the concentration of the crosslinker PEGDA or adjusting the mass ratio of AA/XH yields hydrogels that, at pH = 2, demonstrate a minimal \( S_{eq} \) of approximately 5.0. Conversely, at pH = 8, these hydrogels exhibit a remarkable maximum \( S_{eq} \), reaching 48.9. Upon further elevation to pH = 10, the \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) hydrogels manifest a slight decrease in the swelling ratio. These results underscore the remarkable sensitivity of the prepared \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) hydrogels to environmental pH variations.

In Fig. 6, we further present a schematic representation detailing the pH-responsive mechanism of the hemicellulose-based \( \text{Fe}_3\text{O}_4@\text{XH-Gel} \) hydrogel at various pH values. Considering the known pK\(_a\) of -COOH, which is 4.6, we note that at pH levels below 4.6 (as in our study with pH = 2/4), the concentration of H\(^+\) is
elevated. Protonation of -COO- forms -COOH, diminishing electrostatic repulsion between groups (-COO-). Excessive H\(^+\) in the environment forms intramolecular hydrogen bonds with -COOH, restraining the hydrogel's swelling (Fig. 6(a)). As the solution's pH gradually rises from 4.6 to pH = 6/8, -COOH deprotonates into -COO\(^-\). The augmented presence of -COO- enhances electrostatic repulsion within the hydrogel, and hydrogen bonding between hydrophilic groups (-COO\(^-\)) and H\(_2\)O intensifies, significantly promoting the hydrogel's swelling (Fig. 6(b)). However, with a further increase in the buffer solution's pH to 10, the ionic strength in the solution increases, and the metal ions (Na\(^+\)) are combined with the -COO\(^-\) on the polymer chain of the hydrogel network, which reduces the electrostatic repulsive force and generates the charge screening phenomenon (Fig. 6(c)). Additionally, due to the different osmotic pressure of the hydrogel network inside and outside the solution, increasing the metal ions (Na\(^+\)) concentration reduces the ratio of -COO\(^-\) inside the hydrogel to the positive ions of the external solution, thereby reducing the osmotic pressure difference. Consequently, the hydrogel network contracts into a relatively compact structure, leading to a decrease in the swelling ratio. This bio-based Fe\(_3\)O\(_4\)@XH-Gel nanocomposite hydrogel, sensitive to pH changes, holds promise for biomedical applications, particularly in drug release scenarios\[^{60–62}\]. One prominent application involves leveraging the substantial pH difference between the human stomach (pH ≈ 1.5) and intestines (pH ≈ 7.4). If the Fe\(_3\)O\(_4\)@XH-Gel hydrogel is loaded with drugs, it can remain insensitive to the acidic stomach environment but undergoes swelling, dissolution, or drug release upon entering the alkaline intestinal environment, ensuring controlled drug release without causing harm to the stomach and optimizing therapeutic efficacy.

3.6 Magnetic responsiveness characteristics

The biobased Fe\(_3\)O\(_4\)@XH-Gel hydrogel, synthesized in this study, presents another crucial physical attribute—magnetic responsiveness. Illustrated in Fig. 7(a), the BET specific surface area of Fe\(_3\)O\(_4\) nanoparticles measures 103.76 m\(^2\) g\(^{-1}\), while Fig. 7(b) indicates an average particle size of 208.2 nm for Fe\(_3\)O\(_4\) MNPs, underscoring their nanoscale structure and substantial BET surface area. Figure 7(c) portrays magnetic hysteresis loops of Fe\(_3\)O\(_4\)@XH-Gel magnetic hydrogels, revealing a superparamagnetic behavior. The saturation magnetization (M\(_s\)) of Fe\(_3\)O\(_4\) particles is 57.2 emu g\(^{-1}\), confirming their superparamagnetic nature. Distinct concentrations of Fe\(_3\)O\(_4\) in the Fe\(_3\)O\(_4\)@XH-Gel hydrogels exhibit varying saturation magnetization values (1.78, 3.17, 6.61, and 7.13 emu/g for 5 wt.\%, 10 wt.\%, 15 wt.\%, and 20 wt.\% Fe\(_3\)O\(_4\), respectively), significantly lower than pure bulk Fe\(_3\)O\(_4\) (57 emu g\(^{-1}\)). This reduction is attributed to the presence of other antiferromagnetic substances, such as polymers, in the hydrogel. The Fe\(_3\)O\(_4\)@XH-Gel hydrogel, being bio-based, displays no apparent magnetic hysteresis, signifying its superparamagnetic characteristics. The concentration-dependent saturation magnetization suggests tunable magnetic responsiveness by adjusting Fe\(_3\)O\(_4\) nanoparticle concentration. In Figs. 7(d), 7(e), and 7(f), the captured images demonstrate the controlled movement of pH/magnetic dual-responsive Fe\(_3\)O\(_4\)@XH-Gel hydrogel within a water-filled bottle under an external magnetic field. Notably, higher Fe\(_3\)O\(_4\) concentrations result in a darker color and increased ease of movement under the same magnetic field intensity, highlighting enhanced magnetic responsiveness (seen in Videos S1, S2, S3 and S4)\[^{63}\].
While single pH-responsive hydrogels hold promise for protein drug delivery, pH/magnetic dual-responsive hydrogels offer superior capabilities for rapid response and remote control, meeting stringent medical requirements[64]. The hydrogels with magnetic responsiveness can achieve pulsatile and controllable drug release through external oscillating magnetic fields, extending drug residence time at the target site. Therefore, this designed biomimetic Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel, with pH and magnetic responsiveness, emerges as a formidable contender for drug delivery. The envisioned drug release mechanism utilizing this bio-based and biodegradable pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel was depicted in Fig. 8. Upon oral administration of the drug-loaded hydrogel carrier, the hydrogel traverses the upper respiratory tract to reach the stomach. In the acidic environment of gastric juice (pH ≈ 1.5), the hydrogel undergoes minimal swelling, resulting in an exceedingly low drug release. Subsequently, under the induction of an external magnetic field, the hydrogel advances to the human intestine. In the alkaline pH environment of the intestinal tract (pH ≈ 7.4), the hydrogel experiences maximum swelling or dissolution. This pH-dependent and remote-controlled behaviors facilitate efficient and precise drug release, achieving the targeted treatment at the root of the intestinal disease.

### 3.7 *In vitro* drug loading and release

This study utilized *Acetylsalicylic acid* and *Theophylline* as model drugs to investigate the drug release behavior of the dual-responsive nanocomposite hydrogel Fe$_3$O$_4$@XH-Gel. Acetylsalicylic acid, well-studied and reported as an antiplatelet drug for preventing cardiovascular diseases, is employed to prevent cardiovascular events such as myocardial infarction and vascular occlusion in the brain and peripheral circulation. In Figs. 9(a-c), the *in vitro* cumulative release curves of acetylsalicylic acid at 37°C in solutions with pH values of 1.5, 7.4, and 10.0 are presented. The release process exhibits two regions: an initial rapid release phase (within 2 h) and a subsequent stable slow-release phase (between 2 to 6 h). Notably, the cumulative drug release rate of acetylsalicylic acid in pH = 7.4 solution reaches approximately 90% within 6 hours, significantly surpassing the release rates in pH = 1.5 and pH = 10 buffered solutions. This is attributed to the higher swelling ratio, resulting in an increased size of the polymer matrix and consequently a higher degree of drug release. At pH = 1.5, representing gastric pH, low swelling ratio restricts the release of acetylsalicylic acid from the Fe$_3$O$_4$@XH-Gel. Conversely, in a mildly alkaline environment (pH = 7.4 simulating intestinal conditions), the drug-loaded pH/magnetic dual-responsive nanocomposite hydrogel Fe$_3$O$_4$@XH-Gel experiences a substantial increase in water absorption, leading to a uniform drug release after 6 hours. The release kinetics demonstrate zero-order drug release kinetics without an initial burst release, a characteristic observed in other reported hydrogels. However, the presence of the COOH group in acetylsalicylic acid, undergoing dissociation influenced by solution pH, may impact drug release from the bio-based Fe$_3$O$_4$@XH-Gel hydrogel, explaining the lower cumulative release at pH = 10.

Theophylline, a xanthine derivative used for the chronic treatment of bronchial asthma and bronchospasm diseases, is also utilized as a model drug to study the controlled release of the prepared nanocomposite hydrogel. Figures 9(d-f) depicts the drug release curves of the biomass-based hydrogel Fe$_3$O$_4$@XH-Gel loaded with theophylline in pH = 1.5, 7.4, and 10.0 buffered solutions. Similar to acetylsalicylic acid, the release process of theophylline includes an initial rapid release phase and a stable slow-release phase.
Theophylline exhibits a burst release pattern in the first 2 h, reaching a maximum release of 80% after 6 hours. The difference in cumulative release between pH = 1.5 and 7.4 solutions is less pronounced compared to acetylsalicylic acid. However, the total cumulative release of theophylline in pH = 7.4 solution surpasses that in pH = 1.5 and 10.0 solutions, sustaining release for 5–6 h in pH = 7.4 solution.

To further understand the release mechanisms of *Acetylsalicylic acid* and *Theophylline*, the data were fitted to some different models including WeibullCDF and Herschel drug-release models also shown in Fig. 9 [65, 66]. Comparatively, Logistic model (Eq. 4) gives the best fit to the drug release kinetics of Fe$_3$O$_4$@XH-Gel nanocomposite hydrogels. The correlation coefficients (R$^2$) of all samples are over 0.97. The detailed parameters of Logistic model and other two drug release models are displayed in Table 2 and Table S1, S2, respectively. The best fit to the Logistic model emphasizes the S-shape release for the *Acetylsalicylic acid* and *Theophylline* from the pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel hydrogels.

$$y = \frac{A_1 - A_2}{1 + \left(\frac{x}{x_0}\right)^p} + A_2$$

4

In summary, whether acetylsalicylic acid or theophylline is used as a model drug, the maximum cumulative drug release is achieved at pH = 7.4, showcasing effective sustained drug release within 6 h. The application of *Acetylsalicylic acid* and *Theophylline* as model drugs in the biomass-derived Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel for *in vitro* release studies indicates that this biomimetic hemicellulose-based hydrogel possesses controlled release characteristics and serves as an effective carrier for site-specific drug delivery in the intestines.

**Table 2** Parameters obtained by fitting the Fe$_3$O$_4$@XH-Gel release profiles to Logistic model.

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters</th>
<th>Acetylsalicylic acid in various pH buffer solutions</th>
<th>Theophylline in various pH buffer solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pH = 1.5</td>
<td>pH = 7.4</td>
</tr>
<tr>
<td>$y = \frac{A_1 - A_2}{1 + \left(\frac{x}{x_0}\right)^p} + A_2$</td>
<td>$A_1$</td>
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<td>0.0782</td>
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<td></td>
<td>$A_2$</td>
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<td>87.46447</td>
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<tr>
<td></td>
<td>$x_0$</td>
<td>1.19392</td>
<td>0.97825</td>
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<td></td>
<td>$p$</td>
<td>1.8676</td>
<td>2.20179</td>
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<td></td>
<td>Reduced Chi-Sqr</td>
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<tr>
<td></td>
<td>R-square</td>
<td>0.99533</td>
<td>0.98728</td>
</tr>
</tbody>
</table>

4. Conclusions
In this study, a cutting-edge pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel was successfully crafted via an in-situ graft polymerization technique on natural XH, as validated through comprehensive analyses encompassing FTIR, NMR, and XRD. SEM-EDS imaging authenticated the encapsulation and even distribution of Fe$_3$O$_4$ MNPs within the hemicellulose-based gel network structure. Exploration of the pH-responsive characteristics of the Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel unveiled notable pH sensitivity, evidenced by an $S_{eq}$ ranging from around 5.0 (pH = 2) to an impressive 48.9 (pH = 8). VSM measurements underscored the superparamagnetism of the biomimetic hydrogel, with magnetic responsiveness exhibiting augmentation proportional to the Fe$_3$O$_4$ particle content. Furthermore, the $S_{eq}$ displayed a nuanced trend, initially increasing and subsequently decreasing with escalating crosslinking agent PEGDA dosage and AA/XH weight ratio. In the realm of practical applications, Acetylsalicylic acid and Theophylline served as model drugs to evaluate drug release from the pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel. Our findings support its efficacy as a carrier for targeted drug delivery, particularly in intestinal applications. This study underscores the potential of the synthesized hydrogel as a versatile biomedical platform, emphasizing its multifaceted responsiveness and controlled release capabilities.

**Declarations**

**Author contributions**

Conceptualization, data analysis, review & editing, funding resources, Qiwen Yong; experiment, data analysis and curation, writing-original draft, Guangliang Zhou; measurement, data analysis, review, Xiaomeng Yu, Jiayun Xu and Liqiu Hu; raw materials, review & editing, Andrey Pranovich; conceptualization, experimental facilities, review & editing, guidance and supervision, Jilan Long and Zhihui Xie; conceptualization, raw materials, supervision and modification, funding resources, Chunlin Xu; All authors have read and agreed to the published version of manuscript.

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The authors declare there is no conflict of interest.

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Figures

Figure 1

Outlines and mechanistic insights into XH-Gel hydrogel formation
Figure 2

(a) FTIR Spectra and (b) XRD spectra of XH, Fe₃O₄, and pH/magnetic dual-responsive Fe₃O₄@XH-Gel hydrogel; (c) ¹H-NMR spectra of XH and XH-Gel hydrogel.
Figure 3

(a-b) SEM photographs of pH-response XH-Gel and (c-d) pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel, (e-h) along with elemental analysis depicting the distribution of C, O, and Fe elements within the Fe$_3$O$_4$@XH-Gel composite hydrogel.
Figure 4

(a) Impact of crosslinker PEGDA concentrations and (b) AA/XH weight ratios on the swelling ratios of pH/magnetic dual-responsive Fe₃O₄@XH-Gel hydrogels.

Figure 5

Impact of (a) varying PEGDA concentrations and (b) diverse AA/XH weight ratios on the $S_{\text{eq}}$ of pH/magnetic dual-responsive Fe₃O₄@XH-Gel hydrogels across different buffer solutions with pH ranging from 2 to 10.
Figure 6

pH-responsive mechanism of the hemicellulose-based Fe₃O₄@XH-Gel hydrogel
Figure 7

(a) BET surface area and (b) particle size of Fe$_3$O$_4$ MNPs; (c) VSM and (d), (e), (f) photographs of the pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel moving along the wall of a water-filled bottle under the influence of an external magnet.
Figure 8

Drug control release mechanism of biobased pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel nanocomposite hydrogel in human tissues.
Figure 9

*In vitro* cumulative drug release curves of drug-loaded pH/magnetic dual-responsive Fe$_3$O$_4$@XH-Gel hydrogels in various pH-buffered solutions at 37 °C: (a-c) acetylsalicylic acid and (d-f) theophylline, and the corresponding release kinetics fitted with Logistic, WeibullCDF and Herschel drug-release models, respectively.

**Supplementary Files**
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- 02032024Supplementarymaterials.zip