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Review

Pectin hydrogels for controlled drug release: Recent developments and future prospects

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ABSTRACT

Pectin hydrogels have emerged as a highly promising medium for the controlled release of pharmaceuticals in the dynamic field of drug delivery. The present review sheds light on the broad range of applications and potential of pectin-based hydrogels in pharmaceutical formulations. Pectin, as a biopolymer, is a versatile candidate for various drug delivery systems because of its wide range of properties and characteristics. The information provided on formulation strategies and crosslinking techniques provides researchers with tools to improve drug entrapment and controlled release. Furthermore, this review provides a more in-depth understanding of the complex factors influencing drug release from pectin hydrogels, such as the impact of environmental conditions and drug-specific characteristics. Pectin hydrogels demonstrate adaptability across diverse domains, ranging from applications in oral and transdermal drug delivery to contributions in wound healing, tissue engineering, and ongoing clinical trials. While standardization and regulatory compliance remain significant challenges, the future of pectin hydrogels appears to be bright, opening up new possibilities for advanced drug delivery systems.

1. Introduction

Pectin is a prominent polysaccharide that has enjoyed extensive use in food and pharmaceutical sectors (Cao et al., 2020). Its value lies in its health-enhancing attributes and capabilities in gelling, thickening, and emulsifying various products, thereby contributing to the enhanced quality and functionality of several goods in these industries (Li et al., 2021). Pectin, a naturally derived polysaccharide, creates 3D hydrophilic polymer networks, thereby granting softness, flexibility, and biocompatibility properties to pectin hydrogels (Piriyaprasarth et al., 2016). These hydrogels excel over other biopolymers, showcasing rapid gelation, elevated melting points, and effective potential for flavor

Abbreviations: EGC, (−)-epigallocatechin; Gal A, (1 → 4)-α-D-galacturonic acid; AH, acylhydrazide; AG, arabic gum; BSA, bovine serum albumin; CEC, carboxyethyl chitosan; DSC, differential scanning calorimetry; DHA, dihydroartemisinin; DOX, doxorubicin; HPC, hawthorn pectin; HM, high-methoxyl; HG, homogalacturonan; HYA, hyaluronic acid; LDL, low-density lipoprotein; LM, low-methoxyl; MM, medium-methoxyl; NAR, naringenin; OCMC, oxidized carboxymethyl cellulose; PBS, phosphate-buffered saline; PEG DA, polyethylene glycol dialdehyde; PEI, polyethyleneimine; QCS, quaternized chitosan; ROS, reactive oxygen species; RG-I, rhamnogalacturonan-I; SEM, scanning electron microscopy; TMPT, tenebrio molitor protein; TGA, thermogravimetric analysis; 3D, three-dimensional; XGA, xylogalacturonan.

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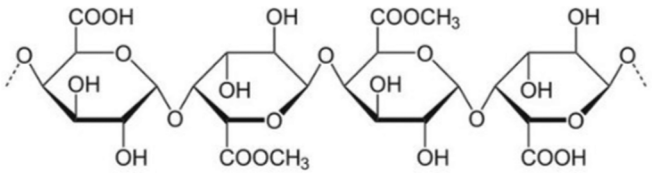

Fig. 1. Structure of pectin (reproduced with CC BY 4.0 license from Kitir et al., 2018).

encapsulation and fat-barrier applications (Said et al., 2023).The present review offers an in-depth investigation of existing pectin gelation mechanisms and categories of pectin hydrogels, including a comprehensive analysis of crosslinking methods, as explored in various global research initiatives. This concise review focuses on recent advancements in pectin-based hydrogels for drug delivery applications and on the production of hydrogels using pectin polymers, offering valuable resources for researchers by summarizing the latest progress in pectin hydrogel systems. In addition, our study explores potential applications and challenges in pectin-based hydrogel drug delivery systems.

Hydrogels can be fabricated through diverse polymerization approaches modifying natural or synthetic polymers, or synthesizing hydrophilic molecules. Hydrogels' porous architecture enables efficient drug loading and controlled release, making them pivotal in biomedical applications. The hydrogels exhibited significant biocompatibility, biodegradability, low immunogenicity, high water content, and a structure resembling the natural extracellular matrix (Hussain et al., 2022). Hydrogels showcase remarkable versatility, finding applications in diverse fields such as controlled drug delivery devices, metal ion and dye removal, pH sensing, biosensing, tissue engineering, wound dressings, contact lenses, and even injectable hydrogels for spinal cord reformation, exemplified by supercapacitor hydrogels (Batool et al., 2023). Pectin based hydrogels stand out for their distinctive functional groups, biocompatibility, and easy gelling, making them ideal for innovative drug delivery systems. Their cost-effectiveness and modifiability further enhance their potential, offering a promising avenue for advancing drug delivery technologies (Aslam et al., 2023). The pectin-based hydrogels offer precise management of drug frequency, mitigating systemic side effects linked to elevated doses, and ensuring controlled, gradual drug release to eliminate the risk of dose dumping. The hydrogels are currently revolutionizing nanocomposite development by integrating nanomaterials into their framework, resulting in a robust and biocompatible system (Yasmin et al., 2023, Mahmood et al., 2024). Pickering emulsions offers a promising avenue to enhance the efficacy of water-insoluble medications in oral drug delivery systems. A collection of Pickering emulsions incorporating dopamine-modified pectin was developed, presenting promising applications in the realm of anti-inflammatory medication (Zhang et al., 2023). The resveratrol Pickering emulsion with pectin hydrogel beads emerges as a potential carrier for directing resveratrol specifically to the colon, showcasing promising prospects in targeted applications for health benefits (Li et al., 2023).

2. Pectin in pharmaceutical formulations

2.1. Overview of pectin as a biopolymer

Pectin is a natural polysaccharide derived primarily from the cell walls of plants, particularly fruits, such as citrus and berries. Pectin has gained significant attention in the pharmaceutical industry because of its remarkable properties, rendering it a versatile biopolymer for various pharmaceutical formulations (Freitas et al., 2021). More specifically, pectin has found wide application in food and pharmaceutical industries over the last years due to its significant health benefits, as well as its gelling, thickening, and emulsifying properties. Despite its importance, the full determination of its chemical structure remains challenging as a result of its complex nature (Bostanudin et al., 2019). In principle, pectin consists of (1 → 4)-α-D-galacturonic acid (Gal A) residues with various neutral sugar branches. Pectin chains can be divided into "smooth regions," which are linear anionic backbones without side chains, and "hairy regions," which contain nonionic side chains ((Sriamornsak, 2003, Meng et al., 2020). The structure of pectin is depicted in Fig. 1.

Pectin can also be classified into different polymeric forms, including homogalacturonan (HG), rhamnogalacturonan-I (RG-I), and xylogalacturonan (XGA) (Sotanaphun et al., 2012). HG comprises approximately 65 % of plant pectin, and it is composed of α-1,4-linked Gal A linear chain. Furthermore, RG-I, which accounts for approximately 20–35 % of pectin in plants, consists of branched Gal A with α-1,2-linked rhamnose residues that are sometimes substituted with β-1,4-galactan, branched arabinan, and arabinogalactan side chains (Shitrit et al., 2019). Finally, XGA makes up less than 10 % of plant pectin, and it is substituted with xylose residues via covalent β-1,4 linkages. The proportion of RG-II in plant pectin is similar to that of XGA, and it is characterized by its high chemical complexity, with 12 types of glycosyl residues and numerous glycosidic bonds (Assifaoui et al., 2013). HG, representing approximately 65 % of plant cell wall composition, is primarily composed of linear chains that consist of α-1,4-linked Gal A, and some of these chains may undergo methylation or acetylation modifications. Pectin can be grouped based on methylation percentage of low (<25 %), medium (from 25 % to 50 %), and high (>50 %), which confer not only different structural characteristics but also hydrophobicity. In addition, rhamnogalacturonan-I, which accounts for approximately 20 %–35 % of the plant cell wall, features branched galacturonic acid molecules with α-1,2-linked rhamnose residues, which may also be adorned with β-1,4-galactan, branched arabinan, and arabinogalactan side chains. XGA constitutes less than 10 % of the plant cell wall composition, and it is characterized by the presence of xylose residues that are covalently linked via β-1,4 linkages. In plant cell walls, the proportion of rhamnogalacturonan-II is similar to that of XGA. The ability of pectin to form gels and interact with various substances is exploited in drug delivery systems, where it helps to control the release of medications over time. Furthermore, pectin has been used as a binder and disintegrant in pharmaceutical tablets to ensure proper drug absorption and effectiveness (Meng et al., 2020).

2.2. Properties and characteristics of pectin

The chemical composition and structure of pectin play a pivotal role in shaping its characteristics and performance in diverse applications, with its gelling ability being the most critical one (Liu et al., 2020). Gel formation is the result of interactions that occur within and between pectin chains, involving hydrogen bonds, hydrophobic interactions, and ionic bonds among different hydroxyl groups, as well as carboxyl groups, in their methylated or amidated states. These interactions collectively contribute to gel formation (Li et al., 2021).

The content of methylated carboxyl groups, which is often measured as the degree of esterification, directly affects the gelling ability of pectin. High-methoxyl pectin (HM) forms gels in acidic, sugar-rich environments by sequestering water from the pectin chains, with the presence of H^+ ions reducing the electrostatic repulsion between molecular chains. In contrast, low-methoxyl (LM) and medium-methoxyl (MM) pectin can also form gels with polyvalent metal ions at milder pH conditions without any added sugar, in accordance with the "egg-box" model (Wan et al., 2019).

These gels rely on the coordination between pectin chains and polyvalent metal ions, where pH influences the type of gel network, forming rigid, non-shear reversible gels at low pH values, and spreadable, shear reversible gel networks at higher pH values. The structure and properties of LM and MM pectin-based gels are also influenced by the distribution of methoxyl and acylamino groups (Li et al., 2023).

Pectin also serves as an effective thickening and stabilizing agent, and it is distinguished into two primary types. HM pectin has a degree of

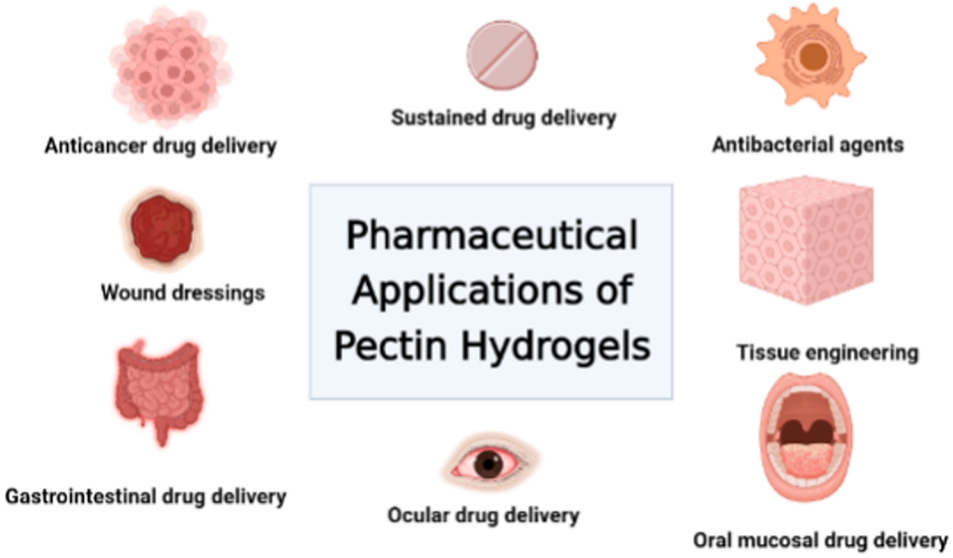

Fig. 2. Various pharmaceutical applications of pectin hydrogels.

esterification that exceeds 50 %, and it is widely used in pharmaceutical formulations as an excipient due to its thickening and gelling properties. This distinction underscores the versatility of pectin in enhancing the texture and consistency of various products, while also serving a crucial role in the pharmaceutical industry as a key ingredient for drug delivery systems (Freitas et al., 2021).

2.3. *Pharmaceutical applications of pectin*

Pectin hydrogels find valuable pharmaceutical applications owing to their biocompatibility, controlled drug release capabilities (Güner et al., 2021), and versatility in formulation. These hydrogels are employed in oral drug delivery systems (Choi et al., 2023), where they protect sensitive drugs from the harsh gastric environment and enable controlled

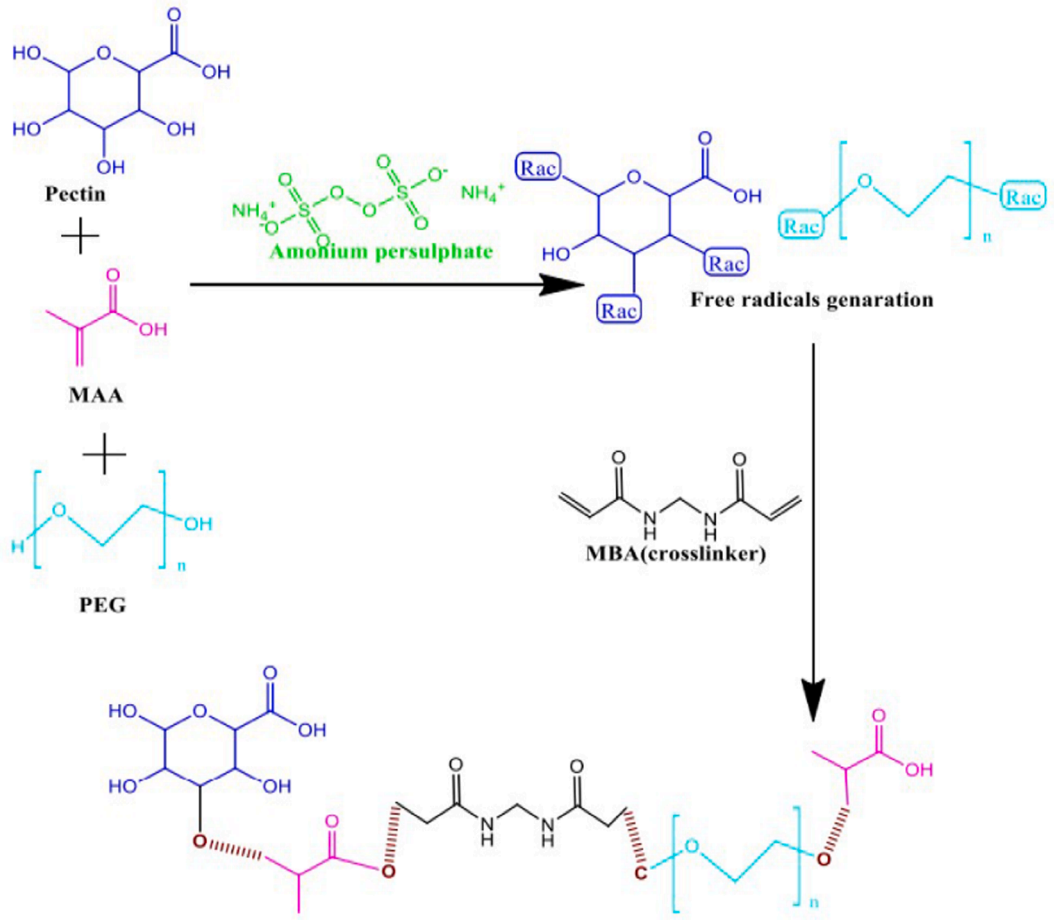

Fig. 3. Schematic representation of hydrogel formation (reproduced with permission from Abbasi et al., 2023).

release in the intestinal tract, enhancing drug bioavailability and patient compliance. In addition, pectin hydrogels are used for targeted and sustained drug delivery to specific sites (An et al., 2021), rendering them suitable for treating various ailments, including gastrointestinal disorders and chronic diseases. Their biodegradability and nontoxic nature further contribute to their significance in pharmaceutical formulations. Fig. 2 depicts the various pharmaceutical applications of pectin hydrogels.

3. Pectin-based hydrogels for drug delivery

3.1. Definition and types of hydrogels

Pectin-based hydrogels are three-dimensional (3D) crosslinked networks made from pectin, a natural, biocompatible polysaccharide. They are characterized by their ability to absorb and retain a significant amount of water while maintaining their structural integrity (Tortorella et al., 2021).

Chemically crosslinked pectin hydrogels are a type of hydrogels, where chemical crosslinking can take two of the following main forms: ionic and/or covalent crosslinking. On the one hand, in ionic crosslinking, hydrogels are generated by crosslinking pectin using di- or trivalent cations, such as calcium ions (Ca^{2+}) (Thakur et al., 2019). This process hinges on ionic interactions between pectin molecules and calcium ions, ultimately resulting in the formation of a robust gel network but reversible. On the other hand, covalent crosslinking involves the modification of pectin through chemical methods, typically by the introduction of specific functional groups that have the capacity for covalent bonding. This variant of pectin-based hydrogels may necessitate chemical reactions, including esterification, to form strong covalent linkages, thereby enhancing the overall structural integrity and properties of the hydrogel (Yoshimura et al., 2005). However, covalent derivatization of pectin requires extensive purification processes to eliminate byproducts.

Due to its heteropolysaccharide structure and a large number of hydrophilic functional groups, pectin composite hydrogels generally have poor tolerance to water. Zafar et al. (2023) developed a targeted release system for tapentadol hydrochloride, fabricating interpenetrating networks (IPNs) using a blend of natrosol-pectin copolymerized with acrylic acid and methylene bisacrylamide (Zafar et al., 2023). Pectin, modified with folic acid, was skillfully combined with eight-arm polyethylene glycol carrying dihydroartemisinin (DHA), resulting in the development of prodrugs named FA-pectin-8armPEG-DHA. It is embedded with hydroxycamptothecin by using self-assembly of hydrophilic and hydrophobic drugs carriers to fabricate FA-pectin-8armPEG-DHA/hydroxycamptothecin NPs (Liu et al., 2019).

To enhance the stability of pectin-Ca^{2+} gels in oral colon-specific drug delivery, chemically cross-linked pectin carriers were crafted using succinic anhydride and glutaric dialdehyde as cross-linking agents, mitigating instability concerns in the upper gastrointestinal tract. This innovative approach ensures a reliable and controlled drug release system (Wang et al., 2019).

A novel nanoparticle platform, fabricated from pectin-DHA conjugates, autonomously assembles for the synergistic delivery of anticancer drugs. The developed pectin-DHA/hydrooxycampothecin NPs exhibit a blend of pectin's water-friendly segment and DHA/hydroxycamptothecin's drug components, enhancing drug capacity, elevating water dispersibility, and facilitating precise drug release for enhanced therapeutic efficacy (Liu et al., 2018). Wang and colleagues explored a novel hydrogel using acylhydrazone-derived whole pectin, serving as a promising injectable drug delivery system. This innovative injectable drug delivery system using a comprehensive pectin-based hydrogel. fabricated through the synthesis of oxidized pectin and diacylhydrazine adipate-functionalized pectin connected by acylhydrazone linkage. The investigation on drug release revealed a sustained liberation of 5-fluorouracil over a period exceeding 12 h, characterized by a gradual and consistent release profile (Wang et al., 2023). Abbasi et al. (2023) introduced an innovative hydrogel for precise drug delivery, utilizing a grafting approach that combined polyethylene glycol (PEG) and methacrylic acid (MAA) with pectin through free radical polymerization (Fig. 3). Sulfasalazine served as the prototype medication for incorporation into the tailored hydrogel formulations. Investigation into swelling and release behaviors demonstrated the hydrogels' capacity for targeted drug release under colonic pH conditions, with subsequent toxicological assessments affirming their safety in mouse models (Abbasi et al., 2023).

A relatively recent addition to the pectin-based hydrogel family is the composite pectin hydrogel, where hydrogels are ingeniously blended with various supplementary materials, such as nanoparticles or polymers (Han et al., 2022).

Farris et al. (2011) developed composite hydrogels by combining a protein, gelatin, and LMpectin, creating a unique system with improved properties. Through ionic interactions, the authors formed reversible physical hydrogels characterized by a uniform molecular arrangement, enhancing mechanical strength and water resistance, without compromising thermal stability. Subsequent introduction of 0.3 % w/w glutaraldehyde led to the formation of permanent chemical hydrogels with heterogeneous crosslinking domains, resulting in significantly reduced swelling behavior, approximately 10-fold compared with gelatin-only films (Farris et al., 2011). Besides, glutaraldehyde residues are toxic even at low concentrations and must be removed before use in biological systems.

In a recent study by Lopez-Sanchez et al. (2017), composite pectin hydrogels were meticulously prepared by combining LM pectin with cellulose. This innovative approach explored the unique properties of these hydrogels and their potential for diverse applications. By varying the order of assembly of the cellulose/pectin networks, the degree of methyl esterification of pectin, but also the concentration of calcium, the structural and mechanical aspects of these composite hydrogels were investigated (Lopez-Sanchez et al., 2017).

3.2. Advantages and challenges of hydrogel-based drug delivery

Pectin-based hydrogels enable precise and sustained drug release, thereby improving treatment efficacy due to their biocompatibility and protective properties. More specifically, biocompatibility allows them to closely mimic the natural tissues of the body, thereby reducing the risk of adverse reactions and rendering them well suited for in vivo applications. These hydrogels also act as protective barriers for sensitive drugs, shielding them from external factors that could compromise their stability. Because of their versatility, hydrogels can potentially accommodate various drug types and administration routes, making them adaptable for diverse therapeutic applications (Ganguly and Margel, 2021).

A review of hydrogel-based drug delivery for cancer treatment underscores the emerging prominence of these carriers (Sun et al., 2019). Hydrogels offer a more favorable side effect profile than systemic chemotherapy, and also allow sustained drug delivery to tumor sites. Their exceptional biocompatibility and biodegradability, along with reduced toxicity compared with nanoparticle carriers, make them an attractive choice. Notably, smart hydrogels, which are responsive to environmental stimuli, such as heat, pH, light, and ultrasound, enable in situ gelation and controlled drug release, significantly enhancing the efficiency and convenience of drug delivery. Another relevant characteristic is that pectin, as polyhydroxylic biopolymer and with free carboxylic residual groups can be easily tailored to show novel functionalities such tracing with fluorescent probes, and tailoring using some cellular markers to obtain targeting delivery.

Pectin-based hydrogel drug delivery systems face significant challenges in achieving precise drug release kinetics and stability. Drug loading limitations can be an issue for high-dose medications. Consequently, it is essential to tune the biodegradation rate to match the

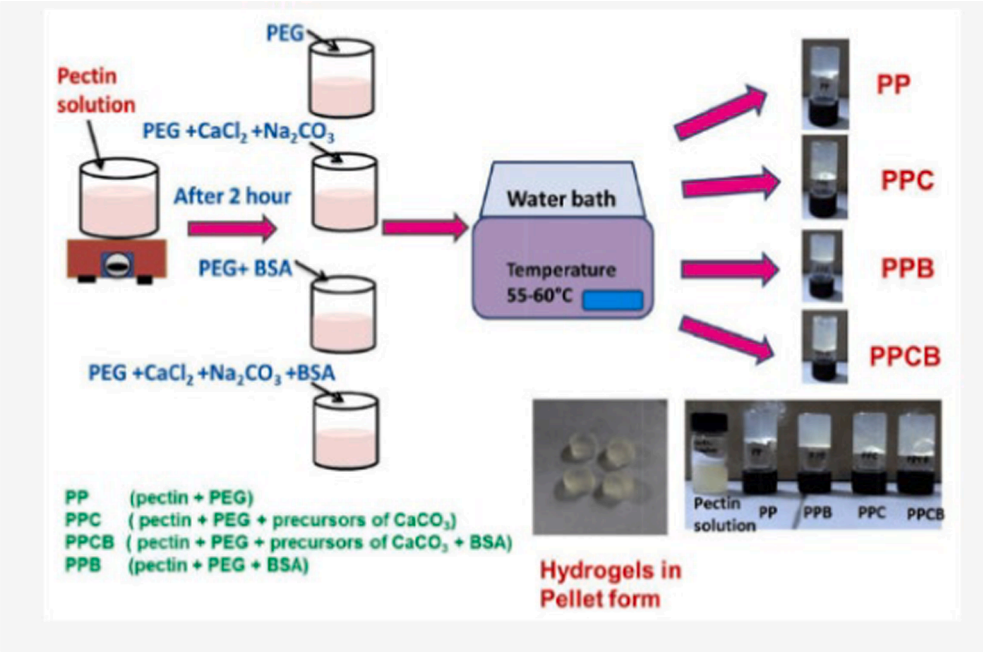

Fig. 4. Illustration of the process of creating pectin-based hydrogels (reproduced with permission from Gautam and Santhiya, 2019).

required drug release durations. There is often a limitation on the amount of drug that can be loaded into hydrogels, which may not suffice for medications with high therapeutic doses. The biodegradation rate of hydrogels must be carefully tuned to match the required drug release kinetics (Kikuchi et al., 2017).

3.3. Limitation of pectin hydrogels

Pectin based hydrogels encounter obstacles in bio-applications, grappling with issues like rigidity, susceptibility to water, and vulnerability in physiological settings (Farris et al., 2011).

Pectin-based hydrogels may exhibit variations in mechanical strength, which can affect their ability to withstand different forces or environments. Pectin hydrogels can be sensitive to environmental conditions, such as pH and temperature. Changes in these factors may influence the stability and performance of the hydrogel. Balancing biodegradability with the need for sustained stability is a consideration in designing pectin hydrogels for specific applications. Achieving precise control over the release kinetics of drugs from pectin-based hydrogels can be challenging. The rate at which drugs are released from the hydrogel may vary, impacting the therapeutic efficacy and dosage control. While pectin is generally considered biocompatible, the addition of other components in the hydrogel formulation may influence its overall biocompatibility.

3.4. Role of hydrogels in controlled drug release

Pectin hydrogels play a pivotal role in controlled drug release, because their unique properties allow the precise modulation of drug release kinetics, making them ideal for various pharmaceutical and biomedical applications. Pectin hydrogels can enhance therapeutic efficacy by ensuring the gradual, sustained release of drugs or bioactive compounds.

Kocaaga et al. (2022) employed molecular dynamics simulations to predict the optimal drug concentration for loading on LM pectin hydrogels. This approach preserves the hydrogel's structural integrity while achieving precise control over drug release and ensuring efficient therapeutic delivery. Pectin hydrogels containing 30 mg of procaine per gram exhibited a minimal degradation rate of 0.001 g/min. A previous in vitro study showed that these hydrogels displayed controlled drug release, effectively releasing the entire amount of 30 mg of procaine from a 670 mg hydrogel within 24 h (Kocaaga et al., 2022).

Furthermore, Islam et al. (2022) pioneered the development of a novel superabsorbent hydrogel by modifying cellulose with pectin and mucin. This innovative hydrogel design was engineered for the controlled release of curcumin. Previous findings demonstrated that the release of curcumin was significantly influenced by factors such as the swelling ratio, mechanical properties, and erosion behavior of the hydrogel matrix. The pectin-mucin-modified hydrogels exhibited a slower and sustained release of curcumin in a simulated blood environment. This phenomenon indicates hydrophobic interactions between curcumin and biopolymers, which enhances its retention capacity (Islam et al., 2022).

3.5. Formulation strategies for pectin hydrogels

Formulation strategies for pectin hydrogels focus on the optimization of factors such as methylation degree, crosslinking methods (Sarioglu et al., 2019), pectin concentration (Sarioglu et al., 2019) and the inclusion of additives to achieve desired properties. These strategies aim to fine-tune the hydrogel's mechanical strength, swelling capacity, and drug-release kinetics, ultimately rendering them versatile for many applications in drug delivery, wound healing, and tissue engineering applications.

Calcium carbonate microparticles have been synthesized within a pectin/polyethylene glycol hydrogel blend for localized delivery of bovine serum albumin (BSA) at the targeted colon site, providing a controlled drug-release system. The encapsulation efficiency of BSAin the blended hydrogels is approximately 98 %. In vitro studies showed that the hydrogels release the protein over a period of approximately 9 h at the colon site, indicating its potential as a drug carrier (Gautam and Santhiya, 2019). Fig. 4 illustrates the process of preparing pectin hydrogels.

Lemos et al. (2021) pioneered the creation of magnetic hydrogel microspheres using chitosan coated with pectin for innovative smart drug-release applications. In that study, magnetic pectin microspheres were prepared by ionotropic gelation followed by polyelectrolyte complexation with chitosan. Metamizole was successfully loaded into

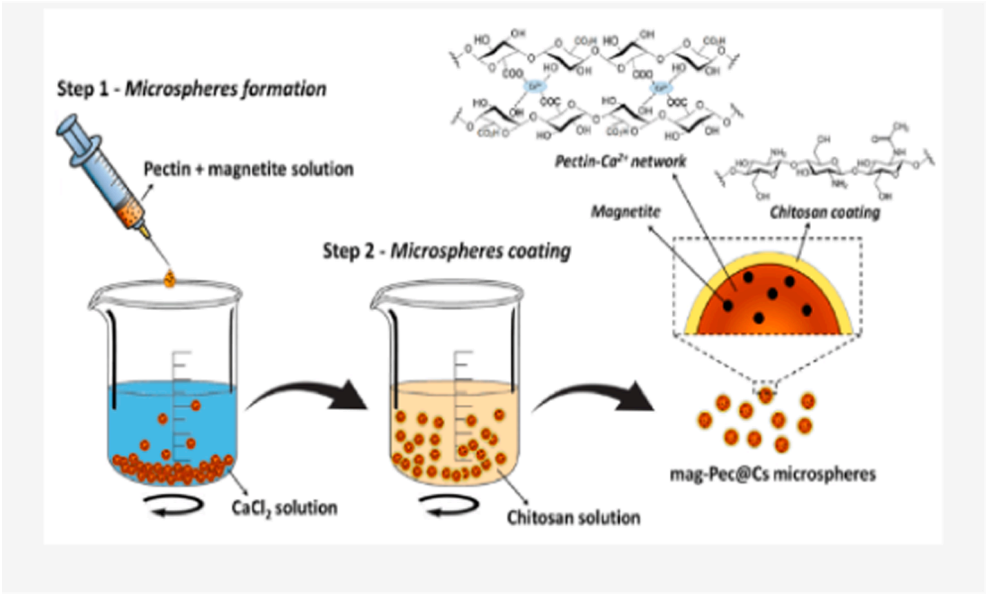

Fig. 5. Experimental method employed for the fabrication of chitosan-coated magnetic pectin microspheres (reproduced with permission from Lemos et al., 2021).

the system, exhibiting an impressive encapsulation efficiency of 88 %. Notably, the in vitro drug-release profiles at pH 1.2 and 6.8 revealed a distinct pH-dependent behavior, suggesting the potential for controlled drug-release applications. Under pH 6.8 conditions, drug release reached 75 % within 12 h. The introduction of a magnetic field further enhanced drug release to 92 % at pH 6.8, indicating its magnetic responsiveness (Lemos et al., 2021). Fig. 5 describes the formulation of magnetic pectin hydrogels coated with chitosan.

3.6. Crosslinking techniques and methods

Crosslinking is an essential process for shaping the structure and characteristics of pectin hydrogels. Multiple crosslinking techniques have been utilized, each offering specific benefits and applications. These methods encompass chemical, physical, enzymatic, and radiation-based approaches, allowing for tailored pectin hydrogels with diverse properties to suit a range of applications.

Chen et al. (2021) innovatively created a composite hydrogel by chemically crosslinking pectin and cellulose. Wu et al. (2020) successfully designed a physically crosslinked pectin-based hydrogel characterized by remarkable stretchability and toughness, making it a promising candidate for biomedical applications. In addition, Abbasi et al. (2023) introduced a novel multifunctional adsorbent material, namely acacia gum phthalate/pectin hydrogel, which was synthesized via a microwave-assisted process. This material was statistically optimized for the efficient sequestration of mefenamic acid from contaminated water.

3.7. Characterization of pectin hydrogels

To assess the suitability of pectin hydrogels for various applications, it is essential to evaluate several key parameters, including swelling ratio, gel fraction, mechanical properties, degradation rate, rheological behavior, chemical composition, surface morphology, biocompatibility, release kinetics, and thermal properties. The choice of parameters depends on the intended application, ensuring a comprehensive evaluation of the hydrogel's performance.

3.7.1. Swelling ratio

The swelling ratio is a critical parameter that quantifies the hydrogel's water-absorption capacity and its ability to retain moisture. This characteristic holds significant importance in various applications, such as drug delivery systems and wound dressings, where controlled hydration is essential for optimal performance (Sriamornsak et al., 2007). Pandey et al. (2021) investigated the swelling behavior of hydrogels across different phosphate buffer pH levels, including 1.5, 5.8, and 7.4. The swelling percentage exhibited a gradual increase from pH 1.5 to 7.4, with the highest swelling observed at pH 7.4. Notably, the transition from pH 5.8 to 7.4 showed a less pronounced increase in swelling behavior.

3.7.2. Rheological examination

Rheological analysis was employed to investigate the viscoelastic properties and flow behavior of pectin hydrogels. This characterization is crucial for understanding the gel's response to stress and deformation, and its potential applications in various industries. Zarandona et al. (2021) investigated the rheological properties of a chitosan–pectin system to identify the optimal hydrogel composition for 3D printing.

3.7.3. Zeta potential

The determination of the zeta potential of pectin hydrogels is a critical tool in assessing the surface charge and stability of the hydrogel particles or colloids. This measurement, typically conducted using specialized instruments, such as a Zeta-meter, provides valuable insights into the electrostatic interactions between particles, which is crucial for predicting the stability, dispersion behavior, and potential applications of pectin hydrogels (Beigi et al., 2023).

It is commonly accepted that particles with zeta potential higher than ± 30 mV are stable under the measurement conditions, but the advantage of the particles with positive charge is the mucoadhesiveness, a relevant property for drug delivery. Slavutsky and Bertuzzi (2019) evaluated the zeta potential of a hydrogel formulation consisting of pectin and brea gum. Patlay et al. (2023) conducted a zeta potential evaluation of hydrogel films and nanoparticles using low-esterified pectin, focusing on their potential use in anticancer applications.

3.7.4. Scanning electron microscopy

Scanning electron microscopy (SEM) is a valuable tool for evaluating pectin hydrogels, providing high-resolution images of their microstructure. SEM enables researchers to observe the surface morphology and structural features of pectin-based hydrogels, offering insights into their texture, pore distribution, and overall architecture

(Cheewatanakornkool et al., 2018). This method aids in understanding how changes in the formulation or crosslinking methods affect the physical characteristics of the hydrogel (Alsakhawy et al., 2022).

3.7.5. Thermal analysis

Thermal analysis is a valuable technique for assessing the properties of pectin hydrogels. Differential scanning calorimetry (DSC) (Song et al., 2023) and thermogravimetric analysis (TGA) (Fernandes Filho et al., 2023) are commonly employed thermal analysis methods. On the one hand, DSC helps to identify phase transitions and determine the thermal stability of the hydrogel, offering insights into its potential applications, but also regarding the temperature ranges over which it remains intact. On the other hand, TGA provides information about the hydrogel's weight loss as a function of temperature, elucidating its degradation behavior and thermal decomposition profiles.

4. Drug entrapment in pectin hydrogels

The entrapment of drugs within pectin hydrogels is a fundamental aspect of drug delivery systems, enabling controlled and targeted drug release. The ability of pectin to form a 3D network structure, and its responsiveness to different physicochemical environmental factors, such as pH, ionic strength, and temperature, make it an ideal candidate for encapsulating various pharmaceutical compounds. This entrapment process involves the formation of a drug-loaded matrix, in which drug molecules are distributed within the hydrogel. Pectin hydrogels have garnered considerable attention in the development of drug delivery platforms that offer precise control over drug-release rates, ultimately enhancing the efficacy and safety of various therapeutic treatments (Vesvoranan et al., 2022).

4.1. Mechanisms of drug encapsulation

The mechanisms of drug encapsulation in pectin hydrogels involve intricate and complex processes primarily driven by the physicochemical properties of the drug and the hydrogel matrix, but also by the environmental conditions. Electrostatic interactions (Said et al., 2023), hydrogen bonding (Feng et al., 2023), and molecular entrapment are key factors influencing drug entrapment. Additionally, the porous structure of pectin hydrogels allows for diffusion and absorption of drugs into the matrix (Moghaddam et al., 2019). Understanding and manipulating these mechanisms is essential for the optimization of drug loading and release characteristics in pectin-based drug delivery systems, providing a foundation for tailored and effective therapeutic applications.

4.2. Factors affecting drug loading and release

In principle, several factors influence the loading and release of drugs from pectin-based hydrogels. The drug's physicochemical properties, including its solubility, free functional groups, and molecular weight and structure, impact loading efficiency (Sungthongjeen et al., 2004; Sriamornsak, 2011). The selection of crosslinking agents and their concentration in the hydrogel formulation affect drug-release kinetics (Kocaaga et al., 2019). The degree of pectin crosslinking, the pH of the surrounding environment (Ajaz et al., 2020), and the hydrogel's mesh size all play crucial roles in determining drug release rates (Li and Mooney, 2016).

4.3. Case studies of drug-loaded pectin hydrogels

Biocompatible self-healing hydrogels play an essential role in drug loading and release applications, particularly in the context of antitumor therapy. It is relevant to mention that pectin itself showed a beneficial activity in colon cancer such as antiproliferative activity, cell cycle arrest and apoptotic activity in cancer cells (Ornelas et al., 2022). The ability of pectin hydrogels to encapsulate and release therapeutic agents in a controlled manner holds great promise for targeted cancer treatment. A biocompatible self-healing hydrogel was developed using pectin acylhydrazide crosslinked with polyethylene glycol dialdehyde (PEG DA). The potential of this hydrogel as a carrier for delivering doxorubicin (DOX) in tumor treatment was extensively explored. DOX exhibited a gradual and controlled release pattern when exposed to different pH buffers, with release rates inversely correlated with decreasing pH levels. In a pH 5.4 buffer, DOX released 42 %, 52 %, and 52 % in 12 h, 24 h, and 48 h, respectively. However, upon transitioning to a pH 6.5 buffer, DOX release proportion decreased to 36 %, 39 %, and 49 %, respectively, at the same time intervals. A previous mouse xenograft CT-26 tumor model experiment clearly showed that the hydrogel encapsulated with DOX exhibited substantial inhibition of tumor development when compared with direct injection of DOX (Zhou et al., 2022).

Yang et al. (2023) developed pectin hydrogel beads reinforced with caseinate (PCHG-CAS) to enhance the stability of (−)-epigallocatechin (EGC) and prevent its degradation. The authors found that PCHG-CAS exhibited a compact network structure due to hydrogen bonding between caseinate and pectin, leading to excellent EGC encapsulation efficiency (93.39 %). EGC exhibited a rapid initial release from PCHG-CAS within the first 30 min, followed by a stabilization phase between 30 and 120 min, ultimately achieving a release rate of 76 %. Upon the introduction of protein, EGC release from PCHG-CAS was notably decelerated, highlighting the influence of protein on the release kinetics. Furthermore, these hydrogels effectively delayed EGC release in water while ensuring controlled release under simulated gastrointestinal conditions. Importantly, EGC remained chemically stable in PCHG-CAS during a 6-day storage period at 37 °C, preventing epimerization, oxidation, dimerization, and trimerization (Yang et al., 2023).

4.4. Factors influencing drug release

Several key factors influence drug release from pectin hydrogels. The choice of pectin type (Sungthongjeen et al., 1999), its degree of esterification (Tiwary and Rana, 2016), and molecular weight can significantly impact drug diffusion and release kinetics. Additionally, the pH and ionic strength of the surrounding medium (Ali et al., 2020), as well as the drug's physicochemical properties (Pushpamalar et al., 2021), play vital roles in determining release profiles. The design and composition of pectin-based hydrogels must carefully consider all these factors to achieve precise and controlled drug release, facilitating a versatile platform for pharmaceutical applications.

4.5. Release mechanisms in pectin hydrogels

Release mechanisms in pectin hydrogels are a complex interplay of various factors that influence the controlled delivery of bioactive compounds (Groult et al., 2021). These mechanisms typically involve a combination of diffusion (Siddiqua et al., 2022), erosion (Quadrado et al., 2022), and relaxation of the hydrogel matrix. As the hydrogel absorbs water, it swells, creating channels through which the entrapped drugs or molecules diffuse. Simultaneously, the pectin matrix may degrade over time, releasing the encapsulated substances. The release rate can be tailored by modifying the hydrogel composition, crosslinking density, and nature of the loaded compounds (Bustamante-Torres et al., 2021). Understanding and optimizing these release mechanisms is fundamental for designing effective pectin hydrogel-based drug delivery systems for diverse pharmaceutical and biomedical applications.

4.6. pH-responsive pectin hydrogels

The value of pH significantly impacts pectin hydrogels, influencing their swelling behavior, solubility, and drug-release kinetics. Therefore, changes in the pH value can tailor these hydrogels for precise applications, such as controlled drug delivery (Li et al., 2021).

Ajaz et al., 2020 fabricated hydrogels using pectin – copolyacrylic acid (PCPA) for the controlled release delivery of nifedipine. The authors investigated the swelling capacity of PCPA hydrogels under acidic conditions (pH 1.2) and at a pH value of 7.4 to simulate the stomach and colon environment, respectively. Their findings revealed that the PCPA hydrogels exhibited significant swelling at pH 7.4 compared with pH 1.2. The reduced swelling of PCPA hydrogels at pH 1.2 was attributed to the unionized state and the collapsed carboxylic groups of PCPA because of the lower pH compared with its pKa. Conversely, at pH 7.4, ionized carboxyl groups created electrostatic repulsion, causing the hydrogels to expand, resulting in high swelling. The results indicated that the dynamic swelling coefficient was higher at pH 7.4 than at pH 1.2, with disks exhibiting greater swelling under alkaline conditions (Ajaz et al., 2020).

Furthermore, Ullah et al. (2019) successfully produced lactic acid hydrogels by employing free radical polymerization techniques using pectin as a key component in the fabrication process. The developed hydrogel systems exhibited approximately 49 % entrapment efficiency for loaded oxaliplatin, and demonstrated controlled drug-release profiles, with 19 % at pH 1.2, 42 % at pH 6.8, and 48 % at pH 7.4. In MTT assays, drug-loaded hydrogels showed controlled inhibition of HCT-116 and MCF-7 cells (Ullah et al., 2019).

A recent study detailed the development of pH-responsive hydrogels incorporating zein protein nanoparticles and a pectin biopolymer for the controlled encapsulation of DOX. DOX-loaded hydrogels exhibited enhanced cytotoxicity against cervical cancer cell lines. Furthermore, these hydrogels demonstrated pH-dependent DOX release within the acidic cytosolic environment of HeLa cells. The novel combination of zein- and pectin-based hydrogels demonstrated enhanced drug-release control, prolonged drug stability, and the ability to create a conducive drug microenvironment (Kaushik et al., 2020).

Bostanci et al. (2022) investigated curcumin release from photo-crosslinked pectin/gelatin hydrogel. Methacrylated derivatives of pectin (PCMA) and gelatin were successfully synthesized and subsequently used to create hydrogels with various compositions. The hydrogels containing the highest PCMA content (P1/G1) displayed an average pore diameter of 44 μm. P1/G3 exhibited exceptional stability, retaining approximately 38 % of its initial weight after 21 days in phosphate-buffered saline (PBS) incubation. It displayed a moderate modulus of approximately 22 kPa, along with good oxygen permeability (6.58 mg/mL), and demonstrated effective resistance to bacterial penetration. In a PBS aqueous solution (10 mM) at pH 7.4, curcumin exhibited a release rate that was approximately four times faster than that observed in a medium with pH 5.0. Disk diffusion tests demonstrated the effectiveness of these hydrogels against *S. aureus* and *E. coli*. Additionally, Alamar blue assays confirmed the hydrogels' compatibility with L929 fibroblasts, also indicating their cytocompatibility (Bostancı et al., 2022).

4.7. Temperature and environmental factors

Temperature significantly influences the properties of pectin hydrogels. In general, higher temperatures lead to increased molecular mobility, resulting in enhanced swelling and reduced mechanical strength in pectin hydrogels. This thermal sensitivity is a key factor in tailoring the performance of pectin hydrogels for various applications (Said et al., 2023).

Zheng et al. (2022) employed an ultra-low temperature enzymatic approach in which pectin underwent a modification process involving phenylalanine. The aim of that study was to enhance the gel properties of pectin, and the grafting ratio of phenylalanine amidated with pectin was investigated under varying reaction conditions. The maximum ratio (30.25 %) was attained at a reaction temperature of −5°C for 12 h. The findings indicated that phenylalanine-amidated pectin could autonomously form a robust hydrogel in acidic environments, eliminating the necessity for excessive soluble solids or divalent cations as additives. When used as a drug carrier, phenylalanine-amidated pectin hydrogel exhibited enhanced sustained-release properties, resulting in a more consistent and complete drug-release profile.

4.8. Influence of drug properties on release

Drug release from pectin hydrogels is notably affected by various drug properties. For instance, factors such as drug solubility (Sriamornsak and Kennedy, 2007; Gujral et al., 2018; Li et al., 2021) molecular weight and structure (Sarioglu et al., 2019), functional groups, and charge can significantly impact release kinetics. Highly soluble drugs may exhibit faster release rates if they have no interaction within the gel chains (Chen et al., 2021), whereas larger molecules and charged compounds tend to diffuse more slowly from the hydrogel matrix. These drug-specific properties should be carefully considered when designing pectin hydrogel-based drug delivery systems to achieve sustained and tailored release profiles.

5. Pectin hydrogel applications in drug delivery

Hydrogels are increasingly utilized in drug delivery due to their unique characteristics, including hydrophilicity, biocompatibility, biodegradability, moisture retention, and cost-effectiveness (Eivazzadeh-Keihan et al., 2022; Manzoor et al., 2022).

5.1. Oral drug delivery

Since pectin is commonly used in many foods, it is considered one the best alternatives to deliver different types of molecules. For example, pectin – low-density lipoprotein (LDL) nanogels, combined with alginate hydrogel beads, have been effectively produced using the ionotropic gelation technique. More specifically, the developed pectin – LDL nanogels were encapsulated within alginate-based hydrogel beads, preserving their inherent properties, and curcumin was loaded into the pectin – LDL nanogels to evaluate their pH-dependent characteristics. Incorporating nanogels into alginate hydrogel beads was shown to significantly extend the release of curcumin, exhibiting a slightly slower release rate under simulated gastrointestinal conditions. This in turn suggests the potential of this system as an effective oral drug delivery method (Zhou et al., 2018).

An alternative approach encapsulated Ca^{2+} along with vitamin D and iron ions (Fe^{2+}) paired with vitamin C within an edible matrix composed of pectin and polyethylene glycol. This innovative method led to the development of distinct hydrogel formulations known as PPCAD and PPFEC. In vitro experiments confirmed the effectiveness of the edible hydrogel blends PPCAD and PPFEC. These hydrogels demonstrated the ability to protect nutrients within the harsh gastric environment and achieve controlled codelivery in simulated intestinal fluid (SIF) over a 3-h duration, following a zero-order kinetic release profile (Gautam and Santhiya, 2019).

5.2. Transdermal and topical delivery

Pectin hydrogels have gained attention for their potential in transdermal and topical drug delivery. These hydrogels offer a promising platform to deliver medications through the skin, providing controlled release and improved therapeutic outcomes in various pharmaceutical and dermatological applications (Krathumkhet et al., 2021).

Paradee et al. (2021) presented a novel approach for transdermal ibuprofen delivery using pectin-bacterial cellulose (BC)/polypyrrole hydrogel composites. Polypyrrole, a conductive polymer, was effectively integrated into the pectin-BC hydrogel composite as a drug encapsulation host, enabling controlled release when an electric field is applied. Drug release reached its peak at 30 % w/w BC, further increasing when an electrical potential was applied, resulting in the highest release (80 %) observed in drug-loaded polypyrrole-infused composites under a 7-V

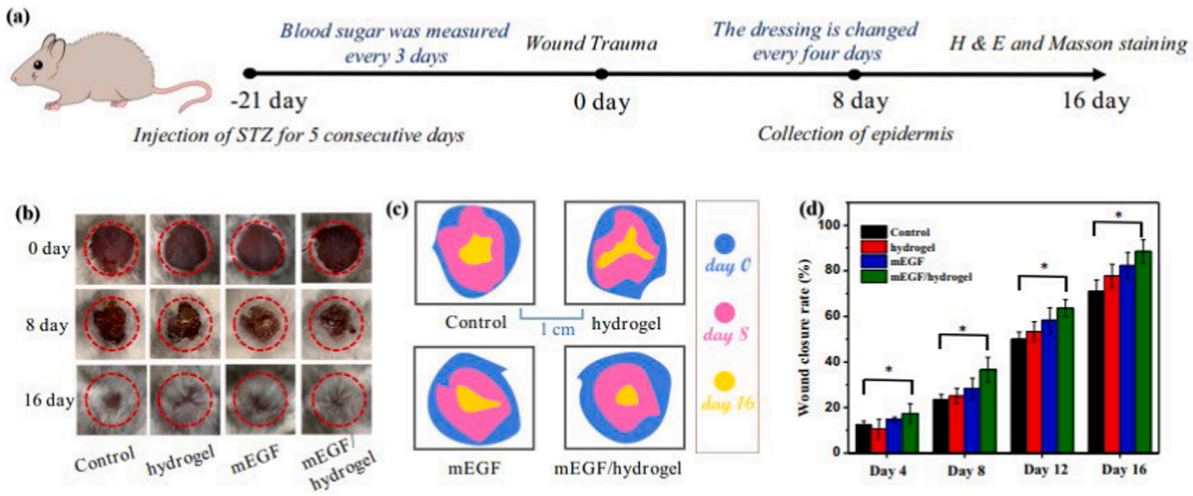

Fig. 6. Visual representation depicting the in vivo healing of diabetic wounds (reproduced with permission from Chen et al., 2023).

electrical stimulus (Krathumkhet et al., 2021).

In addition, Martinez et al. (2013) investigated the potential of enrofloxacin and immobilized keratinase incorporated within pectin-PVA cryogel patches in antimicrobial treatment. In vitro investigations of enrofloxacin release from pectin-PVA cryogels at a pH resembling human skin demonstrated the release of 17 % of the free antibiotic over 5 h, following first-order kinetics at 37 °C. Interestingly, when keratinase was introduced under identical conditions, only 6.9 % of enrofloxacin was released, indicating the enzyme's impact on controlled drug release within the skin-mimicking environment.

5.3. Gastrointestinal and colon-targeted delivery

Pectin hydrogels have garnered attention in gastrointestinal and colon-targeted drug delivery systems, because their pH-responsive properties render them ideal as protecting drugs in the stomach. Furthermore, their targeted release in the colon enhances the effectiveness of certain treatments while minimizing side effects. This innovation holds promise for improving therapeutic outcomes in various medical applications (Das, 2021).

Aslam et al. (2023) synthesized ecofriendly superporous hydrogel sponges using quince and pectin, aiming for pH-responsive and sustained release of domperidone, a medication often employed in gastrointestinal therapies. The authors found that drug loading in the fabricated hydrogel was 70 %–85 %. Furthermore, these prepared hydrogel sponges exhibited pH-sensitive swelling behavior, with the highest swelling observed in a phosphate buffer (pH 7.4), while minimal swelling was identified in a pH 1.2 acidic environment. These hydrogel sponges exhibited impressive stimulus-responsive behavior, precisely controlling the release of domperidone for up to 10 h at a pH of 7.4. Histopathology results revealed that critical organs, including the liver, intestines, lungs, kidneys, and heart, exhibited normal cellular function. Notably, there were no indications of inflammation in the cellular structure, thereby affirming the safety of the hydrogel sponge.

Wu et al. (2022) developed hydrogel beads by varying the alginate and pectin ratios for encapsulating Pickering emulsions loaded with resveratrol. These beads were crosslinked with Ca^{2+}, demonstrating a versatile approach for controlled drug delivery systems. In simulated gastrointestinal conditions, alginate/pectin hydrogel beads displayed pH-responsive behavior, reducing resveratrol release in stomach-like simulated gastric fluid and enhancing its release in SIF, thereby improving its bioaccessibility (Wu et al., 2022).

A novel enzymatically triggered and pH-sensitive hydrogel composed of pectin and polyacrylamide was recently engineered to enable precise budesonide delivery to the colon, offering a promising approach for ulcerative colitis treatment. SEM analysis confirmed the presence of the porous structures in the hydrogels, which is an ideal property for drug loading. Moreover, the hydrogels exhibited pH-responsive swelling and contraction under acidic conditions. In vitro release studies of budesonide from the hydrogel revealed a sustained-release pattern characterized by non-Fickian diffusion, indicating a controlled and extended drug-release mechanism. The F3 compound exhibited an encapsulation efficiency of 81.2 %, while its drug loading was 8.95 %. The correlation coefficient values for F3 were calculated to be 0.98, 0.88, 0.99, and 0.94 for the zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, respectively (Pandey et al., 2021).

Finally, Mala and Anal (2021) investigated the protection and controlled release of bromelain through encapsulation within hydrogel beads composed of pectin and acid-resistant starch from maize. The specific weight-to-weight ratio (4.5:1.5 w/w) of pectin and acid-resistant starch led to a statistically significant improvement in the encapsulation efficiency, achieving an impressive 81.25 % rate. The inclusion of acid-resistant starch enhanced bromelain entrapment, leading to superior swelling characteristics, sustained release, and increased gastric stability compared with isolated pectin hydrogels. Bromelain encapsulated in hydrogels demonstrated a faster release rate in SIF (pH 7.4) than in simulated gastrointestinal fluid (pH 1.2).

5.4. Pectin hydrogels for wound healing

Pectin hydrogels have gained attention for their potential role in wound healing. Their natural origin, biocompatibility, and ability to create a moist wound environment make them promising materials for promoting tissue repair and accelerating wound healing. Researchers have been exploring various formulations and applications of pectin hydrogels to enhance their effectiveness in wound management (Giusto et al., 2017).

For example, Chen et al. (2023) have successfully developed a biodegradable self-healing hydrogel that incorporates bioadhesive properties inspired by mussels, offering effective antioxidation capabilities. A hydrogel was custom-engineered using dopamine-conjugated pectin hydrazide (pectin-DH) and oxidized carboxymethyl cellulose (OCMC) to facilitate the encapsulation of modified epidermal growth factor (mEGF) for its application as a diabetic wound healing dressing. Findings indicated the rapid formation of pectin-DH/OCMC hydrogel, offering effective coverage of unequal wounds with strong sealing properties. The structure of catechol enhances the hydrogel's capacity to scavenge reactive oxygen species (ROS), mitigating ROS-related adverse effects and fostering efficient wound healing. The bovine serum albumin (BSA) release from the sample was 24.5 % after 48 h in a pH 7.4 PBS

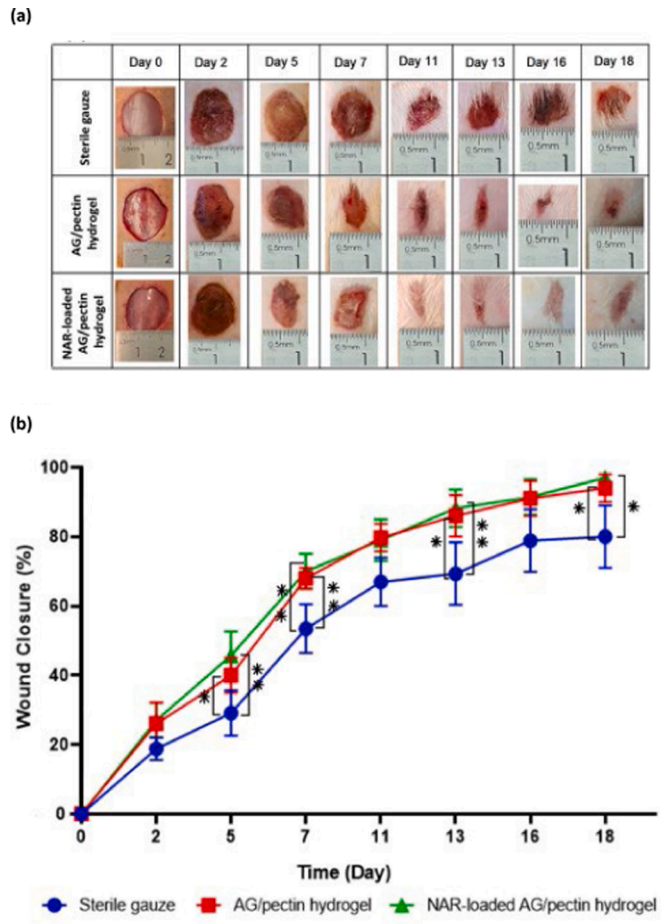

Fig. 7. Photographs depicting wound healing progression in animals with skin excision wounds across distinct treatment groups (a) and the percentage of wound closure (b) (reproduced with permission from Alsakhawy et al., 2022).

environment. The drug release rate increased to 37.5 % when the pH of the PBS was lowered to 5.2. In an in vivo experiment focused on diabetic wound healing, it was evident that the hydrogel, serving as a carrier for mEGF, significantly accelerated the rate of diabetic wound repair in a murine model. As illustrated in Fig. 6**a,** an experiment involving a diabetic wound model was conducted on the dorsal area of BALB/c mice. The aim of the study was to evaluate the ability of pectin-DH hydrogel loaded with mEGF to promote in vivo wound healing. A progressive reduction in the unclosed wound area and a corresponding increase in the wound closure ratio can be observed in Fig. 6**b and c**. Notably, the mEGF-hydrogel group exhibited the most substantial improvement in the wound repair rate, with the hydrogel group also displaying a notable reduction in the unclosed wound area when compared with the control group. By day 16, the wound in the mEGF-hydrogel group had nearly completely healed, in contrast to the control group which still exhibited persistent open wounds. The ratio of the statistical wound closure is presented in Fig. 6**d** for clarity. On day 4, the control group exhibited a higher closure ratio, likely due to skin shrinkage, whereas the pectin-DH hydrogel maintained a moist microenvironment (Chen et al., 2023). The sustained BSA release from pectin-DH hydrogels was significantly effective for wound dressings, particularly when loaded with mEGF to boost tissue regeneration.

Furthermore, Alsakhawy et al. (2022) employed an arabic gum (AG) and pectin hydrogel for the encapsulation of naringenin (NAR). The NAR-loaded AG-pectin hydrogel demonstrated an outstanding encapsulation efficiency of approximately 99.79 %, along with a notable drug loading of approximately 15.96 %. Visual assessment of wounds, as depicted in Fig. 7**a**, demonstrated the absence of redness or inflammation in the AG-pectin hydrogel and the AG-pectin hydrogel encapsulated with NAR. Conversely, the sterile gauze cohort exhibited signs of inflammation, characterized by redness and edema. By day 11, wounds treated with AG-pectin hydrogel encapsulated with NAR displayed a favorable healing progress, as the hydrogel effectively absorbed wound exudates, thereby promoting a clean and healthy wound environment. As depicted in Fig. 7**b**, the AG-pectin hydrogel and the AG-pectin hydrogel encapsulated with NAR groups exhibited a notable and statistically significant improvement in wound closure percentage compared with the control group that was treated with sterile gauze. Moreover, the AG-pectin hydrogel encapsulated with NAR demonstrated rapid and complete reepithelialization within 18 days, achieving an impressive 98 % wound closure rate. This favorable outcome can be ascribed to the controlled release of NAR, coupled with its antioxidant and antiapoptotic properties. Findings demonstrated that the AG-pectin hydrogel loaded with NAR facilitated accelerated wound healing by promoting angiogenesis and collagen deposition. Moreover, it notably suppressed the mRNA expression of inflammatory markers, such as TNF-α, and factors associated with apoptosis, including BAX (Alsakhawy et al., 2022).

Zhao et al. (2023) fabricated hydrogels using two distinct types of natural polysaccharides, namely oxidized pectin (OPC) and carboxyethyl chitosan (CEC), and polyethyleneimine (PEI)-CEC-OPC. The CEC was used as a matrix, while PEI and OPC were employed as crosslinking agents. When CEC and OPC solutions were combined at 4 % w/w and 9 % w/w mass fractions, the resulting hydrogel demonstrated remarkable antibacterial efficacy, exceeding 97 %, effectively combating *S. aureus* and *E. coli*. Incorporation of 0.75 % w/w PEI into the hydrogel was found to enhance antibacterial efficacy, achieving more than 98 % effectiveness. The PEI-based hydrogel demonstrated marked effectiveness in treating bacterial infections in wounds (Zhao et al., 2023).

A combination of quaternized chitosan (QCS) and pectin was also employed to enhance water solubility and antibacterial properties of hydrogel films. In addition, the incorporation of propolis into these films was shown to augment their wound healing capabilities. Moreover, the combination of QCS and pectin resulted in enhanced tensile strength of the hydrogel films. This blending strategy improved film stability in the medium and exerted control over the release properties of propolis from the hydrogel matrices. The propolis-loaded hydrogel films exhibited antioxidant activity ranging from 22 % to 37 %. The highest propolis-release percentages observed were approximately 22 % for propolis-loaded QCS, 78 % for pectin, and 64 % for the QCS–pectin hydrogel films. The wound closure for propolis-loaded QCS hydrogel films was approximately − 3.25 %, and the addition of pectin to the hydrogel significantly improved wound closure to approximately 53.13 %. These films also demonstrated significant antibacterial effects, particularly against *S. aureus* and *S. pyogenes*. The propolis-based hydrogel films demonstrated nontoxicity toward NCTC clone 929 mouse fibroblast cells (Phonrachom et al., 2023).

5.5. Pectin hydrogel in cancer

Pectin hydrogels have garnered attention in cancer therapy because of their biocompatibility and ability to encapsulate anticancer agents. These hydrogels enable targeted drug delivery, enhancing therapeutic efficacy and minimizing systemic side effects. Their potential in localized cancer treatment holds promise for improved patient outcomes (Cheewatanakornkool et al., 2017; Cheewatanakornkool et al., 2018).

A prominent example was shown by Yin et al. (2023), who successfully created a biodegradable hydrogel by incorporating silibinin within a blend of pectin and OCMC. Silibinin, an agent with anti-lung cancer properties, selectively targets the TMEM16A ion channel. Consequently, the authors investigated the effect of encapsulating silibinin within a pectin-OCMC hydrogel for therapeutic use in a mouse model of lung cancer. In the CCK-8 assay, it was observed that a pectin-OCMC hydrogel containing silibinin (100 mg/L and 200 mg/L) reduced

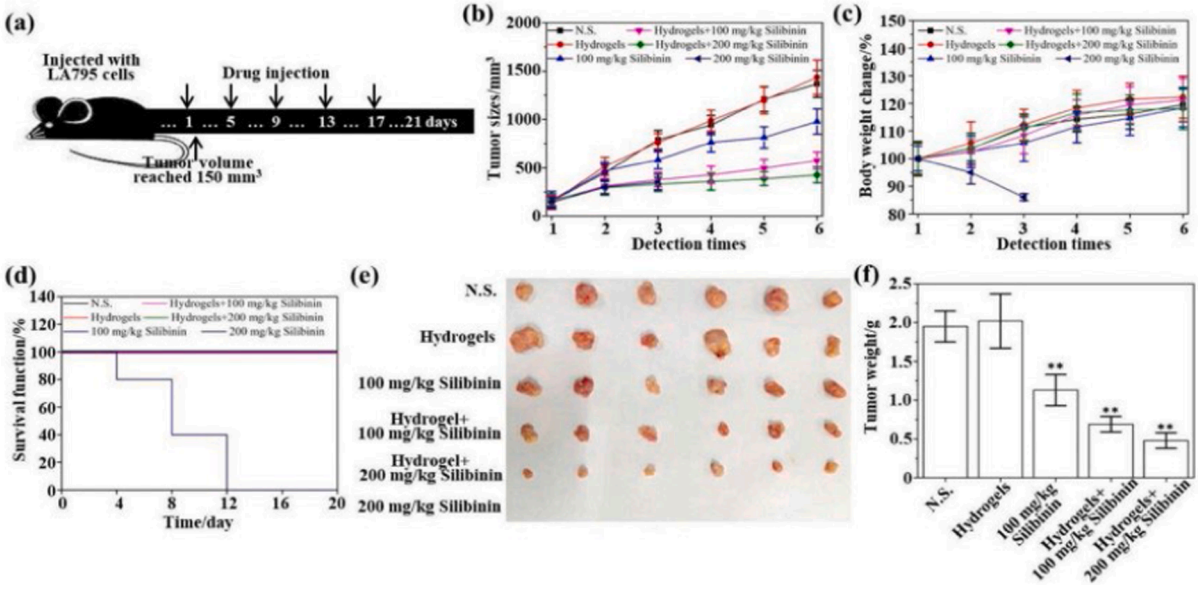

Fig. 8. In vivo experiment for evaluating the antitumor effect of silibinin incorporated in a hydrogel matrix; (a) graphical representation of the experimental setup; (b) evaluation of tumor size; (c) body weight characterization; (d) mice survival rate; (e) dissected tumor images; (f) tumor weight with respect to different formulations (reproduced with permission from Yin et al., 2023).

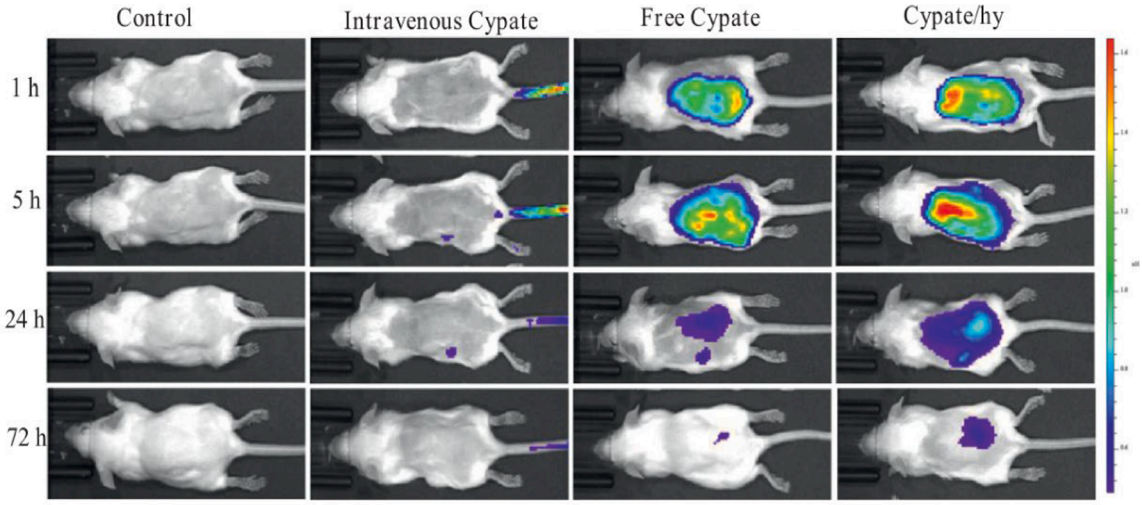

Fig. 9. Monitoring drug retention and accumulation in a hydrogel via NIRF imaging after intravenous and intratumoral cypate or cypate/hydrogel injections at various time points (reproduced with permission from An et al., 2021).

LA795 cell viability to 73.25 % and 31.25 %, respectively. In vivo anticancer assessments of silibinin incorporated in a hydrogel matrix were performed using a murine model, as depicted in Fig. 8**a.** The tumor proliferation inhibition efficacy was enhanced in the hydrogel combined with the silibinin group (200 mg/kg), as evident by the reduction in tumor size illustrated in Fig. 8**b.** Throughout the experiment, mice in the hydrogel, silibinin (100 mg/kg), and hydrogel combined with silibinin groups (100 mg/kg and 200 mg/kg) exhibited a consistent increase in body weight, with no statistically significant differences, compared with the control groups, as shown in Fig. 8**c.** In the silibinin group (200 mg/kg), the mean body weight of mice decreased to 78 % of that of the control group, and mice experienced successive mortality before the 4th dose, as illustrated in Fig. 8**d.** Following the 6th measurement, mice were euthanized, and tumor specimens were extracted for comparative analysis. Notably, the silibinin-hydrogel group exhibited significantly reduced tumor sizes, compared with the control and direct silibinin groups, as presented in Fig. 8**e.** In Fig. 8**f,** the group treated with hydrogel combined with silibinin (100 mg/kg) exhibited a notable tumor weight reduction, compared to the silibinin group (100 mg/kg), while the hydrogel combined with 200 mg/kg silibinin group displayed an even greater reduction in tumor weight. This hydrogel was rapidly formed and exhibited pH-sensitive sustained drug release owing to its acylhydrazone bond crosslinked networks, rendering it suitable for injectable use (Yin et al., 2023).

Furthermore, An et al. (2021) pioneered pectin-based, injectable, and biodegradable hydrogels, unlocking the potential for advanced enhanced anticancer therapies. A hydrogel was synthesized using biodegradable pectin aldehyde (pectin-CHO) and a polymer blend of poly(N-isopropylacrylamide-stat-acylhydrazide). Injectable hydrogels can effectively encapsulate and deliver anticancer drugs, such as DOX hydrochloride and combretastatin A4 disodium phosphate (CA4), directly to tumor sites. Incorporating DOX into hydrogels can significantly impede the growth of CT-26 cells. The authors found that hydrogel encapsulated with DOX and CA4 treatments led to significantly

Table 1
Pectin hydrogels applications in drug delivery.

Polymer employed/type of pectin	Drug encapsulated	In vitro/in vivo studies	Outcome	Reference
Acylhydrazone/oxidized pectin	5-Flurouracil	The release ratio exceeded 76 % at pH 6.8 and surpassed 80 % at pH 7.4. After a 24-h exposure, Gel 3, Gel 4, and Gel 5 all demonstrated inhibition of MCF-7 cell lines, with cell proliferation ratios falling below 80 %.	The pectin-based hydrogel demonstrated excellent cytocompatibility with L929 cell lines. A significant inhibitory effect was observed against MCF-7 cell lines.	(Wang et al., 2023)
Carboxymethyl cellulose/pectin hydrazide	Silibinin	Silibinin exhibited a sustained release pattern, with less than 5 % released after 24 h in pH 7.4 PBS and less than 10 % when the pH shifted to 5.4 within the same time frame. According to the CCK-8 assay, the silibinin-pectin hydrogel at concentrations of 100 mg/L and 200 mg/L reduced LA795 cell viability to approximately 73.98 % ± 10.25 % and 29.26 % ± 5.56 %, respectively. The tumor weight in the hydrogel + 100 mg/kg silibinin group showed a significant decrease compared to the group receiving 100 mg/kg silibinin alone. The hydrogel combined with 100 mg/kg silibinin exhibited significantly enhanced inhibition of tumor growth due to sustained drug release.	The findings indicated that the silibinin-loaded hydrogel substantially improved in vivo anti-tumor efficacy while markedly decreasing silibinin associated toxicity.	(Yin et al., 2023)
Poly (3-methoxydiphenylamine)/ pristine pectin	Ibuprofen	When pristine pectin hydrogels are crosslinked with Fe under a 1-V electric potential, the scaling exponent (n) decreases from 1.36 to 0.45 as the Fe crosslinking mole ratio increases. This transition suggests a shift from matrix erosion to a purely Fickian diffusion mechanism. In pristine pectin hydrogels crosslinked with Cit at an electric potential of 1 V, the scaling exponents (n) range from 0.62 to 0.71. These values increase with higher citric acid crosslinking mole ratios, suggesting that the transport mechanism involves anomalous diffusion and matrix swelling.	The release of ibuprofen from the pectin hydrogels was characterized by four distinct modes: Fickian diffusion, anomalous transport, case-II transport, and super case II transport.	(Mongkolkitikul et al., 2018)
Hawthorn pectin (HPC)/ tenebrio molitor protein (TMPT)	Curcumin	Only 16.29 % of curcumin was lost into simulated gastric fluid, when encapsulated within HPC-TMPT. The release of curcumin from HPC-TMPT hydrogel followed the Hixson-Crowell model, indicating sustained release based on a corrosion mechanism.	In vitro digestion studies confirmed that HPC-TMPT hydrogel significantly enhanced curcumin's storage stability and bioavailability	(Bu et al., 2022)
Fe^{3+} crosslinking pectin	Hyaluronic acid (HYA)	The treatment with HYA7PC3 and HYA5PC5 resulted in a 99.9 % reduction of *S. aureus* after 120 min, with complete microbial eradication achieved after 360 min. HYA7PC3 resulted in complete cell death in *P. aeruginosa* after 360 min, while HYA5PC5 achieved the same outcome in 180 min.	The Fe^{3+}-crosslinked HYA/pectin hydrogel, optimized for wound healing, demonstrates exceptional self-healing properties. The hydrogel exhibited antibacterial effects against *S. aureus* and *P. aeruginosa* by releasing Fe^{3+} during degradation. It displayed non-toxicity towards human dermal fibroblast cells.	(Kim et al., 2023)
Quince (Q)/pectin	Domperidone	The drug loading percentage varied between 68 % and 86 %. These hydrogel sponges exhibited pH-responsive swelling behavior, with maximum swelling observed in a phosphate buffer with a pH of 7.4. The formulations exhibited a release range of 62.55 % to 85.12 % at pH 6.8 and 67.23 % to 92.52 % at pH 7.4 in the phosphate buffer solution. Elevating the crosslinker concentration led to a reduction in domperidone release, decreasing from 77.50 % to 66.501 % across formulations QPC1 to QPC3.	The hydrogel sponges exhibited stimulus-responsive behavior, enabling controlled domperidone release over 10 h at pH 7.4, while minimal drug release occurred in acidic pH conditions.	(Aslam et al., 2023)

reduced tumor volumes, compared with free drug treatments. Intravenous administration of the free drug in mice resulted in lower cytopate fluorescence intensity at the tumor site, compared with intratumoral injection groups, as shown in Fig. 9**.** In vitro and in vivo investigations confirmed the hydrogel's exceptional biocompatibility and biodegradability, and also its ability to mitigate drug toxicity effectively while demonstrating controlled drug-release properties (An et al., 2021).

5.6. *Pectin-based scaffolds for tissue engineering*

Pectin hydrogels have gained prominence in tissue engineering because of their biocompatibility, tunable properties, and ability to mimic the extracellular matrix. They serve as a promising scaffold for cell growth, promoting tissue regeneration in various applications, including cartilage and skin tissue engineering. The natural origin of pectin further enhances its appeal in biomedicine (Pandey et al., 2023).

Nejati et al. (2020) introduced an innovative oxygen-releasing electroconductive in situ crosslinkable hydrogel. This hydrogel was crafted from oxidized pectin and grafted gelatin, demonstrating significant potential for tissue engineering applications. Their findings indicated the successful production of spherical particles, averaging 61.25 μm in diameter, with an encapsulation efficiency of 48.65 %. These particles consistently released oxygen over a 14-day period. Research on hydrogels demonstrated that increasing the pyrrole content in gelatin graft polypyrrole from 0 % to 15 % led to notable enhancements in swelling ratio (6.7 % to 12.2 %), pore size (174.25 μm to 296.25 μm),

Table 2
Patents on pectin-based hydrogel for controlled/sustained release.

Publication date	Application number	Title	Document type	Legal status	Reference
08–06-2023	US 202,217,858,562 A	Method of preparing pH-sensitive controlled-release emulsion hydrogel	Patent application	Pending	(Chang Pahn et al., 2023)
19–05-2016	US 201,514,942,435 A	Tunable anti-microbial loaded hydrogels	Patent application	Active	(Shukla and Shukla, 2016)
29–12-2015	US 9,220,681 B2	Mesalazine controlled release oral pharmaceutical compositions	Granted patent	Expired	(Coulter et al., 2015)
27–02-2001	US 6,193,994 B1	Locally administrable, biodegradable and sustained release pharmaceutical composition for periodontitis and process for preparation thereof	Granted patent	Expired	(Lee et al., 2001)
16–02-1993	US 56,339,490 A	Controlled release oral drug delivery system	Granted patent	Expired	(Rubinstein et al., 1995)
27–10-2015	US 2016/0045585 A1	Formulations	Granted patent	Expired	(Coulter et al., 2016)
22–08-2018	US 2022/0265833 A1	Aspartic protease-triggered antifungal hydrogels	Patent application	Active	(Shukla and Vera-Gonzalez, 2022)
24–12-2002	US 6,497,902 B1	Ionically crosslinked hydrogels with adjustable gelation time	Granted patent	Expired	(Ma Peter, 2002)
23–05-2023	CN 116,139,069 A	Porous starch-loaded double-layer heterogeneous microgel delivery system and application thereof in preparation of medicine for treating colitis	Patent application	Active	(Hu et al., 2023)
07–06-2001	US 0031635 W	Delayed total release two pulse gastrointestinal drug delivery system	Patent application	Pending	(Penhasi et al., 2003)
08–07-2021	US 201,615,779,212 A	Gastric-retentive controlled release mono-matrix tablet	Patent application	Active	(Shin Hee et al., 2006)
03–04-2003	US 22,895,602 A	Smart temperature-sensitive hydrogels with antifungal property that perform controlled drug release	Patent application	Expired	(Kanci Bozoglan et al., 2021)
08–07-2022	CN 202,210,373,527 A	Preparation method of wound dressing based on shaddock peel pectin-oxidized chitosan composite hydrogel	Granted patent	Active	(Zhang et al., 2022)
15–01-2014	CN 201,310,296,090 A	pectin/N-isopropylacrylamide interpenetrating hydrogel material	Patent application	Discontinued	(Chen et al., 2014)
18–07-2012	CN 201,110,003,040 A	pectin/cellulose hydrogel material and preparation method thereof	Patent application	Discontinued	(Zhaocheng et al., 2012)
21–04-2015	KR 20,130,120,764 A	Hydrogel composition containing catechin for wound dressing and manufacturing method thereof	Patent application	Discontinued	(이기영 and 김진, 2015)

Note: Abbreviations: US, United States of America; CN, The People's Republic of China; KR, Republic of Korea.

porosity (80.2 % to 93.5 %), and conductivity (0.06 mS/m to 2.14 mS/m). The degree of crosslinking of hydrogels decreased from 67.24 % to 27.35 %. Simultaneously, the compressive modulus decreased from 213.5 kPa to 65.2 kPa.

5.7. Miscellaneous

Many other potential applications of pectin gels were recently published. As an example, Kocaaga et al. (2022) employed molecular dynamics simulations to anticipate the ideal drug concentration for loading onto LM pectin hydrogels. The authors explored LM pectin hydrogel systems, represented as poly galacturonic acid oligomers, which were crosslinked with varying concentrations of procaine and Ca^{2+} (ranging from 0 to 180 mg procaine/g hydrogel). Pectin hydrogels incorporating 30 mg of procaine per gram, exhibited a minimal hydrogel degradation rate at 0.002 g/min, ensuring an in vitro controlled drug release profile. When compared with alternative formulations, these hydrogels effectively released the entire 35-mg procaine from a 670-mg hydrogel over a 24-h period.

Hafeez et al. (2023) designed an innovative pectin-based stimuli-responsive hydrogel system engineered for precise control of ceftriaxone release, offering a potential solution for precise drug delivery. A stimuli-responsive hydrogel developed with a blend of natural polysaccharides, such as chitosan and pectin, synthetic polymer polyvinyl alcohol, and the environmentally friendly coupling agent 3-aminopropyl (diethoxy) methyl silane, presented a versatile platform with applications in controlled drug delivery and tissue engineering. The above-mentioned polymers were combined and underwent crosslinking with different crosslinker concentrations using a solution casting method. The controlled drug release study, performed in PBS, revealed that over 90 % of ceftriaxone was released within 180 min, indicating an effective and sustained release profile.

Zafar et al. (2023) endeavored to design for controlled drug delivery of tapentadol hydrochloride, fabricating interpenetrating networks (IPNs) using natrosol-pectin copolymer, acrylic acid, and methylene bisacrylamide. These IPNs were formulated by employing the free radical polymerization approach. The swelling percentage rose from 85.14 % to 92.53 % with increasing amounts of natrosol and pectin polymers. Conversely, an elevated methylene bisacrylamide content led to a decline in swelling, diminishing from 84 % to 66.89 %. The findings revealed that the release of the drug from the formulated IPN was significantly higher under alkaline conditions with a pH of 7.4, contrasting with a lower release observed at the acidic pH of 1.2 (Zafar et al., 2023). Table 1 describes the different applications of pectin hydrogels involving controlled or sustained drug release.

5.8. Patents on pectin-based hydrogels

Patents concerning pectin-based hydrogels are a prominent domain of research and innovation in biomaterials and pharmaceuticals. Pectin offers versatility in creating diverse hydrogels with distinct properties, driving advancements in drug delivery, tissue engineering, and wound healing. These patents safeguard intellectual property, stimulate technological progress, and hold the potential for enhancing healthcare solutions. Table 2 depicts the different patents related to controlled or sustained drug delivery.

6. Challenges and future directions

Recent advancements in pectin hydrogels have showcased their potential for controlled drug release, offering distinct advantages such as biocompatibility and tunable drug delivery kinetics. However, several challenges still remain, including a way to achieve precise control over drug-release rates, enhance mechanical strength, and ensure stability

under varying physiological conditions. Future directions should focus on optimizing pectin-based formulations, exploring novel crosslinking techniques, and integrating responsive elements for on-demand drug release. Moreover, it is vital to understand the interplay between pectin's structural properties and drug encapsulation in order to tailor hydrogels to specific therapeutic applications. These efforts hold promise in realizing the full potential of pectin hydrogels as versatile and effective platforms for controlled drug delivery, with implications for personalized medicine and improved patient outcomes.

7. Recent advances

Advancements in the utilization of pectin hydrogels as biocompatible scaffolds for tissue engineering signify a notable stride, offering a promising avenue for fostering cell growth and tissue regeneration in therapeutic applications. Scientists are actively refining the composition and structure of these hydrogels to emulate the extracellular matrix, fostering cellular adhesion and facilitating tissue regeneration. Exploring diagnostic frontiers, pectin-derived hydrogels are under scrutiny for biosensor innovation. Tailored to encapsulate bioactive agents, they hold promise in detecting precise biomarkers, advancing the landscape of point-of-care diagnostics.

Recent research has honed in on developing intelligent pectin-based hydrogels, capable of reversible transformations triggered by external cues like pH, temperature, or light. This dynamic feature empowers tailored, on-demand release of encapsulated substances, showcasing a cutting-edge stride in responsive biomaterial innovation.

8. Conclusion

The present review focuses on the development of pectin-based hydrogels for drug delivery, emphasizing their significant properties of biocompatibility, biodegradability, cost-effectiveness, and versatility in design. Pectin-based hydrogels, with their unique functional groups and easy gelation, hold great potential for fabricating effective drug delivery systems. More precise chemical modifications of pectin and its synergistic use with different polymers and nano biomaterials will improve the structural properties of pectin-based hydrogels. This advancement will enable precise control of interactions with drug molecules at molecular and nanoscale levels. Given the significant attributes and increasing research focus on pectin-based hydrogels, the application of pectin in drug delivery are bound to grow. To achieve this, efforts must intensify in advancing pectin-based hydrogel systems for clinical use, addressing regulatory challenges, which are perceived as the primary barrier.

CRediT authorship contribution statement

Conceptualization – BP, PS, Funding acquisition – PS, Data curation – DK, RG, MG, AP, Investigation – DK, RG, MG, AP, Methodology – DK, GC, SS, Supervision – BP, SS, PS, Writing – original draft – DK, BP, PS, Writing – review & editing – BP, SS, GC, PS.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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