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Review article

Hydrogels: Classifications, fundamental properties, applications, and scopes in recent advances in tissue engineering and regenerative medicine – A comprehensive review

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ABSTRACT

Hydrogels are three-dimensional structures that serve as substitutes for the extracellular matrix (ECM) and possess outstanding physicochemical and biochemical characteristics. They are gaining importance in regenerative medicine because of their similarity to the natural extracellular matrix in terms of moisture content and wound and tissue healing permeability. Tissue engineering advancements have resulted in the development of flexible hydrogels that mimic the dynamic characteristics of the ECM. Several approaches have been applied to produce hydrogels from biopolymers with enhanced functional and structural characteristics for different applications in tissue engineering and regenerative medicine (TERM). This review provides a comprehensive overview of hydrogel in wound healing, tissue engineering, and drug delivery systems. We outline different types of hydrogels based on the physical and chemical crosslinking, fundamental properties, and their applications in TERM. This review article provided the recent literature on hydrogels for tissue engineering and regenerative medicine within five years. Recent developments in biopolymer-based hydrogels for state-of-the-art tissue engineering and regenerative medicine have been discussed, emphasizing their significant challenges and future perspectives.

1. Introduction

Every year, millions of Americans suffer from tissue failure or organ loss as a result of disease or trauma, costing the US economy more than $400 billion. Although it is a common treatment, transplantation is restricted because of a shortage of donors. The multidisciplinary area of biomedical engineering applies fundamental concepts from biology, engineering, and the life sciences to overcome these constraints (Aslam Khan et al., 2021, 2021; Khan et al., 2021). Nowadays, biomaterials and biomedical engineering have been used to overcome these medical constraints. Cutting-edge and useful biomaterials have been created using various methods and strategies for producing artificial organs and tissues, which hold promise for essential transplantation (Khan et al., 2020, 2022, 2024). Afterwards, the cells are implanted into 3D-polymeric scaffolds that mimic the body's tissue-specific extracellular matrices (ECMs) (Khan et al., 2021; Al-Arjan et al., 2020). These scaffolds enable the formation of new tissue by moving the cells to the host location within the body. It promotes tissue regeneration with regulated structural and functional properties (Khan et al., 2020, 2020; Shah et al., 2016). Different organs and tissues, such as arteries, bladders, skins, cartilage, bones, ligaments, and tendons, are only examples of diverse tissues developed by biomedical engineering (Khan et al., 2022, 2022, 2022).

Hydrogels are well-known biomaterials made of crosslinked

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polymeric chains holding significant amounts of water and forming 3D structures. Because hydrogels resemble the extracellular matrix, they could be the most accurate models for the minute elements of actual physiological settings (Qu et al., 2021; Khan et al., 2021). The hydrogels have garnered significant attention due to their numerous biomedical uses, such as tissue healing and adhesion. Because the need for biomaterials in the healthcare sector is increasing, researchers have recently started concentrating on hydrogels based on biopolymers (Ouyang et al., 2023; Ding et al., 2022). Hydrogels are biomaterials that can function during therapy and generate the desired effect. Sometimes, hydrogel modifications are made to encourage the migration and adherence of specific cell types that take the place of healing broken or wounded tissue. Potential biopolymers can be taken from bacteria, animals, plants, and algae (Xu et al., 2021; Ding et al., 2023). These are divided into polysaccharides, polypeptides, and polynucleotides based on the subunit of their monomers. They are frequently extracted using various chemical processes and syntheses based on their origin and applications (Nagarajan et al., 2019; Shafiei et al., 2021; Nazir et al., 2021). These procedures significantly influence their physiochemical characteristics, and to address medical issues, hydrogels made of biopolymers imitate the characteristics of the original tissue. Hydrogels based on biopolymers may be used in soft tissue healing, tissue engineering, and medication administration (Khan et al., 2021, 2024). The main objective of regeneration tissue engineering is to optimize the body's natural ability to repair injured organs. Hydrogels were utilized as scaffolds to provide the cells with a culture that can promote cell division and the healing of damaged tissue. Because hydrogels are naturally biodegradable, have low toxicity, and release harmless fragments during the process, they mimic and support biological processes (Neishabouri et al., 2022; Aslam Khan et al., 2021).

There are currently several challenges to integrating these hydrogel systems to react sequentially to the numerous physiological and pathological changes that constantly occur in the human body. Therefore, new hydrogel scaffold technologies must be developed to promote successful tissue regeneration for biomedical applications. In this review, we have reviewed the literature of the last three to five years' worth of advancements in hydrogel technology for tissue engineering. We have focused on the hydrogel system for tissue engineering and regenerative medicine. We first introduce different hydrogel types based on their physical and chemical interaction, then their fundamental physicochemical and biological properties. Next, we provide an overview of hydrogel applications in tissue engineering and regenerative medicine (Fig. 1). Finally, we have discussed the limitations and future perspective of hydrogels with concluding remarks on tissue engineering and regenerative medicine.

2. Classifications of hydrogel based on interaction

In hydrogels, crosslinking can occur through crosslinking polymeric networks or chemical or physical contact. Charge condensation, hydrophobic contacts, hydrogen bonds, supramolecular chemistry, ionic and covalent bonding, or molecular entanglements are some physicochemical interactions that keep them together. The interactions between these hydrogel types are weak. Despite this, they are widespread and necessary to continue intricate operations.

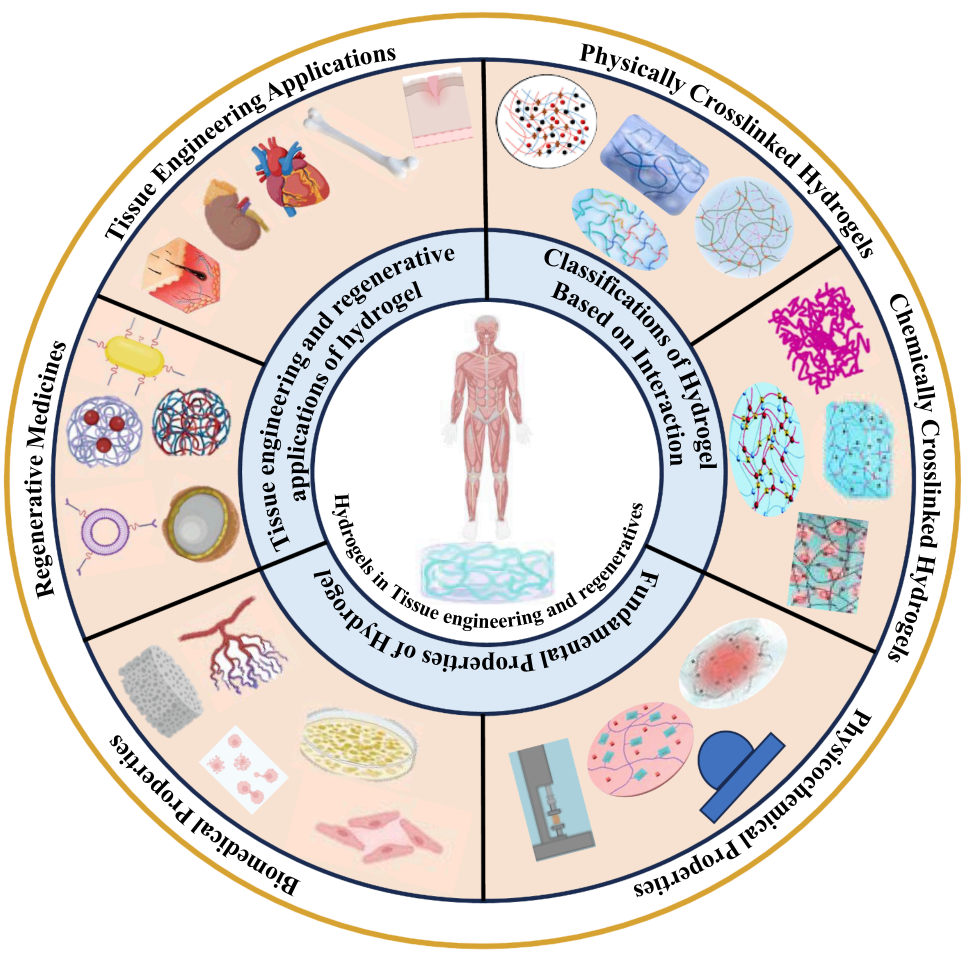

Fig. 1. The graphical abstract illustrates the different types of hydrogels based on interaction, fundamental properties and application in tissue engineering and regenerative medicine.

2.1. Physically crosslinked hydrogels

2.1.1. Hybrid hydrogels

The constituent parts of hybrid hydrogels are significantly different regarding chemistry, function, and morphology. Proteins, microstructures, or nanostructures interact via chemical or physical methods to produce hybrid hydrogels. The biologically active peptides and proteins also help to develop hydrogel for tissue engineering and regenerative medicines (Patkar et al., 2023; Khan et al., 2021). The chemical composition, physicochemical characteristics, fabrication, and use of the hybrid hydrogels must be considerably different from one another and be exchangeable. Hybrid hydrogels have potential properties based on the difference from the parent polymers or components (Rinoldi et al., 2021; Zamri et al., 2021). Mahmoud et al. have developed nanocomposite hybrid hydrogels from bentonite and gelatin for tissue engineering. They have reported that the newly developed nanocomposite hybrid hydrogels are excellent for tissue engineering applications due to enhanced mechanical and cytocompatible properties

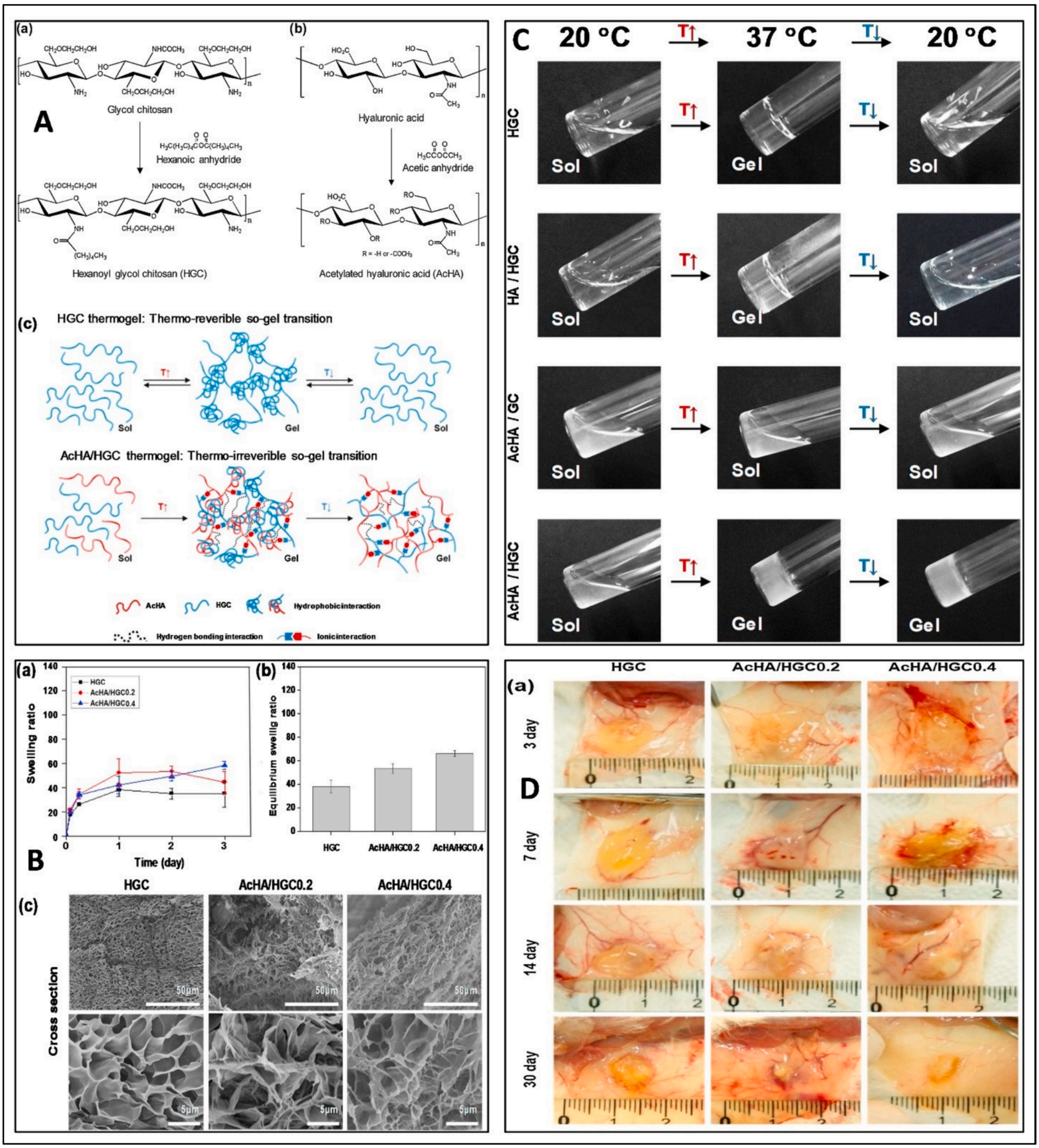

Fig. 2. The thermoresponsive physically crosslinked hydrogels for wound healing applications. (A) Chemical structures of the ingredients and their proposed physical interaction. (B) Digital photographs of the thermoresponsive hydrogels observed at different temperatures. (C) swelling ratio, equilibrium swelling ratio, and morphology of the hydrogels, and (D) Digital photographs of the wound healing after different times (Lee et al., 2020), with permission from Elsevier.

(Sakr et al., 2020). Aleksandra et al. have synthesized hybrid hydrogels from alginate, hyaluronic acid, and gelatin for tissue engineering applications. They observed that the synthesized hybrid hydrogels have different physicochemical, mechanical, rheological, morphological, and biological properties due to the various concentrations of the biopolymers. Based on these, the hybrid hydrogels can be used for different tissue engineering applications (Serafin et al., 2023). Samira et al. have fabricated a composite hybrid hydrogel from soy protein sodium alginate incorporated hydroxyapatite for tissue engineering applications. They studied the structural, morphological, thermal degradation, physicochemical, and biological properties of fabricated hybrid hydrogel and reported that it would be an excellent material for biomedical applications (Alesaeidi et al., 2023). Lee et al. developed hybrid hydrogels from chitosan and hyaluronic acid hydrogels with thermoresponsive properties for skin wound healing applications (Fig. 2). They reported that the thermoresponsive hydrogel exhibited improved structural stability, mechanical robustness, cytocompatibility, and enhanced tissue affinity. The newly developed physically blended hydrogels would be potential hybrid materials with desirable injectability for tissue engineering applications (Lee et al., 2020).

2.1.2. Self-assembling hydrogels

Hybrid hydrogels that self-assemble and include peptides provide the appropriate bio-functionality and biodegradability. For direct biomedical applications, they bore a striking resemblance to biological molecules and structures (Xing et al., 2019). These include drug delivery and cell carriers, which incorporate bioactive sequences from natural proteins (Xing et al., 2022). Polymeric networks are joined to control biomechanical, cytocompatibility, and degradation characteristics by chemically modifying the peptides. These alterations involved peptide-polymer interactions that were either non-covalent or covalently bound (Yuan et al., 2023). Wang et al. developed self-assembled hydrogel from binary small molecules with synergistic antibacterial effects with inhibition of virulence factors and lessening inflammation response to facilitate wound healing. They studied morphological, physicochemical behaviour, biological activities, and in vivo wound closure against mice models. They have reported that the results confirmed that the newly developed self-assembling hydrogel would be a potential material with a synergistic antibacterial effect to promote wound healing applications (Wang et al., 2023). Liu et al. have synthesized the nano-antimicrobial self-assembly hydrogel wound dressing for S. Aureus infected for wound healing applications with enhanced

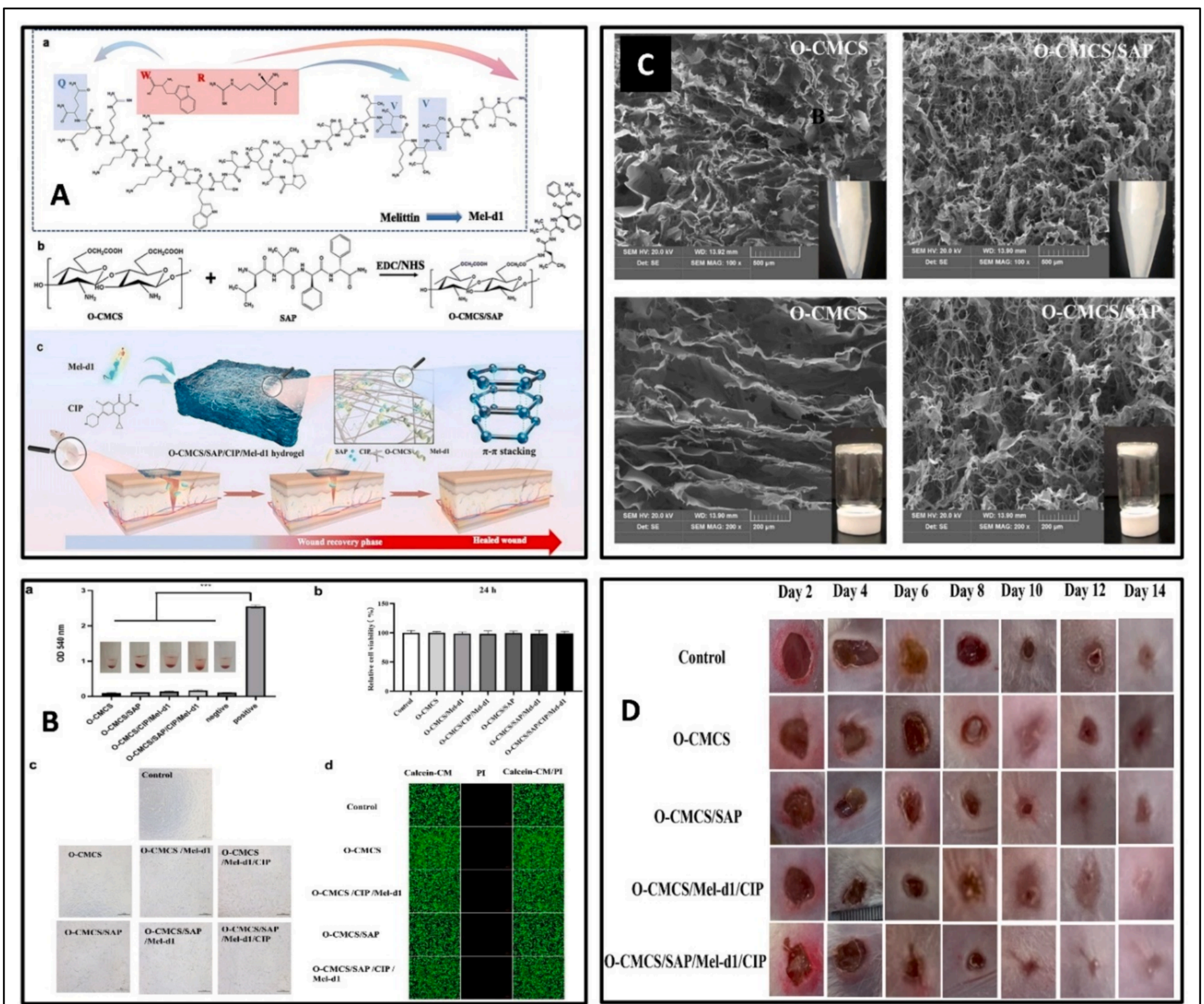

Fig. 3. The self-assembled hydrogels for tissue engineering applications. (A) The proposed chemical interaction of the polymers and schematic illustration of wound healing. (B) Hemolysis, percentage of cell viability, and cell morphologies. (C) The surface morphology of the hydrogels with digital photographs and (D) digital photographs of the wound healing after different time intervals (Huan et al., 2022), with permission from Elsevier.

drug/cytokine-free strategies. Notably, this hydrogel effectively restored an unbroken and thick epidermis akin to normal mouse skin, speeding up the regeneration of a full-thickness-damaged skin wound infected with MRSA. Combined, a self-assembling PCEC-QAS antimicrobial hydrogel is promising for advancing skin regeneration. Without additional medications, the cells, exposure to light, or transport systems inhibit the spread of bacterial infections. They have offered an easy yet efficient method for healing cutaneous wounds (Liu et al., 2020). Huan et al. have synthesized self-assembling hydrogel dressing materials from peptides, carboxymethyl, and chitosan with sustained release of loaded ciprofloxacin, as shown in Fig. 3. They have reported that the self-assembling hydrogel is highly antibacterial and has a sustained release of ciprofloxacin that promotes accelerated wound healing and tissue regeneration (Huan et al., 2022).

2.1.3. Supramolecular hydrogels

By combining particular peptide fragments into a polymer matrix, supramolecular hydrogels are assembled from building blocks of peptides and polymers. The constituents can self-assemble into hybrid hydrogels as specific protein conjugates or incorporate constituent parts,

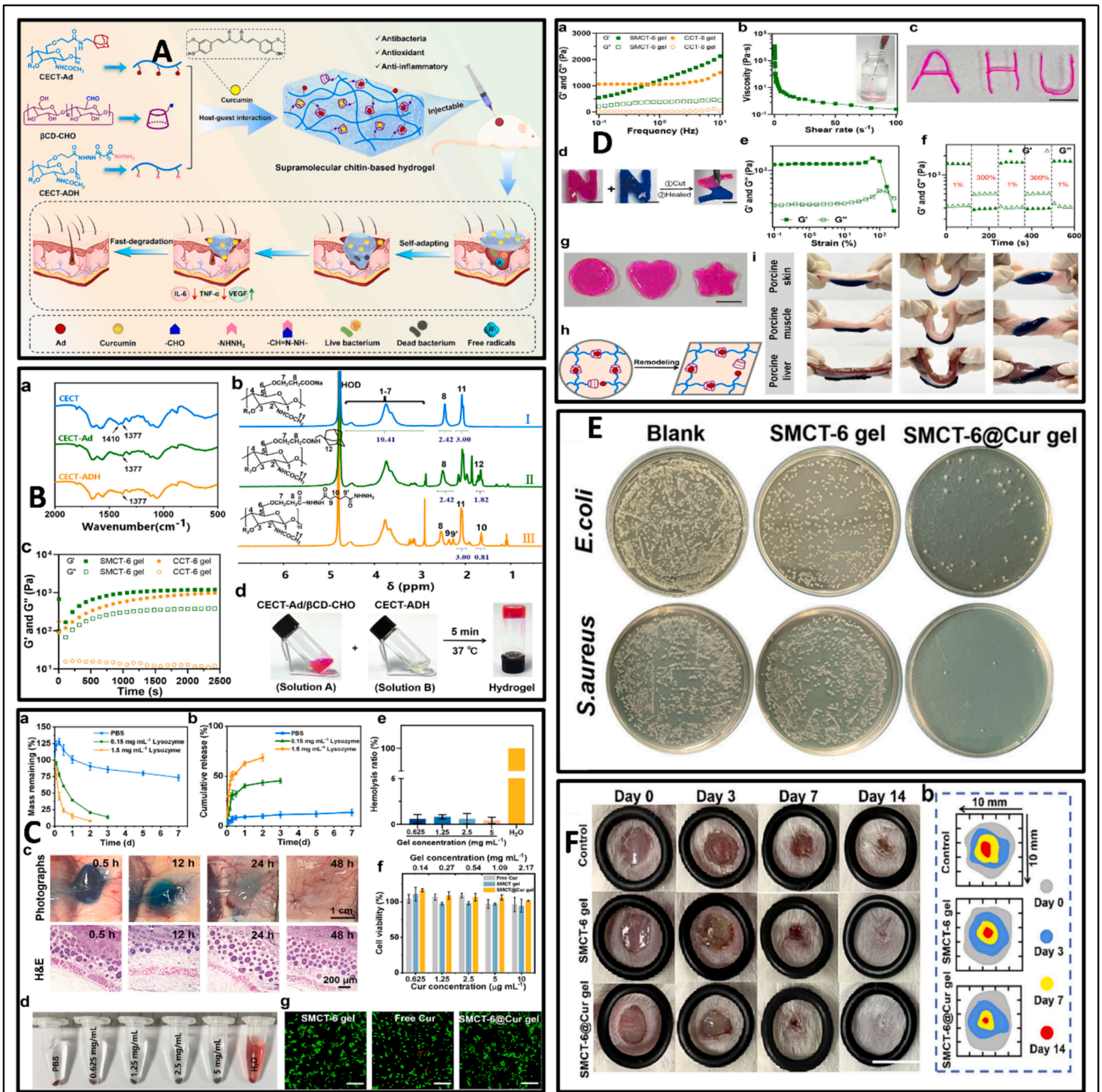

Fig. 4. The development of supramolecular hydrogels for tissue engineering applications. (A) Schematic diagram of supramolecular hydrogels and proposed wound healing application using mice model. (B) The chemical structural analyses, rheological behaviour, and digital photographs of the supramolecular hydrogel. (C) The degradation, drug release, hemolysis, H&E staining, photographs of the hemolytic assay, hemolytic ratio, cell viability, and live/dead staining of L929 cell lines. (D) Rheological behaviour, viscosity analysis, printability, and other structural properties of supramolecular hydrogels. (E) Antibacterial activities of supramolecular hydrogels against Gram-positive and Gram-negative bacterial strains. (F) The wound healing potential of supramolecular hydrogels using mice model after different time intervals (Shi et al., 2024); with permission from Elsevier.

resulting in regulated cell interactions (Yang et al., 2023). These will choose the characteristics of hydrogels, and transformation will control how structures form at the nanometer scale. These characteristics include sensitivity, bioactivity, adaptability, and tightness (Hamley, 2023). The overall structure and unique properties of recently produced materials may be unique. The sequence of amino acids can be maximized to produce functional hydrogels designed primarily for a specific application. Developing and fabricating hybrid polymer molecular hydrogels demonstrated considerable research advancement. They might imitate the cellular processes, dynamic responsiveness, and molecular architectures of the natural protein. The synthetic constituents provided functional properties and biocompatibility (Jeong et al., 2022). Wang et al. have developed high-strength, injectable supramolecular hydrogel and self-assembled for wound healing applications. They have found that the hydrogels are self-assembled, self-healable, and injectable with appropriate in vitro hemocompatibility, biocompatibility, and in vivo wound healing applications. They have reported that the newly developed hydrogels would be potential biomaterials for wound healing applications (Wang et al., 2022). Wenwen et al. have synthesized the supramolecular hydrogels from a chitin-based host–-guest and pre-assembly approach (Fig. 4). They have reported that these hydrogels have desirable structural characteristics with self-adaptive, fast-degradative characteristics that control sustained drug release. They also observed that these supramolecular hydrogels processed antibacterial activities, hemocompatibility, and cytocompatibility with appropriate cell morphology. The supramolecular hydrogels have exhibited fast healing properties and would be excellent dressing materials for wound healing applications (Shi et al., 2024). Zhang et al. have fabricated supramolecular hydrogels with appropriate injectability, self-healing, and conductivity with enhanced antimicrobial activities to promote skin repair and regeneration for wound healing and tissue engineering applications. Commercial dressings and synthesized hydrogels notably expedited the in vivo repair of full-thickness skin injuries. It enhances the thickness of the outer layer of skin and the tissue that forms during wound healing, increases the amount of collagen in the area, and boosts the expression of VEGF. These biomaterials are promising for wound dressings in full-thickness skin repair because they are conductive, self-healing, and antimicrobial (Zhang et al., 2020).

2.2. *Chemically crosslinked hydrogels*

2.2.1. *Covalently crosslinked hydrogels*

Chemically or covalently crosslinked with definite shapes at rest, hydrogels have low flexibility and fracture toughness. Therefore, developing physically and covalently crosslinked hydrogels is preferable (Zhou et al., 2020). Crosslinking agents are used in many double networks of hydrogels produced by double chemical crosslinking or hybrid physicochemical crosslinking. However, crosslinked hydrogels have more structural stability and are primarily non-biodegradable, which may restrict their drug delivery and tissue regeneration. A promising technique is producing new hydrogels with two non-covalently associated networks (Eivazzadeh-Keihan et al., 2022). Tang et al. have developed a covalently crosslinked composite hydrogel from bacterial cellulose and hyaluronic acid for promising biological applications. They have studied structural, morphological, physicochemical, mechanical, and vitro cytocompatible evaluations. They have reported that the chemically cross-linked composite hydrogel could have a promising biomaterial in wound healing (Tang et al., 2021). Wang et al. have developed a novel double-crosslinking hydrogel with optimized injectability, promoted tissue adhesion, and enhanced antimicrobial activities for wound repair and regeneration applications. They have reported that the excellent hemostatic efficacy of hydrogel is attributed to its greater tissue adherence. These have been shown using a hemorrhaging liver model. The hydrogel can significantly enhance the healing process of bacterial-infected wounds. Xuebin Ma et al. have synthesized the covalent hydrogel from hyaluronic acid and poly(glutamic acid) with adaptive behaviour for promising load-bearing applications in tissue engineering. The synthesized hydrogels were reported to possess stable architectures, excellent mechanical characteristics, enzymatic biodegradability, and injectability. NIH 3T3 cells demonstrate good cell viability when subjected to 3D encapsulation using customizable hydrogels. Hence, due to their desired features, the synthesized hydrogels have considerable mechanical stability for tissue engineering applications (Ma et al., 2020). Shichao et al. have synthesized double network toughness hydrogel by freeze crystallization from chitosan and PVA for soft tissue engineering (Fig. 5). The hydrogels require compressive and tensile mechanical behaviour with anti-swelling properties. The prepared hydrogels have the ability for cell adherence that promotes cell viability and proliferation that supports skin wound healing and soft tissue engineering (Bi et al., 2020).

2.2.2. *Click chemistry hydrogels*

Click chemistry was promptly embraced as a revolutionary advancement in synthetic chemistry, inspiring scientists in other scientific fields. The click chemistry process shows fast reaction rates, high specificity, simple reaction conditions, and little byproducts (Hoang et al., 2021). It has been widely used in hydrogel production. It expands the methods used to produce hydrogels to obtain specific architectures and qualities, making hydrogels more readily available to non-specialists in chemistry (Contessi Negrini et al., 2021). It is a broad phrase encompassing multiple reactions sharing similar features rather than a single response. Hydrogels are often formed by using click chemical reactions, including Diels-Alder, azide-alkyne, copper-catalyzed process, and thiol-ene reactions involving thiols with double bonds (Li and Xiong, 2022). The click chemistry crosslinked hydrogels have high reactivity performance, orthogonality, and biological compatibility benefits. Hydrogels produced through click chemistry have several applications, including tissue engineering, wound healing, and drug delivery (Park et al., 2020). Ding et al. have synthesized the thiol-ene click chemistry pH/thermo-responsive injectable hydrogel from chitosan and PNIPAM for promising tissue engineering applications. The histological examinations and human bone marrow mesenchymal stem cells demonstrate that the hydrogel is cytocompatible. After five days of injection in vivo, the subcutaneous tissue is revealed without any symptoms of inflammation. The findings suggest that the novel hydrogel could be an innovative injectable system for drug delivery and tissue engineering applications (Ding et al., 2020). Ali et al. have synthesized injectable hydrogels via click chemistry from gelatin for sustained and controlled drug delivery applications. They have reported that hydrogels processed desirable physicochemical and cytocompatibility for controlled release of doxorubicin (Rizwan et al., 2023).

2.2.3. *Dynamic hydrogels*

Polymer networking with dynamic crosslinks exhibits self-healing, adaptable, and recyclable properties. These qualities are apparent based on the durability and duration of the dynamic bonds. Macroscopic characteristics could be controlled at the molecular scale by adjusting the stability and reactivity of crosslinks (Zheng et al., 2021). Moreover, when crosslink density and dynamics alterations happen due to an external factor, these materials display adjustable macroscopic characteristics. External factors like pH, temperature, and magnetic field were used to reversibly adjust the characteristics of polymer networks (Podgórski et al., 2020). Hydrogels, which have structures and moisture content comparable to tissues, can be enhanced by incorporating features that are adjustable externally and reversed. Conventional stimuli like pH or temperature have limitations in terms of biocompatibility; however, light is considered an optimal stimulus. Light can be externally administered with accurate spatial and temporal regulation at specified wavelengths and intensities (Podgórski et al., 2020). Qiao et al. have synthesized self-healing dynamic hydrogels as wound dressings with conductive and antibacterial activities for infected wound healing applications. The hydrogels exhibit high antimicrobial efficacy,

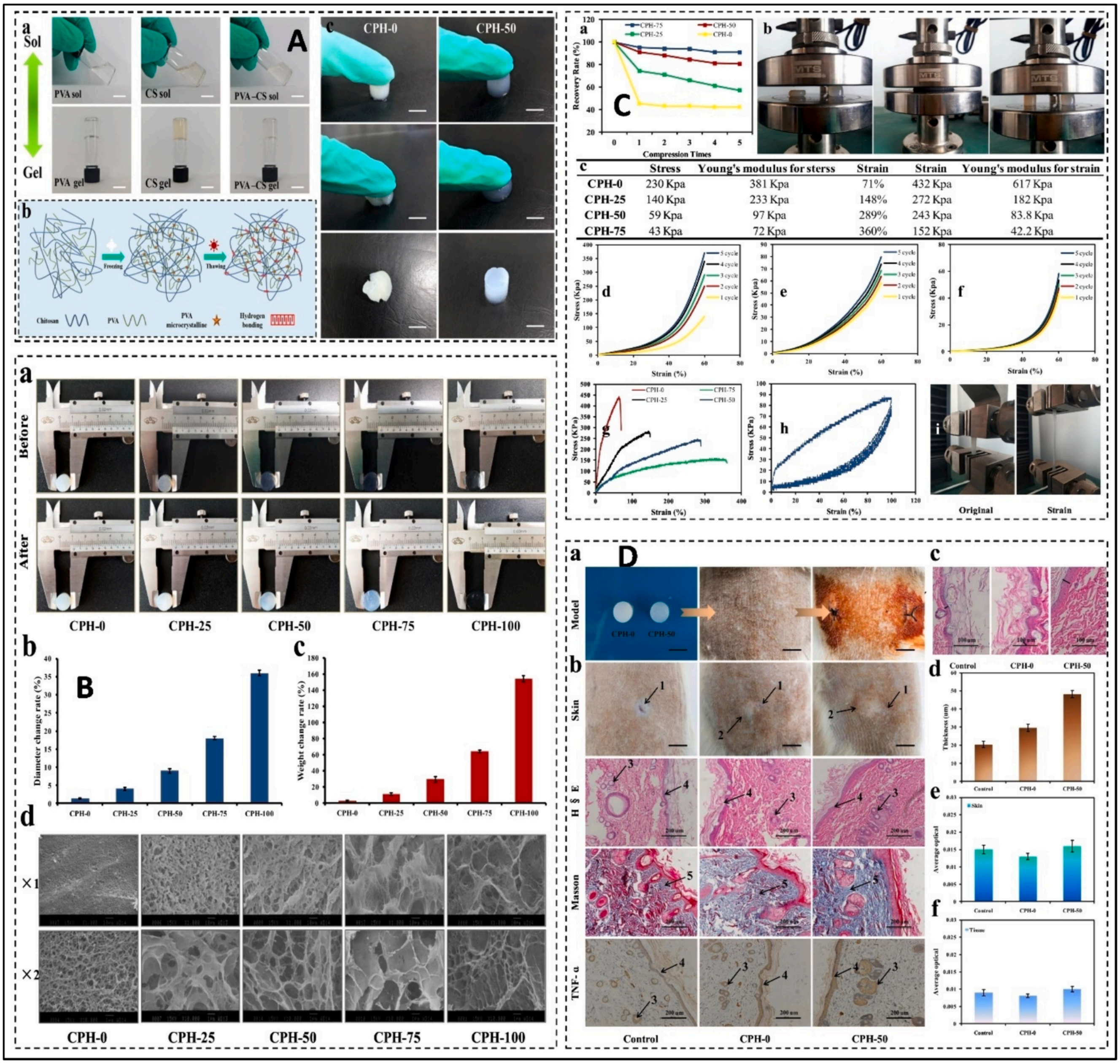

Fig. 5. The chemically crosslinked hydrogels for tissue engineering applications. (A) Digital photographs of crosslinked hydrogels and the proposed chemical interaction diagram. (B)Digital photographs measuring diameter, diameter changing, weight changing, and surface morphology of the crosslinked hydrogels. (C) Different mechanical behaviour of the hydrogels with digital photographs of the machinal testing. The digital photographs of the wound contraction and other assays (Bi et al., 2020) with permission from Elsevier.

appropriate conductivity, excellent self-healing capabilities, strong biological compatibility, hemostatic properties, and antioxidant effects. The results showed that hydrogels are suitable for wound healing, dressing, and treating infected skin wounds (Qiao et al., 2023). Liang et al. have reported the synthesis of dynamic crosslinked hydrogel sealants as wound dressing materials for infected wound healing applications. The hydrogel is injectable, highly biocompatible, exhibits antibacterial capabilities, flexible adhesion, and hemostatic characteristics, and is responsive to near-infrared (NIR) light. The in vivo test in rats utilizing an infected full-thickness skin wound model showed that the adaptable hydrogels were highly effective in healing infected wounds (Liang et al., 2021).

2.2.4. Double-network hydrogels

Hydrogels with a double network show promise as soft-yet-tough materials, and they are incredibly strong and mechanically durable by nature. This is due to their distinctly different network structures, significant interpenetrating network entanglement, and efficient energy dissipation (Liu et al., 2023). The present chemical inventory contains an abundance of network monomers. These offer the chance to investigate the underlying relationship and create innovative Double network hydrogels. Double network hydrogels compare network structures, mechanical characteristics, and hardening approaches (Huang et al., 2022). These support the derivation of novel design concepts for the upcoming tough hydrogels. It has been shown that double-network hydrogels have incredibly high structural strength and durability. In terms of toughness and longevity, these are similar to cartilage and rubber (Aldana et al., 2021). Wan et al. have synthesized the double network hydrogel as a wound dressing from chitosan with controlled release of a small herbal biomolecule with promoted wound healing and repair applications. They have observed that the double network hydrogels have appropriate physicochemical, morphological, and biocompatible characteristics for wound healing applications. The in vivo animal studies showed that the hydrogel patch promoted angiogenesis and collagen formation, leading to more efficient wound repair and regeneration. The developed double network hydrogel would be a potential wound dressing for wound healing applications (Wan et al., 2023). Cao et al. have synthesized the double-network hydrogels via the photo-crosslink method as wound dressing material from gelatin and oxidized sodium alginate for diabetic wound healing applications. The hydrogel significantly reduces inflammation, as exhibited by an in vivo mice model. It has promoted the process of re-growing the outer layer of skin and forming new tissue, showing potential for improving the healing of wounds in diabetic patients (Cao et al., 2023). Zhang et al. have synthesized double network hydrogel as wound dressing from gentamicin sulfate, sodium alginate oxide, and glycidyl methacrylate gelatin. These hydrogels have improved injectability, hemostasis, and antimicrobial activities, and double-network crosslinked hydrogels may effectively meet a wide range of nursing needs, from wound healing to generating epithelium. The results demonstrated promise as a wound dressing material for managing diabetic wound applications (Zhang et al., 2022).

3. Fundamental properties of hydrogels

Tissue growth requires appropriate engineering and design parameters for hydrogels in tissue engineering and regenerative medicines (Fig. 6). Hydrogels must be biocompatible to work appropriately in vivo to avoid cell damage and immune system reactions (Gulfam et al., 2023). Similarity to natural ECM, hydrogels facilitate gene expression, migration, proliferation, and adherence of cells. Desired swelling, degradation, and crosslinking density of the hydrogels influence their mechanical characteristics. Enzyme activity, hydrolysis, or dissolution control the biodegradation of crosslinked hydrogels, enhancing their mechanical characteristics. More robust crosslinked hydrogels may improve cell adhesion, proliferation, and migration to support tissue regeneration because they are more mechanically and structurally stable (Li et al., 2021). The physicochemical and biomedical properties of hydrogels have been summarized in Table 1.

3.1. Physicochemical properties

3.1.1. Degradation

One crucial component of tissue engineering and regenerative medicine is the degradation of hydrogels. The hydrogel breakdown rate can be affected by several factors, including the hydrogel formulation, crosslinking density, environmental factors, and the presence of enzymes. Although certain hydrogels may degrade enzymatically, there are two primary processes by which hydrogels biodegrade (Ahmad et al., 2019). Hydrogels made of peptides or proteins can be biodegradation by proteolytic enzymes such as collagenases or matrix metalloproteinases. Encapsulated therapeutic substances can be released gradually and under control through enzymatic biodegradation. Hydrolytic degradation involves the interaction of water molecules with polymer chains, leading to their disintegration. Water seeps into the polymer network, causing bond cleavage that may lead to a slow degradation of hydrolyzable bonds in hydrogels (Markwalter et al., 2021). Changing the composition and crosslinking density of hydrogels can control the degradation rate and may influence the degradation kinetics. These include altering the length of the polymer chain, adding hydrolyzable links, or varying the degree of crosslinking. The hydrogels can be fabricated with controlled degradation for long-term tissue engineering scaffolds or short-term drug delivery. Hydrogel materials with excellent degrading behaviour are being developed and studied in tissue engineering and regenerative medicines (Liu et al., 2021; Aslam Khan et al., 2024).

3.1.2. Wettability

Wettability is also an essential property of biomaterials that determines their hydrophilicity and hydrophobicity. It is a surface phenomenon, and the wetting behaviour depends upon the chemical composition, surface roughness, and functional groups of the hydrogel (Kencana et al., 2022). The wettability of hydrogels critically determines their performance and applications, particularly in tissue engineering and regenerative medicines. Hydrophilic hydrogel has a small contact angle, usually less than 90° (Chen et al., 2023). It signifies that the water droplet spreads and wets the hydrogel surface, suggesting a great affinity for water. Hydrophilic hydrogels absorb water, making them excellent for wound dressings, medication delivery systems, and tissue engineering applications (Jacob et al., 2021).

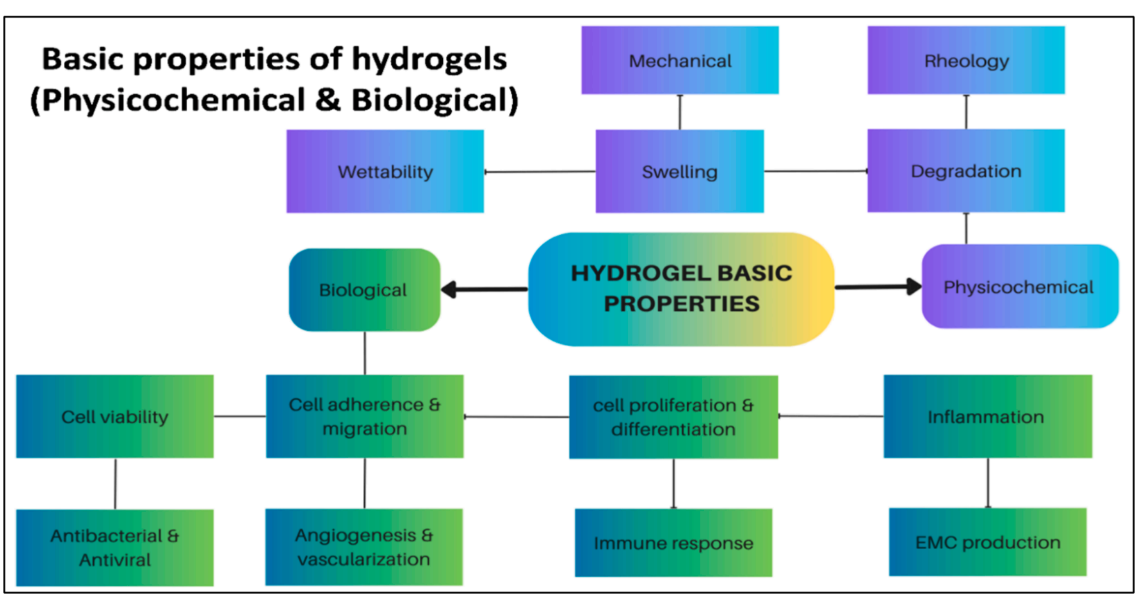

Fig. 6. The basic physicochemical and biological properties of hydrogels in tissue engineering and regenerative medicines.

Table 1
The fundamental properties of hydrogel have been summarized in tissue engineering and regenerative medicine.

Fundamental properties	Parameters	Composition	Hydrogel type	TERM Applications	References
Physicochemical properties	Degradation	Dextran, ethylene glycol	Injectable hydrogel	Drug delivery system Cartilage regeneration	(García-Fernández et al., 2020)
	Mechanical	Hyaluronic acid, chitosan	Injectable tunable gel–sol hydrogel	Drug delivery system	(Guo et al., 2021)
	Rheology	Chitosan	Injectable hydrogel	Cartilage tissue engineering	(Dehghan-Baniani et al., 2020)
	Swelling	Arabinoxylan, chitosan	Composite hydrogel	Drug delivery Skin wound healing	(Khan et al., 2021)
	Wettability	Arabinoxylan, guar gum	Hydrogel film	Drug delivery Skin wound healing	(Khan et al., 2020)
Biological properties	Cell viability and proliferation	Chitosan, guar Gum, polyvinyl alcohol	Hydrogels film	Drug delivery Skin wound healing	(Khan et al., 2021)
	Cell differentiation	Sodium Alginate	Hydrogel membranes	Drug delivery Tissue regeneration	(Khan et al., 2022)
	Cell adherence and migration	Chitosan	Modified hydrogel	Wound healing	(Lin et al., 2020)
	Angiogenesis and vascularization	Gelatin, chitosan	Hybrid hydrogel	Bone tissue engineering	(Jiang et al., 2022)
	Antibacterial and antiviral	Alginate	Hydrogel film	Skin tissue engineering	(Hurtado et al., 2022)

3.1.3. Swelling

When a hydrogel takes in and holds onto water or other liquids, it swells, and the 3D polymeric network and hydrophilicity of hydrogels cause them to expand. Hydrogel's dehydrated polymer chains draw in and absorb solvent molecules such as water. Absorption relies on the hydrogel's composition, crosslinking density, and surrounding environment. It elongates and splits polymer chains, expanding the hydrogel structure. The degree of crosslinking and chemistry influence hydrogel swelling. Hydrogels with greater water affinity and swelling ratios contain more hydrophilic functional groups, like hydroxyl or carboxyl—with reduced crosslinking density, resulting in higher swelling and water absorption ratios. The concentration of ions, temperature, and pH all affect hydrogel swelling. Changes in pH can alter the structures of functional ionization, affecting hydrogel expansion behaviour and electrostatic interactions. Volume phase transitions in thermoresponsive hydrogels can alter their expansion behaviour (Rizwan et al., 2021; Ding et al., 2020). The osmotic pressure and hydrostatic interactions of the electrolytic solution influence hydrogel swelling. Biological applications are impacted by hydrogel swelling. Controlled-expansion hydrogels are used in biomedical applications for tissue engineering and medicinal delivery. Hydrogels can absorb and release drugs, developing a moist environment encouraging cellular activity and tissue regeneration in swelling and fluid retention cases. Hydrogel swelling varies according to usage and composition. Hydrogels can inflate and shrink without causing structural harm. Several hydrogels may swell irreversibly, altering their structure and characteristics due to physicochemical changes in the polymer network (Divyashri et al., 2022).

3.1.4. Mechanical

Hydrogels have considerable and robust mechanical properties due to their high water content and polymer network structure. The main determinants include the kinds of polymers, level of crosslinking, functional groups, and synthesis process. The hydrogels have elastic and viscoelastic properties that make them suitable for several biomedical applications, including tissue engineering, drug delivery, and other biomedical applications (Todros et al., 2022). When force is applied, hydrogels respond elastically, reverting to their previous shape. The elastic response of a polymeric network is its capacity to stretch and change under strain, and it returns to its original shape upon removal of the stressor. The crosslinking density and polymer chain flexibility determine elasticity, and hydrogels act mechanically differently due to swelling. The absorption of water or other solvents causes hydrogels to swell and expand; this process can alter the hydrogels' mechanical characteristics and shape stability (Podstawczyk et al., 2021). Hydrogel strength is influenced by crosslinking density, polymer chain length, and reinforcing chemicals. Hydrogels can undergo deformation without degrading. By varying these factors, hydrogel mechanical strength can be tailored for tissue engineering and regenerative medicine. Young's modulus is a commonly used parameter to characterize the elastic behavior of hydrogels (Jin et al., 2020). It measures the stiffness of the hydrogel; the value is highly dependent on the crosslinking density and composition. The hydrogel's ability to support a force without fracturing is typically measured using its tensile and compressive strengths. For hydrogels to be used in load-bearing applications, they must possess the toughness—the capacity to absorb energy and deform without fracturing (Petelinšek and Mommer, 2024; Fuchs et al., 2020).

3.1.5. Rheology

Understanding how materials flow under mechanical stresses, particularly under shear strain stress, is made easier with rheology, which is the flowing and distorting phenomenon under the tension of hydrogels. Injectable hydrogel design, stability, and force response are determined by the varying rheological and viscoelasticity of complex hydrogels (Bertsch et al., 2022). Hydrogel is viscoelastic due to trapped solvent molecules, crosslinking density, and polymer chain mobility. The physically crosslinked hydrogels with long polymer chains that tangle during the shear experience have more shear-thinning. It is possible to shear-thicken hydrogels containing high polymer chain concentrations or fillers made of particles (Uman et al., 2020).

3.2. Biological properties

Hydrogels are crucial in tissue engineering and regenerative medicine applications due to their biological properties that influence the interaction of hydrogels with host tissues. They may promote tissue repair and regeneration due to their inherent ECM-like behaviour. Here are some essential biological properties of hydrogels in tissue engineering and regenerative medicine as following:

3.2.1. Cell adherence and migration

The hydrogels have promising effects on cell adherence and migration due to the microenvironment provided by the hydrogels. Cell adherence and migration are critical processes in tissue engineering and regenerative medicine. These processes are essential for producing functional and well-integrated tissue replacements, as cell adherence refers to the initial interaction between cells of the host site and the hydrogel surface (Chen et al., 2020). Hydrogels have various functional groups and are loaded with growth factors that stimulate signalling molecules involved in the cell dynamic adhesion process. However, hydrogels promote cell adhesion, and hydrogels can improve it through surface modification, biofunctionalization, surface irregularity, and surface topography. The hydrogels are crucial in tissue engineering due to their multifunctional characteristics that develop interaction with host tissue (Han et al., 2022; Abbaszadeh et al., 2023). The cells migrate throughout the hydrogel scaffold to ensure homogeneous tissue development. Cell-cell interactions with hydrogels and endothelialization are more critical features of the hydrogels during cell adherence and migration (Liu et al., 2020).

3.2.2. Cell proliferation and differentiation

The hydrogels have several available functional groups and active sites, which promote cell adherence properly and lead to cell proliferation, differentiation, and migration to repair and regenerate damaged tissues or wounds. The hydrogels provide a sufficient microenvironment that supports new tissue development through cell differentiation and proliferation. The newly developed tissue or organ has essential mechanisms that are functional and well-integrated (Chen et al., 2019). The hydrogels may control cell division, which increases the number of cells in a tissue, which is called cell proliferation. Proper cell proliferation must be achieved for tissue engineering if the hydrogels bear desirable mechanical behaviour, surface chemistry, and pore size porosity, some of these attributes. The hydrogels with optimized behaviour are crucial for tissue engineering to achieve cell proliferation and differentiation because they allow functional tissue constructs to be produced (Lin et al., 2021; Khan et al., 2022). The hydrogels should be guided in tissue engineering for cell differentiation to repair or regenerate tissues with proper biological properties to maintain function. The microenvironment generated by the hydrogels regulates cell proliferation and differentiation, and the microenvironment can be modified by incorporating growth factors, the structure of hydrogel, etc. It can direct cell division, differentiation, and eventual production of functioning tissues that closely resemble with their native tissue (Nosoudi et al., 2023).

3.2.3. Cell viability

Cell viability is crucial for cell proliferation or differentiation for regeneration and repairing damaged tissue. The microenvironment of hydrogels is efficient enough to produce healthy and functional tissues by providing the active site for cell adherence that leads to cell viability, which is a critical component of tissue engineering. The hydrogel helps maintain cell viability, which promotes tissue repair and regeneration (Zhu et al., 2023). Cell viability is affected by several essential properties of the hydrogels, including cell source, pore size, structure, loading of growth factors, and availability of oxygen and nutrients. The functional behaviour of hydrogels can improve cell viability to repair the damaged tissue that successfully interacts with host tissue by supporting tissue regeneration (Zielińska et al., 2023).

3.2.4. Angiogenesis and vascularization

The hydrogels can potentially promote angiogenesis and vascularization due to their multifunctional and ECM-like behaviour. The angiogenesis and vascularization are crucial to developing viable and functioning engineered tissues and organs in tissue engineering. The hydrogel has a porosity that exchanges the waste products, supply of oxygen, and nutrients, enhancing angiogenesis (Pezzella and Kerbel, 2022). Angiogenesis is essential for assuring the survival and performance of tissue engineering and the signalling molecules under hypoxic conditions (Kes et al., 2020). These essential bioactive molecules that promote angiogenesis are vascular endothelial growth factor (VEGF) and successful vascularization, which access nutrients and oxygen crucial for the regeneration and repair of damaged tissue. Angiogenesis supports the circulation of nutrients and oxygen, which are vital in vascularization. Vascularization still presents a substantial difficulty in tissue engineering, and hydrogels can make it possible by sustaining the release of loaded, stimulating biomolecules (Cho et al., 2022).

3.2.5. Antibacterial and antiviral activities

Antibacterial and antiviral activities are the essential feature of the hydrogels. Several hydrogels have inherent antibacterial activities due to their functional and structural behaviour. The hydrogel also contains several antibacterial and antiviral therapeutic agent, and their sustained release from the hydrogels causes antibacterial and antiviral activities (Hurtado et al., 2022; Zheng et al., 2022). The safety and sterility of repaired or regenerated tissues must be achieved in tissue engineering to avoid infections and other consequences. Infections can be reduced by including antibacterial and antiviral agents in hydrogels (Chen et al., 2021). The hydrogels can be functionalized with antibacterial and bioactive molecules, including antimicrobial peptides, quaternary ammonium compounds, or silver nanoparticles. The implant surface is sometimes coated with antibacterial and antifungal agents that prevent bacteria from sticking and promote tissue regeneration (Xu et al., 2021).

4. Hydrogel applications in tissue engineering and regenerative medicines

Hydrogels have attracted considerable interest in tissue engineering, drug delivery, and other biomedical applications due to their unique properties (Fig. 7). Hydrogels can function as scaffolds to facilitate cell growth, attachment, and proliferation. They imitate the natural ECM and provide a 3D environment to guide cell behaviour and tissue formation (Qazi et al., 2022; Al-Arjan et al., 2022; Khan et al., xxxx). Therapeutic substances, including growth factors and medications, can be delivered in a controlled manner through the engineering of hydrogels. Target tissue can be treated locally and continuously with the gradual release of these therapeutic agents over time from the hydrogel matrix. It works particularly well to encourage tissue repair and regeneration (Wang et al., 2022; Fakhruddin et al., 2021). The moist wound environment that hydrogels with wound-healing capabilities can preserve promotes cell migration, speeds up tissue regeneration, and wards off infection. Because hydrogels mimic the mechanical characteristics of the target tissue, they develop an environment conducive to tissue formation. Researchers are continually developing new hydrogel compositions to get around problems and improve tissue engineering and drug delivery results (El-Husseiny et al., 2022).

4.1. Tissue engineering

Tissue engineering is a biomedical engineering strategy that combines cells, engineering, and materials techniques. It has the appropriate biochemical, physical, and chemical properties components to repair and maintain various tissues (Ding et al., 2022; Aslam Khan et al., 2020). In tissue engineering, cells are frequently used to produce new, healthy tissue for medical applications by being positioned on tissue scaffolds. However, it is not only used in applications that include tissue scaffolds and cells but was formerly regarded as biomaterials (Ghaffarinovin et al., 2021; Hassan et al., 2021). It can now be considered a distinct discipline due to its expanding scope and significance, and tissue engineering refers to techniques to replace or restore organs and tissues, including bone, dental, cartilage, blood vessels, the bladder, skin, and muscles. There are frequently specific mechanical and structural requirements for the tissues involved to function properly. This phrase also describes efforts to use cells inside a synthetic support system to perform specific biochemical operations (Burley et al., 2023).

4.1.1. Bone tissue

Disease-related severe bone damage, such as serious trauma, injuries, and bone cancers, is not able to mend itself. Conventional surgical treatment’s possible adverse effects are infection, irritation, and

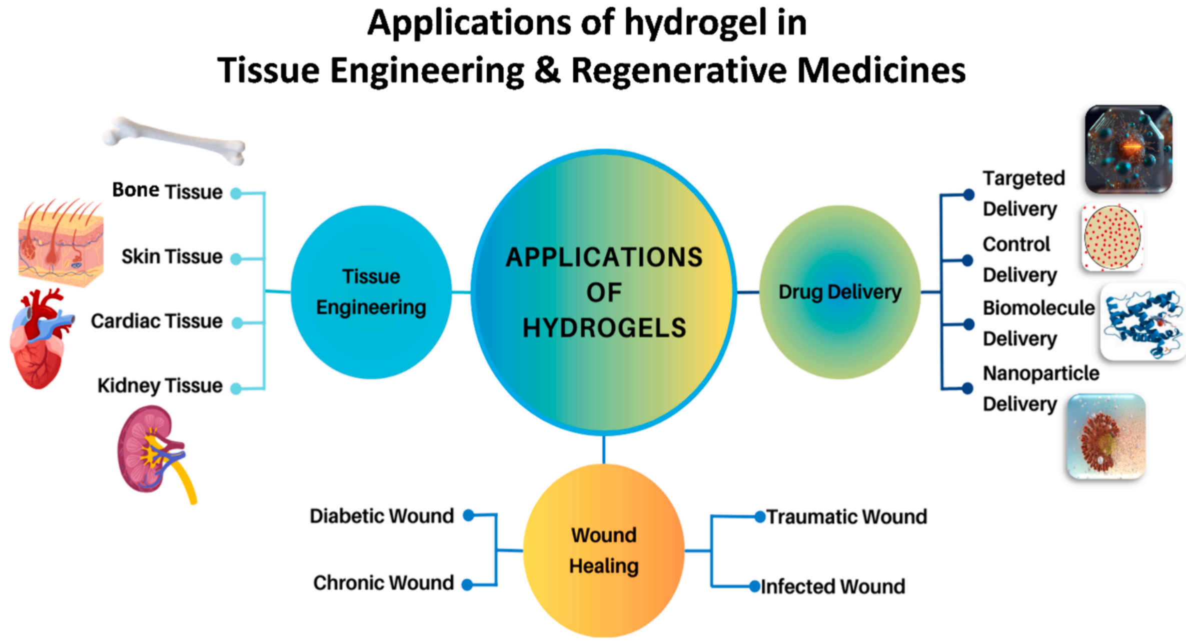

Fig. 7. Different biomedical applications of hydrogels in tissue engineering and regenerative medicines.

discomfort. It is a biocompatible novel biomaterial with tunable mechanical characteristics (Xue et al., 2021). In bone tissue engineering, hydrogel is frequently employed as a scaffold for cell adhesion and growth factor transfer to improve the suitability of hydrogel for treating bone disorders locally. The hydrogel manufacturing techniques should be integrated with superior synthetic materials and cutting-edge technology in various domains to enhance drug release control in terms of timing and orientation (Abdollahiyan et al., 2020). Bin Liu et al. have developed mesenchymal stem cells (MSCs), which incorporate composite hydrogels from gelatin and alginate for critical-sized bone healing. They loaded LAPONITE® into the polymeric matrix of the hydrogels and used rat calvarial as an in vivo defect model. They reported that the loaded cells have exhibited excellent cell viability and proliferation in vitro. They also reported that the composite hydrogels loaded with cells promoted bone healing more than those loaded without cell-loaded hydrogels. They have concluded that these composite hydrogels would be potential composite materials for critical-sized bone healing applications (Liu et al., 2020). Zhe Shi et al. have developed injectable composite hydrogels from nano-hydroxyapatite, nano-silicate-reinforced, and gelatin-methacryloyl with enhanced biomimetic and biocompatibility behaviour for bone tissue engineering. They have observed that incorporating enhanced compositional similarity of composite hydrogel with natural bone. They have reported that MSCs encapsulated hydrogel exhibited more potential for defective bone healing (Shi et al., 2021). Hussain et al. have developed composite hydrogels from GelMA-catechol and surface functionalization by coating FeHAp to enhance their bioactivity and mechanical robustness for bone tissue engineering (Fig. 8). They have conducted structural, morphological, in vitro, and in vivo analyses and reported that the composite hydrogels would be a potential material for bone healing appellations with enhanced structural and robust mechanical characteristics with in vivo bone healing (Hussain et al., 2023).

4.1.2. Cardiac tissue

The most common cause of death globally is coronary heart disease, which is caused by inherited bicuspid valve stenosis, which can be detected by calcifying the aortic tri-leaflet valve. It ranks third in the globe in terms of heart disease prevalence after high blood pressure and heart failure (Zhang et al., 2023; Khan et al., 2023). Alternative treatments are essential for restoring cardiac health after a heart attack because surgery typically replaces diseased heart valves (Chioncel et al., 2023; Khan et al., 2022). Heart valve damage has long been treated surgically with mechanical and bioprosthetic valve replacement. Each of these instruments has significant disadvantages and runs the risk of raising the death and disability toll. Because mechanically operated valves can induce bleeding and thrombosis, they must be treated with lifelong anticoagulation (Kellam et al., 2023; Khan et al., 2023). The artificial valves have a limited lifespan and may cause immunological problems due to deterioration, calcification, and fibrosis. These obstacles have spurred the development of tissue engineering alternatives to valve methods. Yutong He et al. have developed smart sticky hydrogels for the non-invasive prevention and healing of cardiac tissue adhesions (Fig. 9A). According to their findings, the multifunctional hydrogels they developed demonstrated the maturation and functions of cardiomyocytes both in vitro and in vivo. It promotes myocardial infarction healing by lowering oxidative damage and inflammation. It restores the damaged area's blood supply and electrical conditions (Khan et al., 2022; He et al., 2022). These are meant to replace valves in functional tissue constructs using 3D structures that can support cell growth, differentiation, and proliferation. Maintaining unilateral blood circulation through cardiac systole and diastole is the primary function of the heart valves (Vennemann et al., 2020). The cardiovascular valves open and close about four million times yearly without blockages or regurgitation. Therefore, complex substrate geometries are needed for cardiac valve transplantation to supply the valve leaflets with the best possible open and shut actions (Atari et al., 2023).

4.1.3. Skin tissue

Tissue-engineered skin substitutes are primarily intended to treat both recent and ancient wounds. Businesses have used various methods to create products that address these ailments, and skin can be replaced by cellular and acellular materials (Boyce and Kagan, 2023; Khan et al., 2023; Khan et al., 2023). Acellular skin substitutes are used as a model for dermal development, but the topic of this discussion is cellular devices. The first step in approaching the medical applications of biological tissue engineering is understanding the process of the disease's underlying cause (Atari et al., 2023; Khan et al., 2024). It hasn't been used for wound healing, although it's usually straightforward. The mechanism of persistent wound development, maintenance, and treatment has been elucidated mainly by research into the functioning of

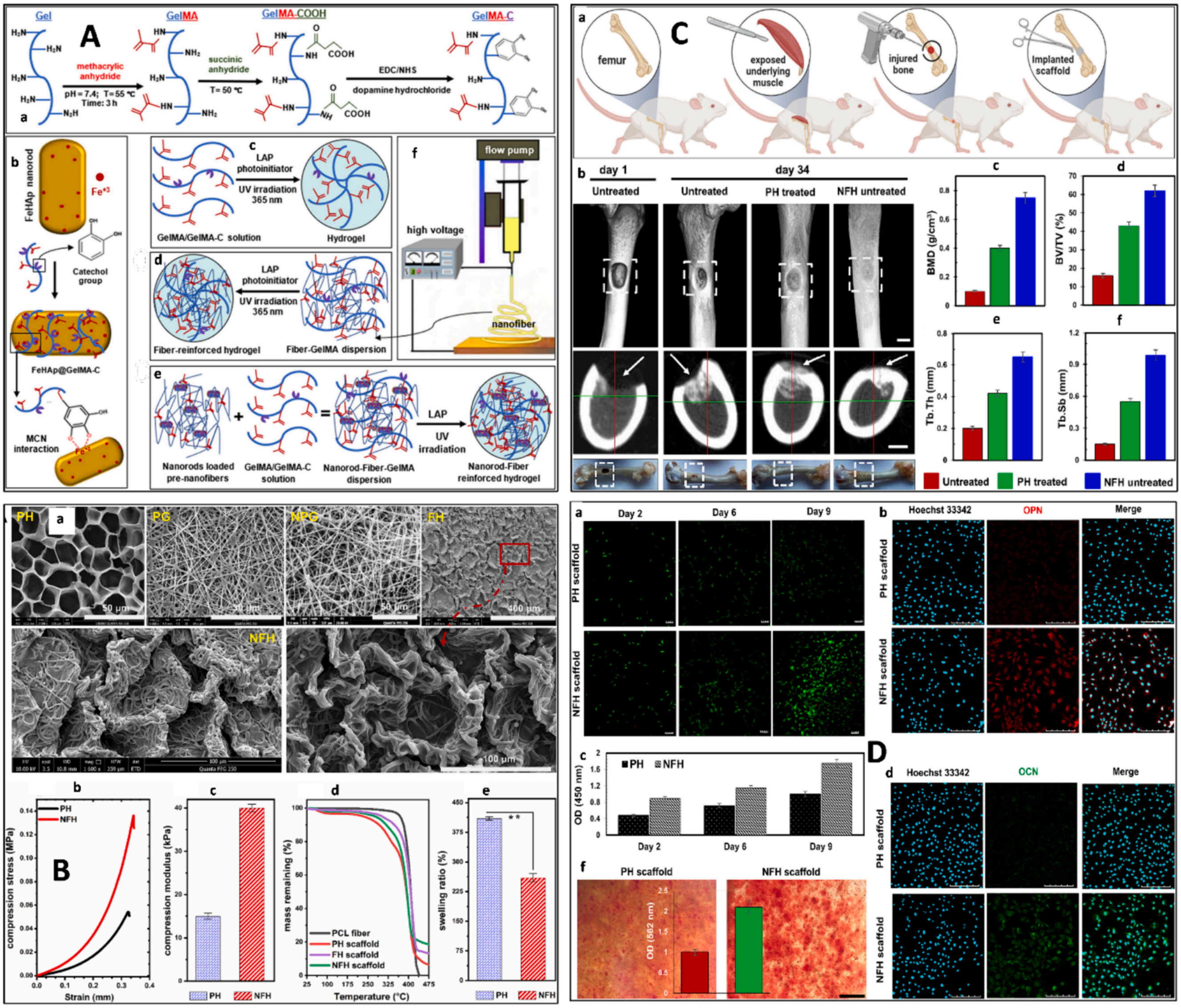

Fig. 8. Composite hydrogels for bone tissue engineering. A) Proposed chemical interaction and development of composite hydrogels. B) Surface morphology, mechanical behaviour, degradation, and swelling. C) In vivo bone healing using SD rat model and D) different in vitro analysis against osteoblast cell lines (Hussain et al., 2023), with permission from Elsevier.

tissue-engineered skin substitutes. A crucial first stage in the healing of acute wounds is the destruction of planktonic bacteria by neutrophils, which allows tissue engineering to repair and regenerate (Sharifi et al., 2023; Khan et al., 2023). Liu et al. reported that the synthesis of thermoresponsive coupled with sodium phosphate promotes skin wound healing (Fig. 9(B and C)). They observed that the synthesized hydrogels are biocompatible, antibacterial, and cell-viable by promoting angiogenesis and that they could potentially be used to heal traumatic skin defects (Khan et al., 2024).

4.1.4. *Kidney tissue*

The WHO estimates that 10 % of people worldwide have acute or chronic kidney disease. As a significant global burden on society, the number of deaths from kidney disease increased by 35 % from 2005 to 2015 (Bikbov et al., 2020). An increasing number of people are experiencing this because of various drawbacks with current therapy, such as the consoling nature of dialysis and the shortage of organ donors for transplants. Furthermore, it is asserted that pharmacological treatment administered to patients is responsible for 19–25 % of all occurrences of serious kidney injury, resulting in drug-induced toxicity (Wong et al., 2022). The lack of reliable and efficient treatments for kidney failure today emphasizes the need for new approaches. Tissue engineering has been emphasized as a potential path to improving our understanding of disease progression and treatment options (Sharifi-Rad et al., 2021). Ge and coworkers have developed a magnetic hydrogel for efficient kidney stone retrieval during ureteroscopy (Fig. 9D). They also reported that the hydrogel is cytocompatible with antibacterial activities (Ge et al., 2023).

4.2. *Wound healing*

Wounds are abnormalities or ruptures in the skin caused by thermal or physical trauma that compromises the structural and functional properties of the tissue. One of the most essential phases in the complex physiological process of wound healing is tissue regeneration (Abbaszadeh et al., 2023; Hu et al., 2019). The primary goal of wound care is to hasten the healing process while preventing scar formation. The dehydrated crusts on the wound's surface prevent epidermal cells from migrating throughout the healing process (Xie et al., 2022; Khan et al., 2024). However, epidermal cells can move through wound

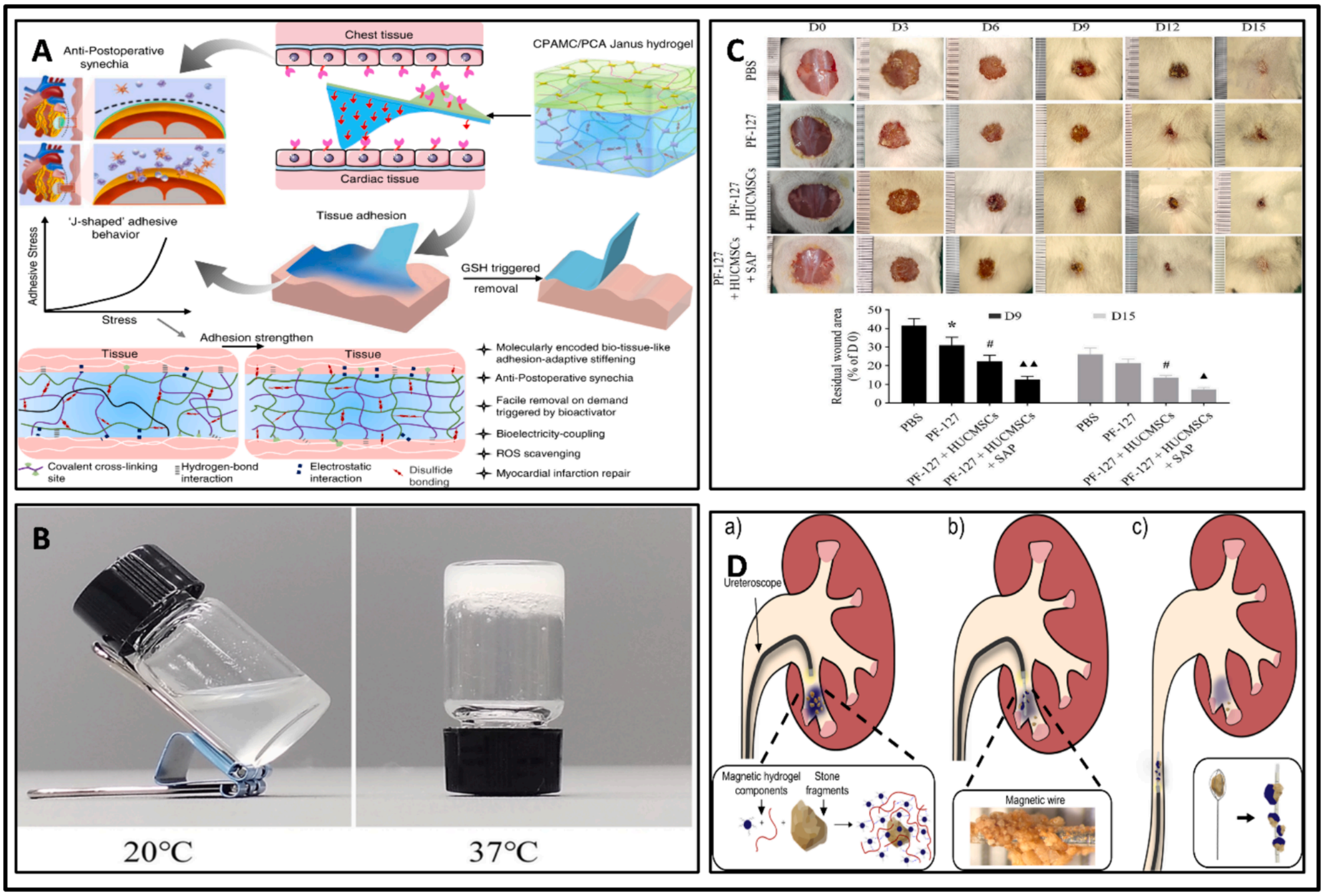

Fig. 9. Tissue engineering application of hydrogels. (A) Non-invasive hydrogel for cardiac tissue repair (He et al., 2022), with permission from Nature Publishing Group. (B) Thermoresponsive hydrogel and its phase transformation at different temperatures and (C) skin wound healing against mice model (Liu et al., 2023), with permission from Nature Publishing Group. (D) Magnetic hydrogel for removal of kidney stones after ureteroscopy (Ge et al., 2023), with permission from Nature Publishing Group.

exudate more quickly when the wound is moist. Besides, wound exudate contains higher levels of fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor than in a non-moist environment (Xu et al., 2022). These will encourage cell proliferation and aid in the regeneration of tissues. The location of a skin injury, such as a blister or skin burn, may cause the skin to become infected with microbes. It prevents the wound from healing and raises the possibility of life-threatening complications or amputation. Bacterial infections can bring on inflammatory responses. Leukocyte infiltration during skin regeneration is the main cause of inflammation; these cells also participate in tissue growth and degeneration and fight against invasive infections. Leucocytes found in the exudate from the injury site help to prevent bacterial growth and lower the risk of infection. Healing of wounds is always aided by increased secretions (Liu et al., 2023). Li et al. have synthesized a photothermal-responsive hydrogel-based oxygen-releasing polymeric system for wound healing (Fig. 10 (A and B). They have reported efficient wound healing without causing major inflammation to promote wound repair and regeneration (Liu et al., 2023). Dressings for wounds help speed up healing while preserving the wound, and conventional dressings like gauze, cotton, and bandages must be changed frequently (Guo et al., 2023). These dressings can't produce a moist environment for wound healing. On the other hand, overuse of antibiotics can lead to the development of super-bacteria and a rise in bacterial resistance. Therefore, even though classic wound treatment procedures still have certain advantages in clinical application, new types of wound dressings are required to solve the shortcomings of conventional dressings (Jiang et al., 2023). Additionally, the disruption of the wound-healing process caused by insufficient angiogenesis or cell migration may damage the wound's physiological integrity. Ischemic ulcers, venous ulcers, pressure ulcers, diabetic wounds, and surgical or traumatizing wounds that do not heal or become infected can also be classified as chronic wounds (Paunică-Panea et al., 2023). Sun et al. have reported synthesizing self-healing injectable hydrogels for burn wound healing applications (Fig. 10(C and D)). They observed that synthesized hydrogels exhibited antibacterial activities against Gram-positive and Gram-negative severe infection-causing bacterial strains. Hydrogels performed suitable adherence, promoting wound healing with reduced inflammation (Sun et al., 2022).

4.3. Drug delivery

Various strategies, formulations, production techniques, preservation methods, and technological innovations can accomplish drug delivery. Many ideas can be used to deliver the therapeutic substance where it is wanted and produce the desired medical effects. Still, hydrogel has become increasingly popular in tissue engineering and regenerative medicine. The target-specific site, administration technique, drug formulation, optimized efficacy and bioavailability, and improved patient comfort and compliance are among the principles of drug delivery (Verma et al., 2021). Different hydrogel formulations are used in drug delivery to modify a medication's pharmacological kinetics and specificity. The medication must have a higher bioavailability and a longer half-life to improve the effectiveness of therapy, even though the administration route and the drug delivery technique are two distinct concepts. Hydrogel has gained recognition in drug delivery because of

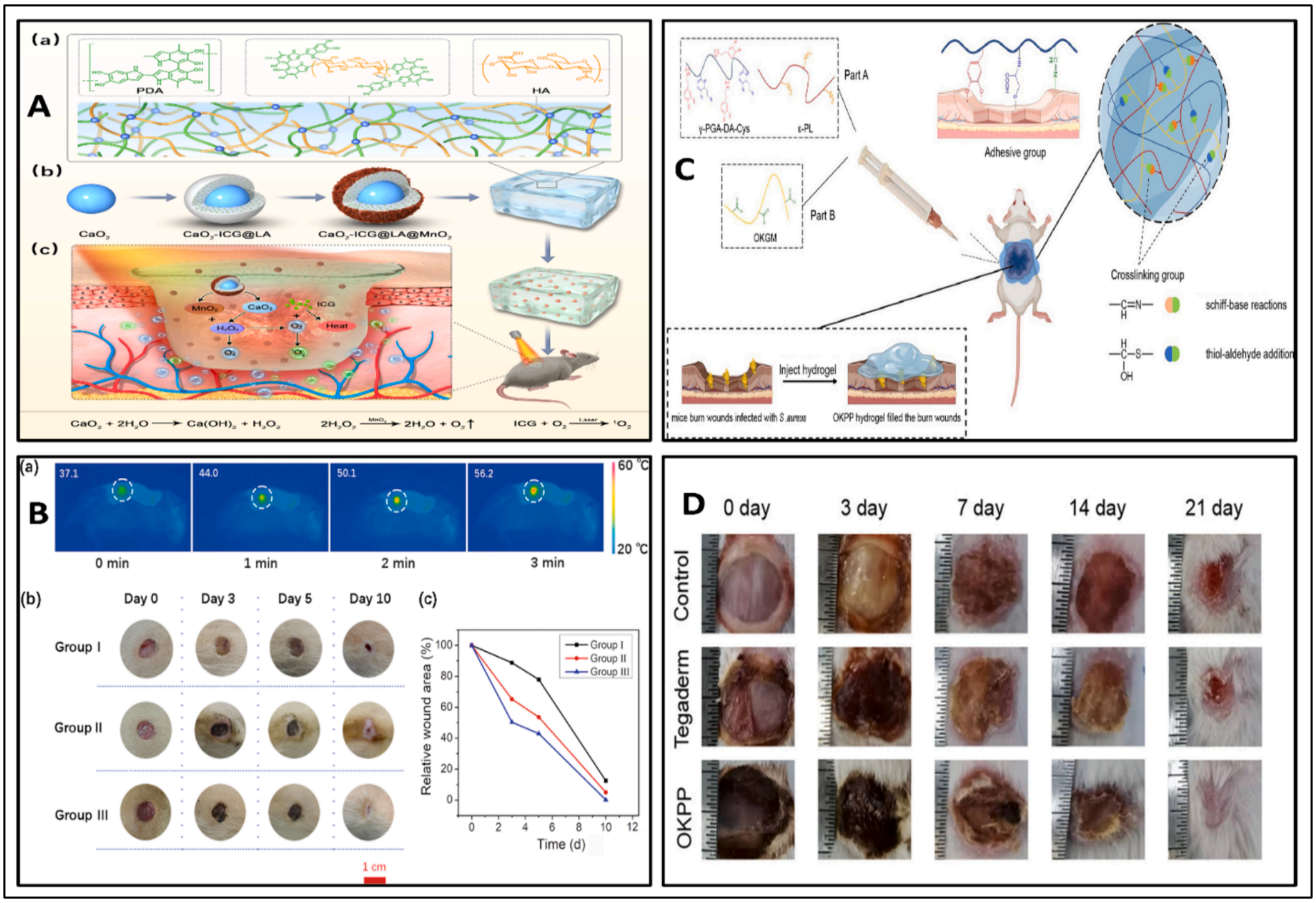

Fig. 10. Hydrogel wound healing potential against different wounds. (A) schematic diagram of synthesized hydrogels incorporated with nanoparticles and (B) relative wound healing using different groups (Liu et al., 2023), with permission from Nature Publishing Group. (C) schematic diagram of hydrogel synthesis and administration and (D) wound healing using mice model at different times against different models (Sun et al., 2022), with permission from Nature Publishing Group.

its versatile structural and functional behaviours (Benson and Roberts, 2021; Sa'adon et al., 2021). The variety of tunability of the hydrogels has delivered drugs in controlled and sustained manners. The rise in the worldwide incidence of infectious and chronic diseases is another factor that might have impacted the development of advanced drug delivery systems. The pharmacological science, pharmaceutical kinetics, and therapeutic effects can be efficiently achieved of different drugs delivery through hydrogels (Adapa et al., 2020).

4.3.1. Targeted drug delivery

Hydrogel has been used in targeted drug delivery loaded with therapeutic agents at a particular site without affecting neighbouring tissues under different stimulating factors, including pH and temperature (Raj et al., 2021). Interest in this field has increased because of the potential advantages of tailored pharmaceutical administration in treating chronic illnesses, cancer, and other conditions. The highly developed drug-targeted system must get past the host tissue's defences and reach the predicted action spot to achieve the desired targeted effect. Tissue engineering has investigated novel nanotechnology, including nanohydrogels and nanogels, for drug delivery to specific tissues to address medical problems (Wang et al., 2021). Huong Thi Hoang et al. have synthesized thermo-/pH-responsive hydrogels from chitosan, polyacrylic acid, and bis-tetrazine-poly(N-isopropyl acrylamide) by "click" chemistry for colon-targeted applications (Fig. 11). They observed the synthesized hydrogels processed with high porosity with sustained drug delivery under pH-responsiveness, and 92 % drug delivery was observed after 48 at 37 °C. They have confirmed that the hydrogels are biodegradable, non-toxic, and cytocompatible against fibroblast cell lines and would be potential drug delivery for colon-targeted systems (Hoang et al., 2021).

4.3.2. Controlled drug delivery

The multifunctional behaviour of the hydrogels is due to a variety of functional groups, and these may interact with therapeutic agents for their sustained release. While conventional drug delivery systems have low bioavailability and plasma levels, the drug delivery system can release therapeutic agents with clinical effects (Zhang et al., 2021). The tightly crosslinked hydrogels provide prolonged release of therapeutic agents that may be ineffective without a reliable delivery system. The drug must also be administered at the intended tissue site at a controlled rate to achieve maximum efficacy and safety (Teymourian et al., 2020). Developing hydrogels with controlled drug delivery is a solution to the issues with traditional drug administration. Over the past 20 years, hydrogel drug delivery technologies have undergone substantial evolution, surpassing micro/nanoscale drug delivery with controlled or sustained distribution (Sun and Hou, 2022). Shangwen Zhang et al. synthesized carboxymethyl chitosan microspheres and loaded them into the polymeric matrix of the hyaluronic acid and gelatin hydrogels with controlled drug delivery to treat inflammatory bowel diseases (Fig. 12). They have reported that the formulation has sustained the release of curcumin in vitro, and pharmacodynamic studies have shown that hydrogel-loaded curcumin has excellent therapeutic approaches to colitis in mice models (Zhang et al., 2021).

4.3.3. Delivery of biological agents

Hydrogels are cutting-edge approaches for delivering agents such as

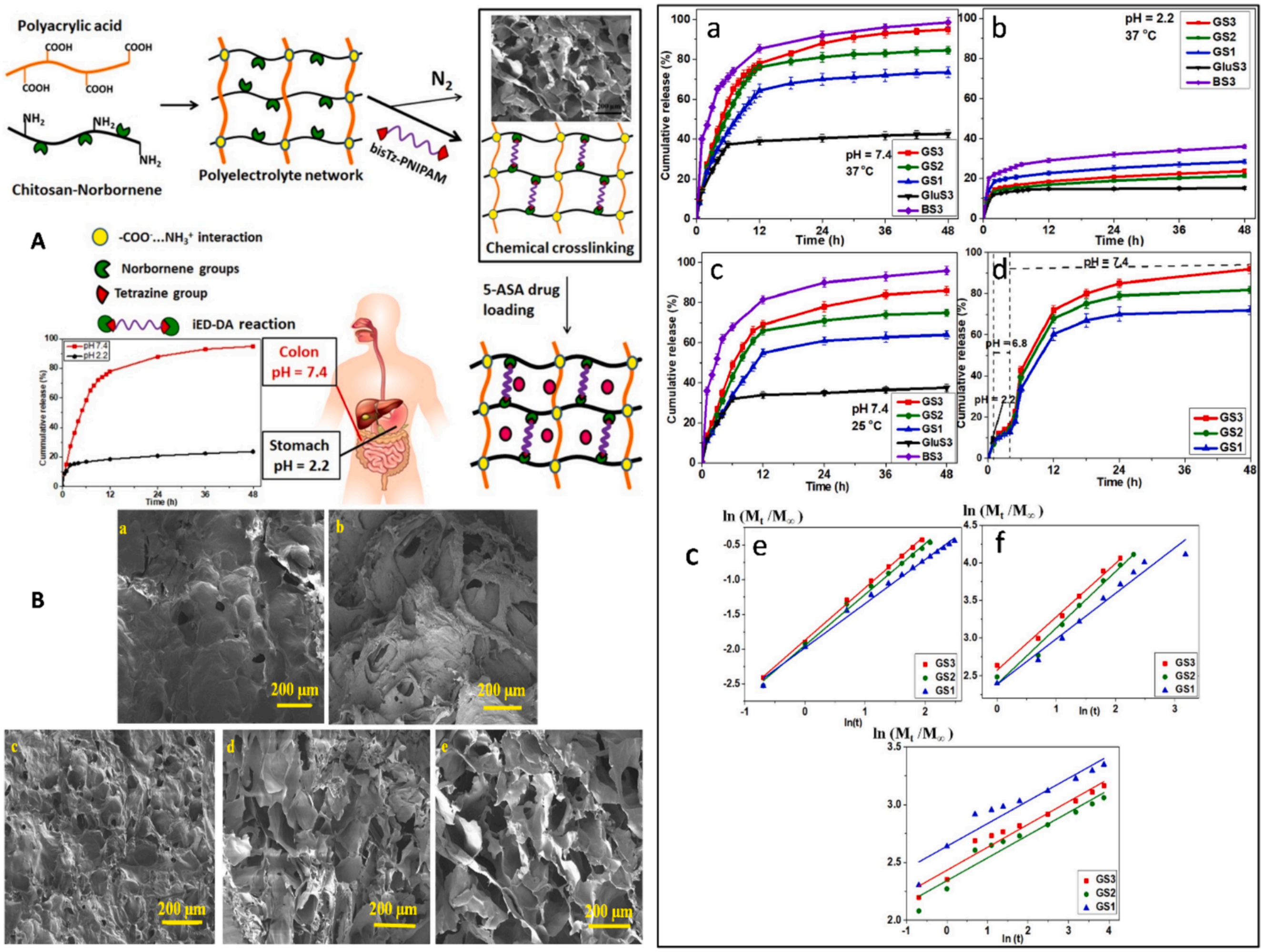

Fig. 11. The targeted drug delivery (A) proposed chemical interaction and targeted drug delivery illustration, (B) surface morphology of the hydrogels and targeted drug release under pH and thermoresponsive behaviour and release kinetics (Hoang et al., 2021), with permission from Elsevier.

peptides, proteins, antibodies, and other biological molecules. Their sustained delivery can be achieved by optimized crosslinking of the hydrogels, their improved structural properties, pore size, polymeric matrix, and electrostatic charges with the biofluids or solvents (Sharma et al., 2023). The hydrogel may undergo enzymatic degradation after being subjected to the body, causing the sustained and controlled release of the biological-based therapeutic agents. Common biological-based therapeutic agents include liposomes, RNA, DNA, peptides, proteins, etc. RNA is the most efficient and common biological agent for inside-cell delivery, such as RNA-based COVID-19 vaccines (Yoo et al., 2022). Since the DNA is administered under biologically stimulating conditions by physically or chemically interacting with the hydrogel, hydrogel-based techniques have also been employed for gene editing drug delivery (Mo et al., 2021).

4.3.4. Nanoparticle delivery

The hydrogel system has been employed to distribute nanoparticles widely used in tissue engineering and biological applications as antibacterial, antiviral, and anticancer actives (Grosskopf et al., 2020). In drug delivery systems, hydrogels containing nanoparticles have gained popularity due to the formation of unique multifunctional structures. These platforms are intrinsically functional and entirely adjustable due to the easy modification of any constituent of the NPs–hydrogel structures. These multifunctional structures can function well in medical problems when using the beneficial properties of the NPs-hydrogel individually, which might lead to less-than-ideal results (Nunes et al., 2022). The administration of therapeutic agents to the brain via systemic administration may be damaging as brain tissues are highly sensitive to the side effects of drugs if these are introduced to the bloodstream directly (Correia et al., 2022).

5. Current challenges and limitations

We have included a comprehensive summary of various hydrogel classifications based on physical and chemical crosslinking interactions already used in tissue engineering and regenerative medicines. Hydrogels, produced synthetically or derived from natural sources, must satisfy specific design criteria for use in this industry. Hydrogels composed of biopolymers offer inherent biological interaction, cell-regulated biodegradability, and biocompatibility with living tissues with sustained and controlled release of therapeutic agents. Nevertheless, they may display batch differences and typically have a small and restricted range of mechanical properties. Unlike biopolymers, synthetic polymers may be produced with exact control over their shapes and functions. Numerous synthetic polymers are not biodegradable in physiological environments. Extensive purification steps may be necessary when non-biocompatible substances are used during fabrication. However, using hydrogel systems comes with certain particular limitations. Because hydrogels have poor mechanical properties, they are challenging to handle for load-bearing applications because they have poor mechanical properties. Because hydrogels are not adhesive, they might need to be secured with a second dressing. Using them to

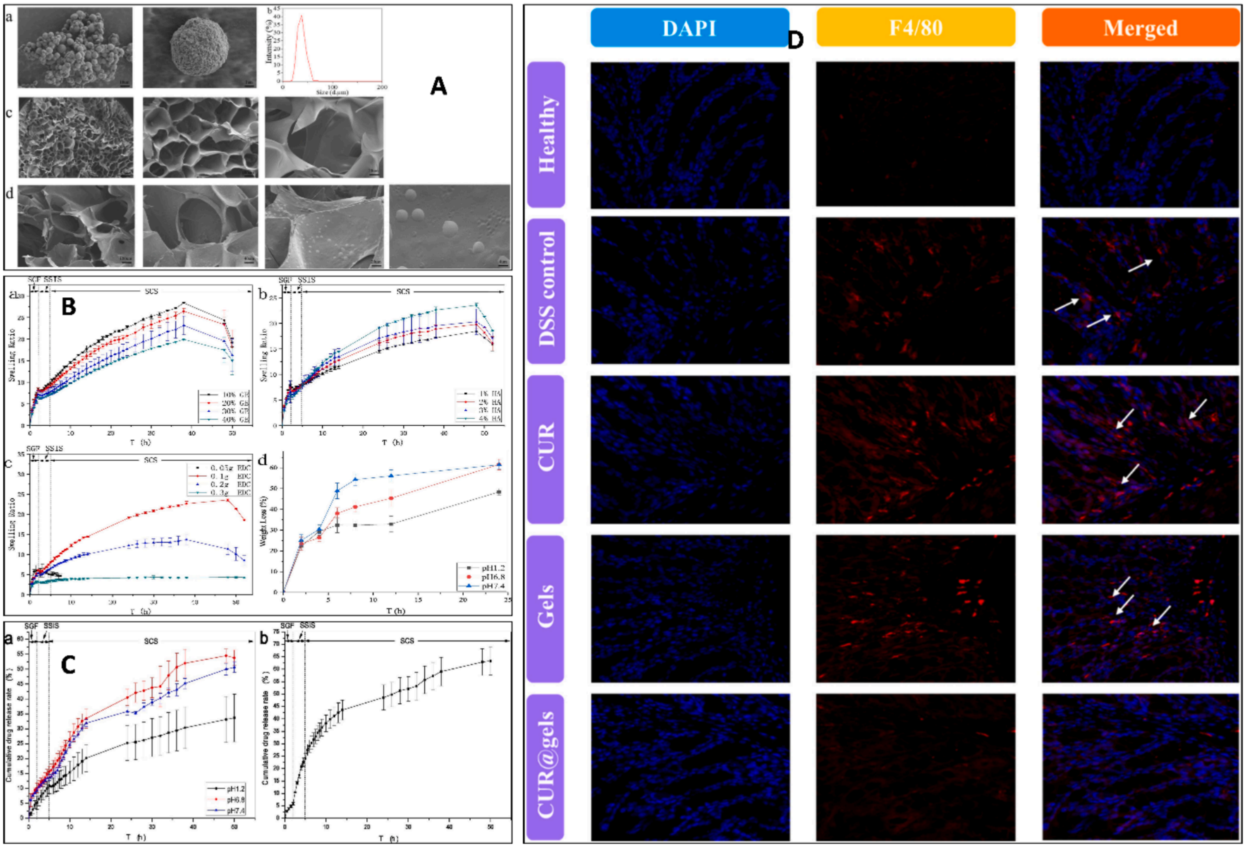

Fig. 12. Controlled drug delivery from microsphere-loaded hydrogels. A) Surface morphology, B) swelling and degradation behaviour, C) Cumulative drug release and D) Immunofluorescence staining assays in colon tissue (Zhang et al., 2021), with permission from Elsevier.

treat wounds with medium to large exudate volumes is not advised. The problem of hydrogel degradation has received significant attention recently, as hydrogels often degrade over time through hydrolysis and enzymatic processes. Biopolymer-based hydrogels are typically biodegradable and commonly biocompatible. One drawback of biopolymer-based hydrogels is the challenge of separating them from living tissue. Since they closely imitate and resemble the native tissue they substitute in tissue engineering, they also have limited flexibility.

Synthetic hydrogels have limitations due to their potential lack of biocompatibility or biodegradability. Another constraint of these systems is the challenge of sterilizing. Sterilizing hydrogels can be more complex than sterilizing other polymers because of the water content in these materials. These can enhance the detrimental impacts of sterilizing procedures. Hydrogels have valuable features and great potential for drug delivery, but they face hurdles due to their sensitivity to traditional sterilizing methods (Nasalapure et al., 2021). For a biomaterial to be approved by regulatory bodies and securely move on with clinical trials, it must endure effective sterilization. Ensuring sterility decreases the occurrence of infections associated with medical devices. It is crucial to acknowledge the unpredictability and infeasibility of forecasting the results of different sterilization technologies to establish certain standard norms and protocols and consider the intricacy of the variables, including material qualities, drug stability, and sterilizing processes. Hydrogels have difficulty controlling how quickly they biodegrade, which varies depending on the application. A faster biodegradation rate would be perfect for biodegradable hydrogels, frequently utilized in cell development as a temporary ECM until new tissue replaces them (Zhang and King, 2020). Hydrogels must remain in the target area for noticeably longer to supply the micronutrients and biologically active materials required for tissue engineering and regenerative medicine. Since biodegradable hydrogels have a unique polymer structure, they will eventually decompose entirely. They behave consistently for a few days to several months. More research is required to fully understand the nature of the degradation and how it relates to tissue engineering applications. Hydrogels are limited by the crosslinking approach's effect on the release mechanism and by the use of chemical cross-linkers. Hydrogel systems help study cell-matrix interactions, which are crucial for tissue regeneration because of their dynamic qualities and flexible characteristics (Xie et al., 2023).

6. Future perspectives and conclusions

The designs, manufacturing processes, characteristics, and uses of hydrogels in tissue engineering have changed dramatically during the last few decades. Large-scale research on producing advanced hydrogel-based matric systems in drug delivery is responsible for this development. Currently, the main focus of research is on changing the molecular structure of biopolymers to greatly enhance the mechanical and biological characteristics of hydrogels. Hydrogels are considered one of the most innovative materials in medical applications due to their unique physical, chemical, and biological properties. These were repeatedly customized for specific applications by closely examining the microenvironments in which they were found and then applying such functional modifications for further tissue engineering and regenerative medicinal applications (Zhang et al., 2021). Despite notable progress in bioengineering methods for hydrogel creation, several criteria exist. These include the following: surface hybridization, reaction times, rates of biodegradation, molecular structures, inflammatory reaction, and immune response. These materials must be carefully considered to produce more cytocompatible hydrogels for tissue engineering applications. Future developments in their structure and function may help us comprehend cell-material interactions more fully. These enable us to develop new tissues through a flexible strategy and a substitute; the hydrogels can offer a far safer and more effective method of addressing various medical problems (Zhang et al., 2022). The evolution of hydrogels since their first usage in biomedical science is the main topic of this concise review. It summarizes the main findings of studies done to change their characteristics, develop new, targeted uses, and the most current developments in drug delivery. Over the next decade, tissue engineering research may provide previously unheard-of breakthroughs in drug delivery. Research findings, however, have not yet been used for applications is an area that will demand excellent study and collaboration between researchers and physicians (Teng et al., 2023). New characterization and modelling techniques will be required in light of research progress and the future to support the systematic exploration of hydrogel application in bioprinting. Hydrogels have the potential to become smart and innovative biomaterials that can transform the area of drug delivery in the future through the use of multidisciplinary techniques (Farasati Far et al., 2024).

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CRediT authorship contribution statement

Muhammad Umar Aslam Khan: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Muhammad Azhar Aslam:** Writing – original draft, Visualization, Software, Resources, Methodology, Formal analysis, Data curation. **Mohd Faizal Bin Abdullah:** Supervision, Project administration, Investigation, Funding acquisition. **Wafa Shamsan Al-Arjan:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – review & editing. **Goran M. Stojanovic:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation. **Anwarul Hasan:** Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis.

Conflicts of interest

All authors declare no conflict of interest.

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