International Journal of Pharmaceutics 681 (2025) 125818

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Tailored polymeric hydrogels for regenerative medicine and drug delivery: From material design to clinical applications

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ARTICLE INFO

Keywords:
Polymeric Hydrogels
Wound Healing
Tissue Engineering
Regenerative Medicine
Drug Delivery

ABSTRACT

Polymeric hydrogels are hydrophilic polymer networks capable of absorbing and retaining large amounts of water or biological fluids, making them highly suitable for biomedical applications. This manuscript presents a comprehensive overview of their fundamental properties, including swelling behavior, biocompatibility, biodegradability, mechanical strength, crosslinking density, and stimuli-responsiveness, which collectively determine their clinical performance. A variety of natural and synthetic polymers are explored in the design of hydrogels, each offering distinct advantages for specific biomedical uses. The clinical versatility of polymeric hydrogels is examined across multiple application areas, including wound healing, bone regeneration, joint therapy, tissue engineering, ophtalmologie, dental medicine, drug delivery systems, and hearing-related treatments. Furthermore, this review presents real-world hydrogel-based products already in clinical use and highlights current innovations and clinical trials that are extending the frontiers of hydrogel technology. Despite these advancements, challenges like scalability, reproducibility in clinical outcomes, regulatory hurdles, and long-term safety are critically assessed, along with emerging opportunities that may shape the future of hydrogel-based therapies. By integrating materials science with clinical perspectives, this review aims to support the development and translation of advanced polymeric hydrogel systems into modern medicine.

1. Introduction

The Greek words polys (meaning “many”) and meros (meaning “parts” or “units”) are the origin of the word polymer (Pal et al., 2009). Polymers have revolutionized modern healthcare through their exceptional versatility, biocompatibility, and functional capabilities. Among these materials, hydrogels – a distinct class of polymers – have attracted particular attention due to their unique structural features and broad biomedical applicability. Polymeric hydrogels consist of interconnected three-dimensional polymer networks that are crosslinked, enabling them to absorb and retains significant quantities of water or biological fluids (Raeisi and Farjadian, 2024). Depending on the formulation, they may swell to over 400 times their initial weight (Yoshimura et al., 2006), more than 20 % of their dry weight (Vervoort et al., 1998), and even hundreds of times their dry weight (Hoffman, 2002).This water retention capacity is primarily driven by the presence of hydrophilic functional groups (e.g., amino, carboxyl, and hydroxyl) and stabilized bt crooslinking interactions, which can be physical (hydrogen bonding, vander waals forces) or chemical (covalent bonding). Hydrogels are further valued for their intrinsic

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https://doi.org/10.1016/j.ijpharm.2025.125818
Received 13 March 2025; Received in revised form 19 May 2025; Accepted 4 June 2025
Available online 7 June 2025

biodegradability, biocompatibility, and tunable mechanical and physiochemical properties (Peppas et al., 2000; Wang et al., 2025a).

Due to their biomimetic structure and capacity for cellular interaction, hydrogels have emerged as promising materials in various therapeutic domains, including tissue engineering, regenerative medicine, and drug delivery (Lu et al., 2025; Patel et al., 2024; Wang et al., 2025a; Wiese et al., 2001). Their high water content and soft-tissue-like mechanisms make them ideal scaffolds for cell encapsulation and tissue regeneration. The design flexibility of hydrogels allow for precise control over degradation rates, mechanical strength, and biological responses (Trucillo, 2024; Lu et al., 2024). More recently, the development of stimuli-responsive hydrogels, capable of reacting to environmental changes such as pH, temperature, or enzymatic activity, has expanded their clinical applicability (Protsak and Morozov, 2025).

The clinical relevance of polymer hydrogels is further underscored through their diverse applications, ranging from wound healing, bone regeneration, and joint therapy to more specialized fields such as tissue engineering, ophthalmology, dental medicine, drug delivery systems, and hearing-related treatments. In regenerative medicine, they provide structural support for cell proliferation and tissue repair in contexts such as myocardial infarction, cartilage regeneration, and chronic wounds (Carton et al., 2024). In drug delivery, their porous structure enables encapsulation and controlled release of diverse therapeutic agents, including proteins, nucleic acids, and small-molecules, by modulating polymer composition and crosslinking density (Hu et al., 2024). In addition, injectable hydrogels have gained attention for minimally invasive delivery of bioactive molecules and cells, that can transport the drugs straight to the location of interest, enhancing the results of targeted treatment Their compability with 3D bioprinting technologies further underscores their versatility (Al-Shanqiti et al., 2024; Hiroki and Taguchi, 2021; Maldonado-Codina and Efron, 2004; Visan and Negut, 2024).. Additionally, hydrogels are widely used in ophthalmic devices, wearable biosensors, and cancer therapy systems (Sun and Chen, 2024; Thirumalai et al., 2024).

To ensure that polymeric hydrogels deliver measurable and meaningful benefits in real-world healthcare settings, they must demonstrate not only biocompatibility but also clinical efficacy, an essential requirement for regulatory approval and market adoption.This demands robust material design strategies, standardized testing protocols and translational research focused on safety, reproducibility and scability. Despite recent advances, limitations such as low mechanical strength, physiological instability, high production costs, and complex regulatory pathways continue to hinder full clinical translation. In order to increase their mechanical qualities and guarantee safety and reliability in medical applications, these challenges must be overcome through sophisticated materials engineering and optimized crosslinking processes.

The purpose of this review is to provide a comprehensive and up-to-date overview of the design, functionality, and clinical applications of polymeric hydrogels in drug delivery and regenerative medicine. We aim to elucidate how material composition and structure influence the performance of hydrogels, highlight their biological interactions in therapeutic contexts and critically evaluate current challenges and future directions for successful clinical translation.

2. Essential properties of polymeric hydrogels

Here's a breakdown of the physical and chemical properties of polymeric hydrogels, including swelling, biodegradability, biocompatibility, mechanical strength, and cross-linking density.

2.1. Swelling behavior

Hydrogel's main property is their capacity to swell and absorb water, which makes them extremely adaptable, particularly for use in biomedical applications. By utilizing natural or synthetic polymers with hydrophilic side groups, hydrogels facilitate significant water uptake and enhance interactions with biological tissues, such as mucous membranes and epithelial layers. When hydrated, hydrogels typically have a soft, rubbery, and nearly viscoelastic texture, which, along with a low interfacial angle with biological fluids, minimizes the risk of adverse immune responses, contributing to their biocompatibility The extent of hydrogel swelling, governed by factors such as temperature, pH, crosslinking density, polymer composition, and the ionic strength of the surrounding medium, significantly influences its mechanical properties and drug release behavior (Lohani et al., 2023). This is particularly relevant in the design of drug delivery systems and implantable devices, where the swelling behaviour directly impacts the timing and efficiency of therapeutic release. However, in the early stages of implantation, the tightly entangled and partially hydrophobic nature of the polymer matrix can hinder water infiltration, delaying both the swelling process and subsequent drug release. As a result, drug mobility within the matrix is initially limited, which restricts its release. Nevertheless, the small amounts of water that that penetrate the implant can initiate hydrolytic cleavage of the polyester chains. One study investigated how polymer swelling affects drug release from implants composed of poly(lactic acid) and poly(lactic-co-glycolic acid). These systems were developed via hot melt extrusion to enable controlled release of dexamethasone. The researchers concluded that polymer swelling plays a central role in regulating mass transport processes by fundamentally changing the microenvironment for drug dissolution and diffusion, ultimately enabling its release following a defined lag phase (Bode et al., 2019). Hydrogel swelling is also a crucial aspect in periodontal structure tissue engineering, as it plays a significant role in cell alignment at the interface between different tissue types. Studies have shown that hydrogels can assist periodontal ligament cells (PDLCs) in aligning with the tooth roots surfaces such as dentin. In one experimental setup, dentin blocks, poly(ethylene glycol) hydrogels, and PDLCs were combined to develop a composite system that allowed for regulated PDLC alignment near the dentin interface. This cell guidance was mediated by hydrogel swelling behavior. According to experimental data, when PDLCs are cultivated within swollen hydrogels, they tend to orient perpendicularly to dentin surfaces. This is an unprecedented discovery, made possible by the synthetic polymer system, which made it possible to control the hydrogel swelling independently of other matrix features. A tensile strain gradient develops when soft hydrogels swell near rigid dentin surfaces. This gradient is strongest at the dentin surface and stimulates PDLC elongation, alignment, and changes in gene and protein expression (Fraser et al., 2022). Overall, swelling-induced strain represents a promising strategy for directing cellular alignment at soft-hard tisuue interfaces.

2.2. Biocompatibility

One of the most crucial characteristics of hydrogels for biomedical applications is their biocompatibility. This refers to the material's ability to interact with body tissues and organs whithout causing significant damage to the surrounding biological environment. Additionally, a biocompatibility hydrogel must not trigger adverse immune responses, while effectively performing its intended therapheutic or diagnostic functionmedical functions (Calo and Khutoryanskiy, 2015). Due to the inherent properties of natural polymers, hydrogels derived from this materials typically exhibit superior biocompatibility. For example, hydrogels design for skin-contact applications, such as joint movement monitoring, must demonstrate excellent biocompatibility to ensure both safety and functional performance.

Among various hydrogel matrices, silk fibroin has been widely studied for bone repair due to its biodegradability, low cost production, and favorable biocompatibility profile. In a recent study, a silk fibroin-based biocomposite hydrogel was developed by integrating tannic acid and MXene nanosheets into a double-network structure composed of polyacrylamide and silk fibroin. This engineered hydrogel displayed notable tensile strength, rapid self-recovery capabilities, and high

biocompatibility when applied topically, reinforcing its potential for biomedical applications (Wang et al., 2025b). Click chemistry has also gained increasing attention as a strategy to enhance hydrogel biocompatibility and achieve rapid and efficient crosslinkingg In a recent report, an injectable gelatin-based hydrogel was developed using click chemistry techniques. Animal studies demonstrated the successful *in vivo* injectable administration of the gelatin hydrogel, with controlled biodegradation extending over 30 days in rats, and no observable inflammatory response (Chauhan et al., 2025). These results underscore the promising role of injectable hydrogels in advancing safe and effectivebiomedical therapies.

2.3. Biodegradability

Biodegradability is a crucial property of hydrogel materials, particularly for biomedical applications like tissue regeneration, where cells require space to grow, migrate, and proliferate (Tanan et al., 2019). It refers to a material's ability to break down after interacting with biological components. Hydrogels derived from natural polymers are often decomposed by enzymes, enabling cells to spread and remodel their environment (Goswami and O'Haire, 2016). Hydrogels are prone to *in-vivo* water degradation because of their hydrophilic nature. Initially, water diffuses into the hydrogel matrix, causing to swelling and disruption of secondary and tertiary structures maintained by weak interactions, such as hydrogen bonds and Van der Waals forces. This process facilitates the hydrolytic cleavage of crosslinkers or polymer chains, ultimately resulting in solubilization of the material. Natural macromolecules and polymers are commonly biodegraded through hydrolysis and oxidation, occurring either directly in the aqueous environment or catalysed by specific enzymes (Garcia-Garcia et al., 2024). The rate of biodegradation is an important consideration, influenced by several factors like polymer's molecular weight, as well as its amorphous or crystalline structure and hydrophilic or hydrophobic characteristics. Aragon-Navas *et al.* recently investigated the biodegradability of two hydrogels design for drug delivery applications. The first hydrogel was synthesized using hyaluronic acid, a naturally occurring polymer, while the second, a thermoresponsive systems, was developed from PLGA-PEG-PLGA (PLGA: poly-(DL-lactic-co-glycolic acid); PEG:polyethylene glycol). According to the authors, hydrogels based on natural polymers demonstrated rapid drug release and fast degradation, making them suitable for for short-term intravitreal treatments. In contrast, hydrogels based on synthetic polymers exhibited sustained drug release and slower degradation, suggesting their potential forlong-term management of chronic intravitreal conditions (Aragón-Navas et al., 2024).

Non-biodegradable electrode materials commonly used in electrotherapy devices present a significant challenges in terms of biocompatibility and environmental sustainability, limiting their long-term application in pain management and muscle recovery. Although conductive hydrogels offer promising alternative, they often face difficulties in balancing electrical conductivity, biodegradability, and biocompatibility. A recent study reports the development of an eco-friendly, electrically conductive double-layer nanocomposite biohydrogel composed of tragacanth gum and polyvinyl alcohol, reinforced with carboxylated graphene and polypyrrole. Compared to conventional single-layer hydrogels, the novel double-layer design significantly improves performance, achieving an remarkable 4.99×10^5 fold increase in conductivity. Moreover, the hydrogel exhibited up to 49 % mass loss over 60 days in soil, indicating exceptional biodegradability, highlighting its environmental compabílity (Vafa et al., 2025). These findings demonstrate the hydrogeĺs potential as an effective and environmentally friendly alternative for next-generation electrotherapy devices, addressing both medical and ecological concerns.

2.4. Mechanical strength

The ability of hydrogels to tolerate external stresses without breaking or deforming is referred to as mechanical strength (Tang et al., 2009). Because of their high-water content, hydrogels are usually soft and flexible, but by adding reinforcing materials like fibers or nanoparticles or boosting cross-linking, their mechanical strength can be increased (Huang et al., 2007). In applications like tissue engineering, where the material must give developing tissues structural support, or in wound dressings, where the material must withstand external stresses without losing its integrity, hydrogels' mechanical qualities are crucial. For these applications, it is essential to strike a balance between softness and strength so that hydrogels can replicate the mechanical characteristics of biological tissues while providing flexibility and durability (Hashemi-Afzal et al., 2025). The development of hydrogels with enhanced mechanical strength is critical for expanding their applicability in load-bearing and dynamically stressed environmentals. In a study conducted by Hu *et al.*, a homogeneous network structure was designed to develop mechanically strong poly(acrylamide)-based nanocomposite hydrogels. The formulation incorporated N,N′-methylenebisacrylamide as acrosslinking agent and calcium hydroxide nanospherulites as reinforcing fillers. The resulting hydrogels showed exceptional mechanical properties, tolerating strains up to 2200 %, compressive stresses of 220 MPa, and tensile stresses reaching 920 kPa. In addition, these hydrogels demonstrated quick shape recovery, returning to their initial configuration within one second after stress released, a property that contributes to mechanical durability under cyclic loading (Hu et al., 2019). These mechanical attributes make them promising candidates for applications such as tissue scaffolds, soft robotics, and biomedical devices, where high strength, pliability, and quick self-healing are required.

Further advancements in mechanical strength have ben demonstrated through the design of frost-resistance organohydrogels. A recent study using polyvinyl alcohol as the polymer matrix and bacterial nanocellulose as a reinforcing filler, combined using a binary solvent system composed of water and dimethylformamide (DMF). The obtained hydrogel exhibited a tensile strength of 2,974 kPa and stretchability of 277 % at room temperature, confirming its high mechanical robustness. Remarkably, it retained substantial mechanical performance even under extreme conditions, withstanding tensile stressesof 508 kPa and a stretchability of 190 % even at −70 °C. These results underscore the potential of solvent-engineered hydrogel systems to maintain mechanical integrity across a broad range environmental conditions, making them suitable for demanding biomedical and engineering applications(Yan et al., 2024).

2.5. Crosslinking density

The degree of interconnections between the polymer chains in a hydrogel is known as the cross-linking density (Wang et al., 2024a). The mechanical strength, swelling characteristics, and rate of disintegration of the hydrogel are all significantly influenced by crosslinking, which can happen chemically or physically. A low cross-linking density leads to a more flexible material that swells more and degrades faster, while a high crosslinking density results in a more rigid structure, less swelling, and slower degradation (Rumon et al., 2025). The crosslinking density can be adjusted to meet the specific requirements of different applications. For example, hydrogels used as tissue scaffolds may require a higher cross-linking density for adequate mechanical support, whereas those used for drug delivery need a comparatively lower cross-linking density to facilitate quicker release of the drug (Lohani et al., 2024). The effect of crosslinking density on the physicochemical characteristics of cyclodextrin-based nanosponges was thoroughly investigated by Hoti *et al.* In their study, pyromellitic dianhydride was used as a chemical crosslinking agent to synthesize β-cyclodextrin nanosponges at different stoichiometric ratios (ranging from 2 to 10 parts of pyromellitic dianhydride). The results indicated that the amount of crosslinker affected the water absorption capacity of the nanosponges. However, increasing the crosslinker concentration led to a decrease in swelling capacity, indicating the formation of a denser crosslinked network. Rheological

Table 1
Overview of commonly used polymers in hydrogel formulation, highlighting their source, physicochemical properties, clinical applications, safety profiles, cost-effectiveness, and eco-friendliness.

	Polymer	Source	Key Properties	Application	Safety	Cost effectiveness	Eco-friendliness	References
Natural Polymers	**Chitosan**	Natural (chitin from crustaceans)	Biodegradable, mucoadhesive, antimicrobial	Wound healing, drug delivery, tissue engineering	Generally regarded as safe	Moderate	Biodegradable, renewable	(Baharlouei and Rahman, 2022; Wang et al., 2024b)
	Alginate	Natural (brown seaweed)	Ionically crosslinkable, biocompatible, gel-forming	Wound dressings, cell encapsulation, drug delivery	Generally regarded as safe status	Cost-effective	Highly eco-friendly	(Sharma et al; 2023; Ribeiro et al., 2024)
	Konjac glucomannan	Natural (konjac plant root)	High water absorption, biodegradable, viscosity-enhancing	Controlled release systems, tissue scaffolds	Safe, used in food and pharma	Economical	Plant-based, biodegradable	(Lohani et al., 2024)
	Gelatin	Natural (collagen derivative)	Thermo-sensitive, cell-friendly, biodegradable	Injectable hydrogels, drug delivery, tissue regeneration	Biocompatible	Inexpensive	Biodegradable	(Huang et al., 2025; Ribeiro et al., 2024))
	Collagen	Natural (animal connective tissue)	High bioactivity, supports cell adhesion, resorbable	Skin regeneration, wound repair, tissue engineering	Biocompatible, immunogenic risk if not purified	Moderate	Biodegradable	(Cao et al., 2024)
	Hyaluronic acid	Natural (animal tissues, bacterial fermentation)	Viscoelastic, hydrating, promotes tissue repair	Dermal fillers, joint lubrication, ophthalmic products	Highly biocompatible	High	Biodegradable, sourced naturally	(Gholamali et al., 2024; Wang et al., 2024b)
Synthetic polymers	Poly(ethylene glycol) (PEG)	Synthetic	Non-immunogenic, hydrophilic, modifiable	Drug delivery, tissue scaffolds, surface coatings	FDA-approved, safe	Relatively expensive	Not biodegradable but low toxicity	(Habibi et al., 2024)
	Poly(vinyl alcohol)	Synthetic	High mechanical strength, film-forming, stable	Artificial organs, contact lenses, wound dressing	Biocompatible	Cost-effective	Limited biodegradability	(Bercea, 2024)
	Polyacrylamide (PAAm)	Synthetic	Highly hydrophilic, tunable porosity, non-biodegradable	Soft tissue engineering, sensors	Low toxicity in crosslinked form	Economical	Not eco-friendly	(Hanyková et al., 2024)
	Pluronic® (Poloxamer)	Synthetic (triblock copolymer)	Thermosensitive, reversible gelation, amphiphilic	Injectable hydrogels, topical delivery	Biocompatible, FDA-approved	Moderate	Synthetic, biodegradable to some extent	(Wang et al., 2024a)

studies further supported the correlation between crosslinking density and the mechanical properties of the nanosponges, confirming the structural stability and rigidity of the network (Hoti et al., 2021). A comprehensive understanding of the impact of crosslinking density on hydrogel characterstics is essential for fine-tuning material properties to meet specific functional requirements. This knowledge enables the design of tailored systems for targeted applications, particularly in drug delivery and tissue engineering, and supports the scability of hydrogel production for industrial use.

2.6. Stimuli-sensitive hydrogels

Stimuli-sensitive hydrogels, sometimes referred to as smart hydrogels or responsive hydrogels, are a class of polymeric materials that, when exposed to particular environmental stimuli, modify their mechanical strength, swelling, or form (Farjadian et al., 2024). These hydrogels are designed to react to many stimuli (including temperature, pH, light, electric and magnetic fields, and the presence of particular molecules or ions). Stimuli-sensitive hydrogels have drawn a lot of interest in a variety of domains, especially in drug delivery and medicinal applications, because of their capacity to respond to internal or external stimuli (Farzanfar et al., 2021; Lohani et al., 2014; Singh et al., 2014). A recent study reported a multifunctional hydrogel with a double-network structure consisting of both chemical and physical crosslinking. The physical network combined chitosan and polyvinyl alcohol, while the chemical network consisted of a of a copolymer of poly(N-isopropylacrylamide-co-acrylamide), endowing the system with tunable thermoresponsive behavior. To enhance the responsiveness to external stimuli, functional materials such as polyaniline, TiC_2 MXene, and eutectic gallium-indium were added. This composition enabled the hydrogel to exhibit mechanical and electrical responsiveness, as demonstrated by over 1000 % change in resistance under 400 % strain and capacitive signal variations to the touch. Additionally, the hydrogel showed pH responsiveness, with an outpt of approximately −13.68 mV per pH unit. With high cell viability, customized antibacterial properties, and compability with 3D printing, this hydrogel presents a promising platform for integrated therapeutic and diagnostic apllipcations (Zheng et al., 2025).

Complementarily, Gai *et al.*, developed a flexible piezoresistive strain sensor based on a hydrogel composed of MXene/bacterial cellulose. The material exhibited high mechanical strength and rapid response (about 130 ms), with a detection limit as low as 0.05 %. Sensitivity was maintained even under submerged conditions, and the hydrogel was capable of monitoring various human actions, such as finger, wrist, and elbow movements, reinforcing its potential in wearable bioelectronic interfaces and continuous healh-monitoring systems(Gai et al., 2024).

3. Polymers used in the clinical application of hydrogels

Polymers used in the clinical application of hydrogels are chosen based on their physical and chemical properties. The biocompatibility and functioning of the hydrogel system are greatly influenced by the polymer selection. The frequently utilized polymers in hydrogels, together with their source type, related therapeutic applications, and distinguishing features, are compiled in Table 1 below.

4. Clinical applications of polymeric hydrogels

4.1. Wound healing

Maintaining the structure and function of the skin is essential to the general health of the human body. In order to repair the wound, a series of overlapping events are initiated as soon as the skin is injured or breaks: (i) inflammation; (ii) hemostasis; (iii) proliferation; and (iv) maturation/remodeling (Gantwerker and Hom, 2011). In certain instances of chronification, wounds may not heal as expected, remaining open for more than a month (Zhu et al., 2022). Chronic wounds are a widespread concern, often referred to as a silent epidemic, impacting a large segment of the global population (Gottrup, 2004). In order to halt the chronification process and avoid wound infections, one of the primary problems in modern medicine is to promote faster wound healing. Hydrogel-based dressings are ideal for wound care due to their multiple benefits: (i) a 3D structure that enhances application (Koehler et al., 2018); (ii) aiding debridement without sticking to sensitive tissue; (iii) providing pain relief through cooling; (iv) maintaining optimal moisture levels; and (v) effectively delivering bioactive agents like drugs, growth factors, peptides, or stem cells to the wound site (Birca et al., 2023). These properties support healing, improve treatment adherence, and create a healing-friendly environment.

Various wound dressings made of hydrogel have already hit the market. A survey estimates that the hydrogel dressings market would increase at a compound yearly growth rate of 4.32 % between 2024 and 2030, from its 2023 valuation of USD 920.32 million (Tavakoli and Klar, 2020). The growing number of acute and chronic wounds is expected to drive up demand for hydrogel dressings (Tavakoli and Klar, 2020).

The principal dressing for moderately to severely leaking chronic and acute wounds, as well as wounds with little bleeding, is Kaltostat® Alginate dressing, which is a calcium sodium alginate (80 % Ca and 20 % Na). The dressing changes from a dry, fibrous state to a firm, moist gel when it comes into contact with wound exudate because its calcium ions exchange with the sodium ions in the exudate. This transformation helps the dressing maintain its integrity while creating a moist environment that optimizes wound healing conditions. The gel also allows for easy and painless removal, enhancing patient comfort (Kaltostat® Alginate Dressing, 2025). Another product on the market is called Comfeel® Plus Contour, which is used to treat low to moderately exuding wounds like pressure and leg ulcers, superficial to superficial partial-thickness burns, skin abrasions, and postoperative wounds. It is made of calcium alginate (to increase absorption) and moisture-absorbing sodium carboxymethylcellulose. Depending on the specifics of the wound, a dressing may be in place for up to seven days (Comfeel® Plus Contour,2025).

Researchers are increasingly focusing on assessing the effectiveness of hydrogel-based polymeric materials for wound healing and tissue regeneration through clinical trials in humans. This effort aims to establish their therapeutic potential and optimize their application in regenerative medicine. The effectiveness of EHO-85 amorphous hydrogel in hastening the initial phases of wound healing in comparison to a widely used standard hydrogel for ulcer treatment was evaluated in a clinical experiment (Verdú-Soriano et al., 2023). EHO-85, a class IIb medical device, consists of purified water, Carbopol 980® (polymer), and Olea europaea leaf extract (an antioxidant), included to regulate free radicals at the ulcer site. Another amorphous hydrogel (VariHesive®, ConvaTec, Barcelona, Spain) served as the positive control. Participants were adults (≥18 years old) with either category II (partial thickness) or III (full thickness with skin loss) pressure ulcers or venous leg ulcers. The treatments were applied three times a week, alternating when possible. Wounds were cleaned with sterile saline and covered with silicone foam dressings (Mepilex®, Molnlycke, Gothenburg, Sweden). Compression therapy was mandatory for venous leg ulcer patients. Random assignment was used to place participants in the VariHesive® or EHO-85 groups. According to the trial, EHO-85 markedly sped up the healing of wounds. In order to establish the ideal healing environment, this hydrogel regulates pH levels and reactive oxygen species in the ulcer environment while combining moisturizing and barrier qualities. The acidification of the wound bed, induced by EHO-85 from the first application, reduces the wound pH, an important factor in inhibiting pathogen growth. Additionally, a slightly acidic pH promotes angiogenesis, enhances macrophage and fibroblast activity, and improves the function of matrix metalloproteinases, which all support tissue repair. The lowered pH also aids in oxygen delivery to the wound, further boosting healing. Overall, the clinical trial demonstrated that EHO-85 significantly outperformed a standard hydrogel in improving wound

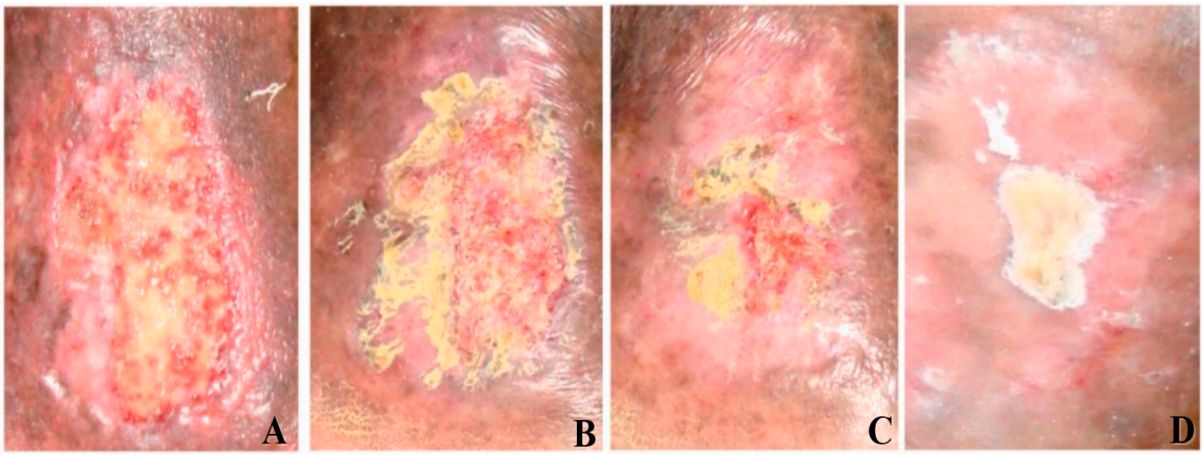

Fig. 1. Images depicting the patient's wound. **(A)**: one day prior to the initiation of PGHF treatment; **(B)**: at the end of week one of PGHF treatment; **(C)**: after week six of PGHF treatment; **(D)**: at the end of week ten of PGHF treatment. Reprinted with permission from Fleck et al., 2016.

healing rates (Verdú-Soriano et al., 2023).

Patients with diabetes commonly acquire wounds that are colonized by bacteria, mainly *Pseudomonas aeruginosa* and *Staphylococcus aureus*, which can both create biofilms. In a clinical study, epidermal growth factor loaded carboxymethylcellulose hydrogel dressing, composed of a 2 % carboxymethylcellulose hydrogel loaded with epidermal growth factor, was examined to determine whether it might lessen colonization and biofilm formation in the chronic wounds of diabetic patients. Of the 25 patients in this randomized clinical trial, 11 received carboxymethylcellulose hydrogel treatment and 14 received epidermal growth factor loaded carboxymethylcellulose hydrogel treatment during a 12-week period. Results showed that *S. aureus* and *P. aeruginosa* strains that colonized chronic wounds treated with epidermal growth factor loaded carboxymethylcellulose hydrogel dressing produced less biofilm than those isolated from wounds treated with carboxymethylcellulose hydrogel (Pessanha et al., 2023).

A 76-year-old woman sought medical help for a chronic, painful, and swollen ulcer on her left leg that was not healing. Over the past year, the ulcer has not improved despite regular standard therapy. Examining the ulcer revealed that it was broad, irregularly shaped, and shallow - it measured around 6.8 × 4.3 cm. It had lustrous granulation tissue on its surface and was situated on the lower left leg (Fig. 1A). After the patient gave written informed consent, a hydrogel-based formulation comprising 2 % (w/w) ethanolic extract of *Punica granatum L.* peels (PGHF) was administered to the ulcer once daily. Oral iron therapy, diuretics, and other supportive care were added to this regimen, and tramadol was provided to relieve discomfort. Antibiotics were not used during the course of treatment. Cotton gauze was used to treat the ulcer following each application. Within six weeks, the ulcer had significantly improved, shrinking to a fourth of its former size. After six more weeks, full recovery was attained, necessitating ninety applications (Fig. 1B–D). Crucially, there were no side effects linked to the PGHF treatment. This result emphasizes the formulation's potential as a therapeutic alternative for wound care, indicating the need for more clinical studies to validate its effectiveness (Fleck et al., 2016).

4.2. Bone regeneration

Bone regeneration is a complex and highly coordinated physiological process that plays a crucial role in the continuous remodeling of bone throughout adulthood and is particularly noticeable during the repair of fractures. Nonetheless, there are intricate clinical scenarios that necessitate substantial bone regeneration, including the reconstruction of extensive bone defects resulting from trauma, infection, tumor excision, and skeletal deformities. Additionally, certain conditions may hinder the regenerative process, such as osteoporosis, atrophic non-unions, and avascular necrosis. Metals, polymers, and ceramics are among the materials used for bone replacement. Research into the utilization of biodegradable polymers, which enable regulated chemical composition and monomer units during manufacturing, has been spurred by the limited degradability of metals and ceramics. Up until now, the majority of polymeric bone substitutes have been prefabricated and inserted via invasive surgical methods. Nonetheless, there is still a therapeutic need for substances that can enter the body through non-invasive techniques like injection. In these methods, the material must solidify after injection and have a low enough viscosity to allow for injection (Logith et al., 2016). It should also work well with the addition of medications, cells, and growth factors before they are administered. Hydrogels represent a category of polymers that possess a significant degree of hydration, fulfilling all the aforementioned criteria.

A study evaluated how well a chitosan hydrogel treats bony abnormalities in patients with periodontitis when used in addition to bone transplants. The study included 20 participants, ranging in age from 30 to 60 years, all of whom had intrabony defects deeper than 3 mm and clinical attachment levels greater than 5 mm. Participants were split into two groups at random: Group 2 (test group) received open flap debridement with a bone graft augmented with chitosan nanohydrogel, whereas Group 1 (control group) received open flap debridement with a bone graft alone. Clinical and radiographic measurements were taken initially, followed by reassessments at three months and six months post-treatment. The results showed that bone grafts combined with chitosan hydrogel led to greater bone regeneration. Group 2 experienced a more significant reduction in clinical attachment levels (from 8.7 ± 0.6 to 1.6 ± 0.8) compared to Group 1 (from 8.6 ± 0.5 to 2.4 ± 0.7). Additionally, probing depths in Group 2 (from 8.3 ± 0.9 to 1.6 ± 0.8) showed a significantly greater reduction than those in Group 1 (from 8 ± 0.8 to 2.3 ± 0.7). Both groups exhibited substantial defect fill from baseline to the six-month follow-up. In summary, the findings indicate that the use of chitosan hydrogel in conjunction with a bone graft significantly improves bone regeneration compared to the application of bone grafts alone (Meenakshi and Sankari, 2021).

In a clinical trial registered as NCT05122299, researchers investigated the effects of CoQ_{10} hydrogel on bone regeneration after mandibular tooth extraction in patients with Type II diabetes. The hydrogel was first prepared and characterized for application. Tooth extraction was carried out using a minimally invasive flapless approach, utilizing rotational and traction movements to reduce soft tissue disruption and prevent damage to the surrounding alveolar bone. Following extraction, the socket was carefully rinsed with normal saline. The sockets were then treated in one of three ways: augmented with

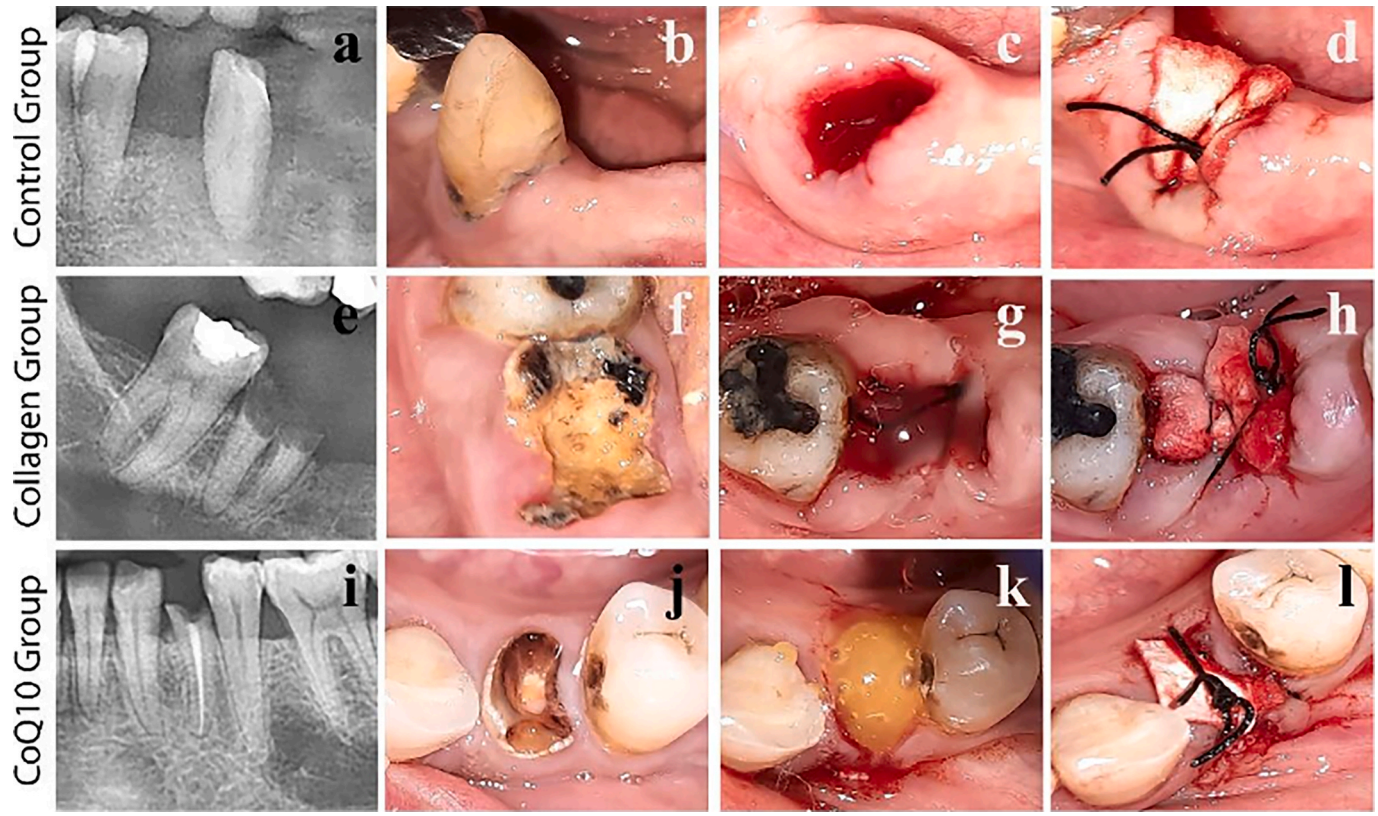

Fig. 2. Dental socket augmentation post-tooth extraction: **(a)** Pre-operative orthopantomogram displaying the tooth scheduled for extraction (control group); **(b)** The right mandibular canine has been indicated for extraction because of periodontal disease; **(c)** Fresh extraction socket left untreated (ungrafted) after tooth removal; **(d)** Surgical suture after a collagen membrane has been positioned; **(e)** Pre-operative orthopantomogram of the collagen group displaying the tooth to be extracted; **(f)** Severely damaged mandibular right second molar designated for extraction; **(g)** Fresh extraction socket filled exclusively with collagen hydrogel after tooth extraction; **(h)** Surgical suture after applying a collagen membrane over the collagen hydrogel; **(i)** Pre-operative orthopantomogram indicating the tooth to be extracted in the CoQ_{10} group; **(j)** Heavily deteriorated mandibular left first premolar selected for extraction; **(k)** Fresh extraction socket filled with CoQ_{10}/Collagen hydrogel post-extraction; and **(l)** surgical suture after application of a collagen membrane on top of the CoQ_{10}/Collagen hydrogel. Reprinted with permission from Ghanemet et al., 2022.

collagen (positive control), filled with CoQ_{10}/collagen hydrogel (study group), or left ungrafted (negative control). The grafting material was applied from the apical to the crestal region of the socket. Following this, a collagen membrane was placed over the socket and secured using 3/0 silk sutures to ensure proper closure (Fig. 2). Three months following the extraction, bone regeneration was measured to gauge the efficacy of the treatment. The purpose of the study was to investigate whether CoQ_{10} hydrogel may help diabetic patients' bones mend (Ghanem et al., 2022).

Cone Beam Computed Tomography (CBCT) scans were conducted at two distinct times to assess bone regrowth in the extraction socket: immediately following tooth extraction (T_0), which served as the baseline to evaluate bone density within the socket and the dimensions (height and width) of the alveolar ridge, and three months post-extraction (T_1), prior to implant placement, to ensure precise implant positioning. All treated ridges underwent CBCT scans before the implant operation in order to assess socket healing, the volume of augmented bone, and labiolingual width, and to choose the appropriate implant size (Fig. 3a). A virtual dental implant was digitally positioned using OnDemand dental planning software to aid in precise surgical planning (Fig. 3b). Overall, Fig. 3c–f shows bone collection during implant surgery and Fig. 3g–l shows implant placement surgery (Ghanem et al., 2022).

Histological analysis of bone biopsies showed the existence of bone lamellae, osteocytes, Haversian systems, and osteoblasts, which indicated mature bone regeneration in sockets treated with CoQ_{10}. After three months, full graft resorption was observed, and trichrome staining provided additional confirmation of bone maturation. The successfully placed implant was made possible by the freshly created bone, which preserved volumetric stability. The researchers came to the conclusion that locally applied CoQ_{10} hydrogel is a simple, economical, and effective way to encourage bone growth and healing in extraction sockets, particularly in individuals with diabetes. In clinical practice, this makes it a viable option for boosting bone repair and guaranteeing implant stability (Ghanem et al., 2022).

4.3. Joint therapy

For significant articular cartilage lesions in the knee joint, a study assessed the clinical results of a hydrogel-based system. A biocompatible and in situ cross-linkable hydrogel based on albumin and hyaluronan has been developed by researchers as a carrier material for matrix-assisted autologous chondrocyte implantation (M−ACI) treatments. One hundred patients with focal full-thickness cartilage lesions that ranged in size from 4 to 12 cm2 underwent treatment. The Knee Injury and Osteoarthritis Outcome Score (KOOS) responder rate at two years was the main outcome measure. The study presented here showed that 93 % of patients were KOOS responders, or improved by at least 10 points from their pre-operative level, two years following ACI therapy of significant cartilage lesions with NOVOCART® Inject plus. M−ACI with NOVOCART® Inject plus has been shown to be a safe and effective treatment option for individuals with severe abnormalities of the knee cartilage in the phase III trial. Overall, early, statistically substantial, and clinically meaningful improvement up to two years follow-up showed

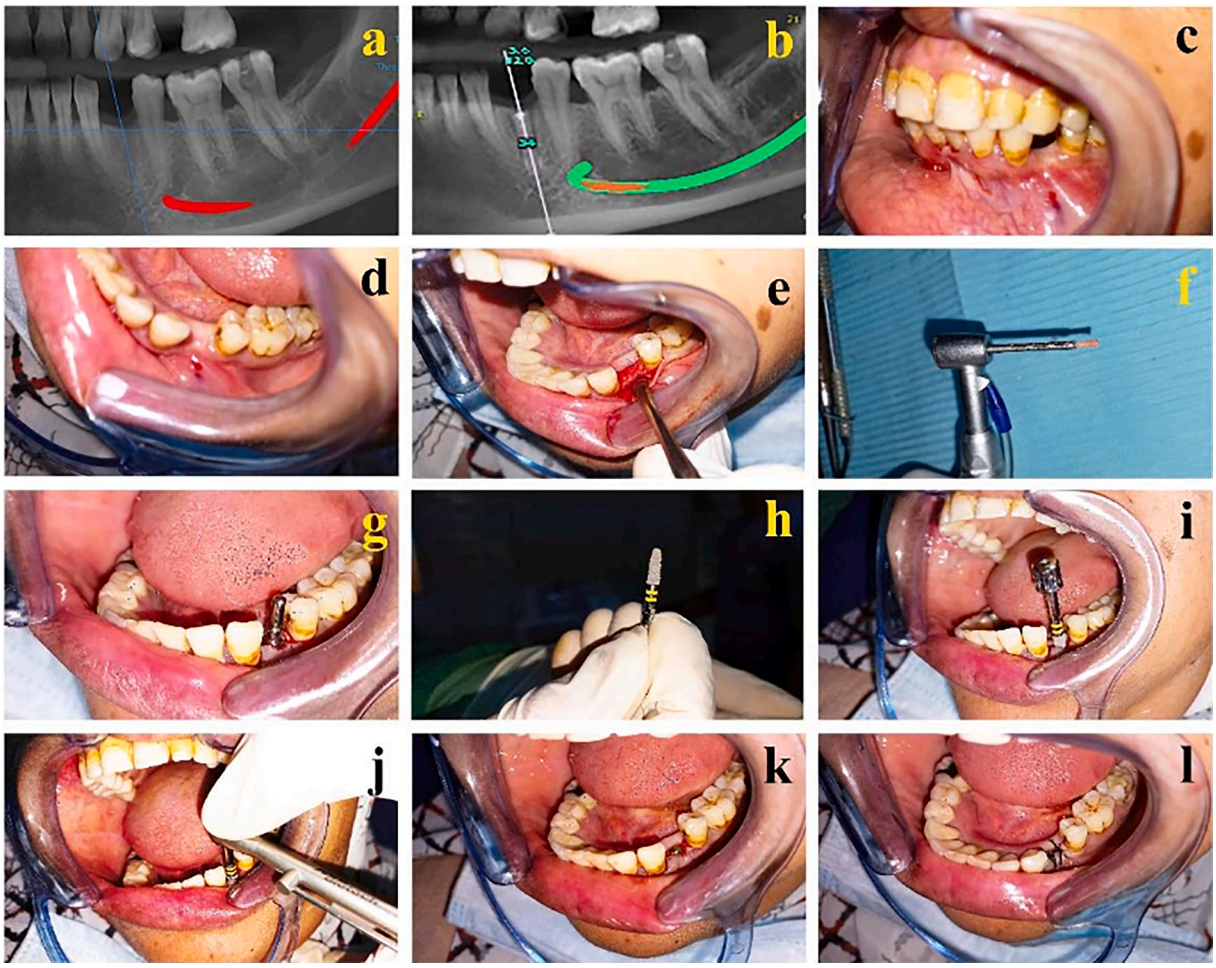

Fig. 3. Three-month surgical follow-up for implant implantation and bone core biopsy: **(a)** Three-month pre-operative CBCT of the extraction site demonstrates full extraction socket healing; **(b)** CBCT showing the virtual implant prior to surgery at the extraction site; **(c)** pre-operative clinical image of the central occlusion's inter-occlusal area prior to implant implantation; **(d)** An intraoral picture showing complete mucosal healing following the initial premolar extraction and prior to implant placement; **(e)** reflection of a full mucoperiosteal flap; **(f)** biopsy of the bone core retrieved by the trephine bur from the enlarged area prior to implant site preparation; **(g)** A parallel pin demonstrating the implant's parallelism to the surrounding teeth; **(h)** NeoBiotech tapered resorbable blast media (RBM) dental implant's macrostructure (3.5 × 11.5 mm); **i)** implant inserted into the osteotomy site; **(j)** complete implant placement utilizing a manual torque wrench in the osteotomy site; **(k)** cover screw placed over the dental implant before closure of the flap; and **(l)** Sutured and relocated mucoperiosteal flap. Reprinted with permission from Ghanem et al., 2022.

that hydrogel-based ACI was a beneficial therapy choice for patients with extensive cartilage lesions in the knee. according to magnetic resonance imaging examinations conducted concurrently with the clinical improvements, the repair tissue was observed to be rearranging, growing, and integrating more in tandem with the therapeutic benefits (Niemeyer et al., 2022).

A clinical study investigated the safety and effectiveness of a single intra-articular injection of Gel-200, a newly developed cross-linked hyaluronic acid formulation, in comparison to phosphate-buffered saline for treating patients with symptomatic knee osteoarthritis. This trial used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore as the primary effectiveness outcome. Secondary outcomes evaluated in the study comprised the total WOMAC score, physical function, stiffness subscores, patient and physician global assessments of disease activity, Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT-OARSI) strict responder criteria, and safety evaluations for Gel-200. Among the 379 randomized patients, safety was analyzed in 377 participants, and efficacy was assessed in 375 patients (98.9 % of the randomized group) within the intent-to-treat population. By week 13, WOMAC pain subscores showed statistically significant improvements with Gel-200. Consistent improvements in WOMAC pain subscores were observed at each follow-up visit, with Gel-200 outperforming phosphate-buffered saline. Additionally, from weeks 3 to 13, Gel-200 demonstrated considerable efficacy in physician global assessments, physical function, and WOMAC total scores. Additionally, from weeks 6 to 13, there were considerably more "strict" OMERACT-OARSI responders. Adverse events, including serious adverse events related to the treatment, were comparable between the two groups. These results highlight Gel-200 as a safe and effective therapeutic option for alleviating symptoms of knee osteoarthritis (Strand et al., 2012).

4.4. *Tissue engineering*

Delivering cells to patients for treatments such as autologous chondrocyte transplantation is expensive and complex, which has limited its widespread use. To address this, researchers developed an acellular biomaterial designed to complement standard microfracture surgery, which often results in poor defect fill and excessive bone growth. Hydrogels, with their cartilage-like mechanical properties, are promising candidates for cartilage repair. Examples include BST-CarGel (Piramal Life Sciences) and GelrinC (Regentis Biomaterials), both of which rely on blood clots or clot components for integration with the surrounding tissue. However, achieving adhesion to the slippery

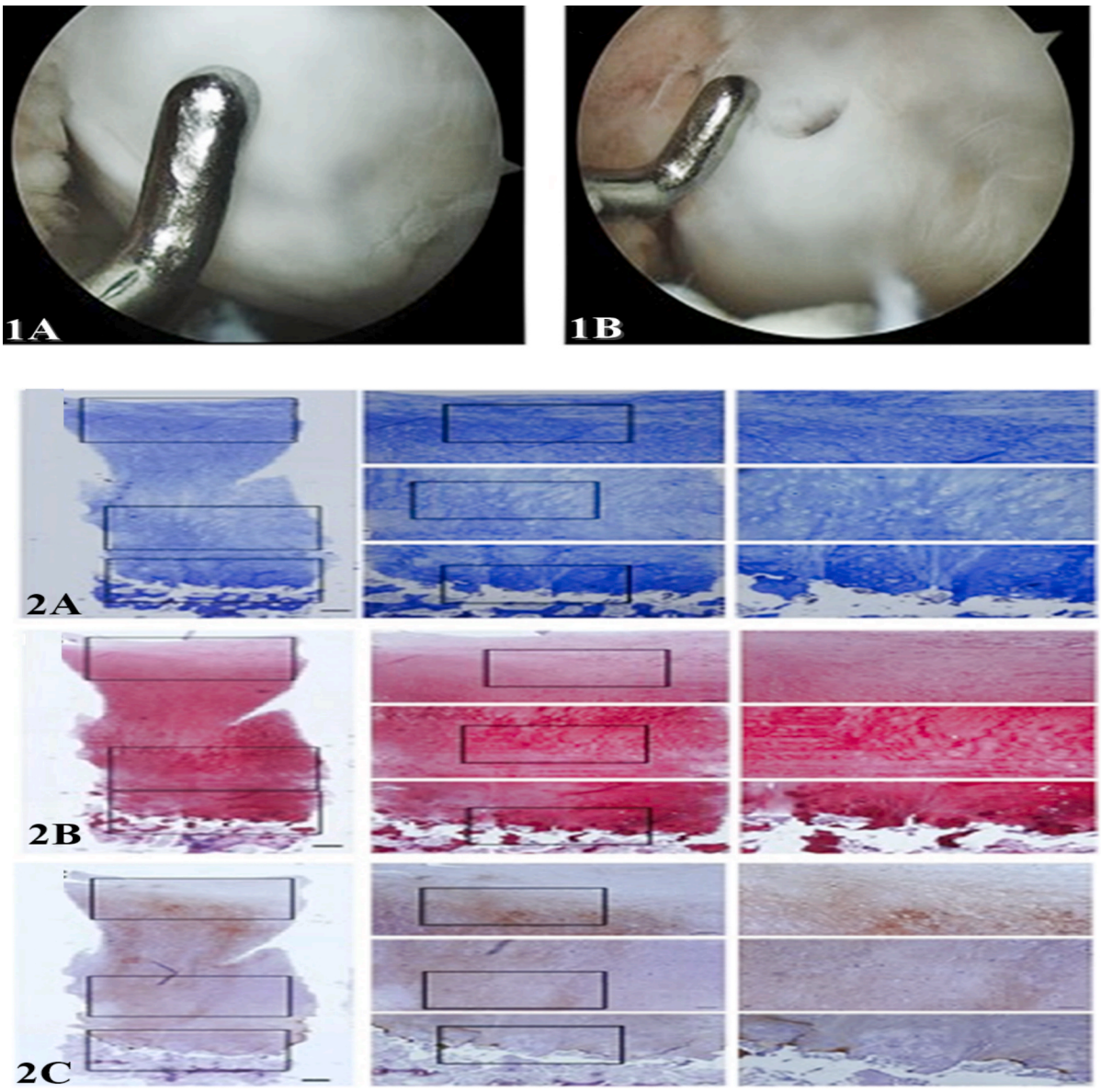

Fig. 4. Findings from secondary arthroscopy conducted one year after transplantation of umbilical cord blood-derived mesenchymal stem cells: **(1A):** Excellent resurfacing was seen at the underlying issue site, with the regenerated cartilage showing a uniformly smooth surface. When probed, the regenerated tissue showed firm consistency, suggesting strong structural integrity. Furthermore, the restored cartilage blended in perfectly with the native cartilage around it. This participant's (ID: 007–004) regenerated cartilage received a grade of 2, indicating a considerable improvement in cartilage quality, according to the International Cartilage Repair Society's (ICRS) grading criteria; **(1B):** Relatively thick and well-developed tissue was seen at the biopsy site when a sample was taken from the regenerated cartilage.

cartilage surface remains a significant challenge. To address this issue, researchers developed a hydrogel composed of poly(ethylene glycol) diacrylate to promote cartilage matrix formation while being easy to apply during surgery. The hydrogel's mechanical integrity surpasses that of the bulk hydrogel when it adheres to a cartilage explant, and cartilage tissue formation is improved *in vivo*. Any hydrogel system can benefit from this cartilage tissue priming technique to enhance tissue integration. A pilot clinical research combining the adhesive-hydrogel technology with conventional microfracture surgery was carried out after preclinical testing in a caprine model. Fifteen patients without widespread osteoarthritis who had isolated, symptomatic cartilage lesions on the medial femoral condyle measuring 2 to 4 cm^2 were included in the study. Three patients got microfracture alone as a control group, and 15 patients received the adhesive-hydrogel treatment following microfracture. When compared to controls, treated patients had noticeably better tissue fill. Over time, magnetic resonance imaging spin–spin relaxation durations (T2) showed better tissue organization and decreased water content. During the six-month evaluation period, knee function ratings improved similarly in both groups and treated patients reported less pain than controls. During the study, no significant adverse events were reported (Sharma et al., 2013).

The safety and efficacy of a combined treatment employing hyaluronate hydrogel and allogeneic umbilical cord blood-derived mesenchymal stem cells for cartilage regeneration in patients with osteoarthritis are investigated in clinical trial research (Park et al., 2017). Conducted as a clinical trial, it primarily aimed to establish proof-of-concept for this treatment strategy and assess its long-term safety. The participants included patients with knee osteoarthritis, who received the composite therapy through intra-articular injection. The key findings indicate that the treatment was well-tolerated with minimal adverse effects, supporting its safety profile. A year later, an arthroscopic evaluation revealed good resurfacing of the lesion site with thick, glossy white cartilage that resembled hyaline. The regenerated cartilage had a smooth, firm surface and showed good interaction with

the native cartilage around it (Fig. 4).

Histological characteristics of the regenerated cartilage: **2A)**: Masson's trichrome staining demonstrated a significant presence of collagen; **2B)**: Safranin O staining indicated a high concentration of glycosaminoglycans; **2C)**: Strong staining for type II collagen, a characteristic of articular hyaline cartilage, was found by immunohistochemical examination. While the deepest portion of the repair site had changed into subchondral bone, which resembles the histological structure of native articular cartilage, the superficial layer next to the articular surface showed lesser staining for Masson's trichrome, Safranin O, and type II collagen antibodies. 200 μm (left), 100 μm (center), and 50 μm (right) are the scale bars. Reprinted with permission from Park et al., 2017.

Over a period of seven years, the clinical outcomes demonstrated improvements in joint function, pain relief, and cartilage regeneration, with magnetic resonance imaging scans showing positive changes in cartilage morphology. The mesenchymal stem cells from umbilical cord blood appear to promote tissue repair, while the hyaluronate hydrogel provides a supportive matrix for cell delivery and retention within the joint. According to the biopsy sample's histologic examination, the regenerated cartilage had a staining pattern resembling that of healthy articular hyaline cartilage (Fig. 4 2A–2C). Notably, the extended follow-up period allowed the researchers to observe long-term benefits and the potential for sustained cartilage regeneration, which is a significant concern for osteoarthritis therapies. The study offers valuable insights into regenerative medicine, particularly in the context of mesenchymal stem cell therapies, which hold promise for treating osteoarthritis and other degenerative conditions (Park et al., 2017).

4.5. Ophthalmology

The human eye's complex structure poses challenges in treating ocular diseases. Hydrogels have emerged as a promising solution in ophthalmology due to their adaptability, biocompatibility, and versatility. They are particularly useful for improving outcomes in intraocular lens technology during cataract surgery and enabling effective drug delivery to the eye's posterior segment (Ahmad et al., 2022). Hydrogels with in situ gelation are highly favored in ophthalmology due to their ease of administration and ability to provide sustained local drug release (Aswathy et al., 2020). They effectively carry hydrophilic drugs through techniques like complex formation or gel matrix modifications. By extending treatment efficacy and reducing the frequency of intravitreal injections, hydrogels address challenges such as discomfort and risks like endophthalmitis and retinal detachment, offering a safer alternative to traditional implants (Ilochonwu et al., 2020; Sarkar et al., 2021).

Hydrogels, known for their high-water content and tissue compatibility, are key components of contact lenses used for vision correction, cosmetics, and extended drug delivery. These lenses enhance drug bioavailability to over 50 % and provide a controlled release for days or months, benefiting chronic and elderly patients who find frequent eye drop use challenging. *In vivo* studies confirm their effectiveness, demonstrating superior clinical outcomes compared to traditional eye drops (Gulsen and Chauhan, 2004).

Building on these promising applications, several clinical trials are currently underway to evaluate the effectiveness and safety of various hydrogel-based formulations in ophthalmic treatments. One such trial evaluated the biological activity, safety, and tolerability of a single hydrogel-based implant OTX-TKI (laboratory code) that contains a small molecule tyrosine kinase inhibitor axitinib, which has anti-angiogenic properties.This randomized, controlled, double-masked, multicentre Phase 1 clinical trial in the United States involved 21 subjects previously treated with anti- vascular endothelial growth factor intravitreal injections and free of excess intraretinal and subretinal fluid. Subjects were randomized 3:1 to receive either a single OTX-TKI 600 μg implant on Day 0 and aflibercept 2 mg at Month 1, or aflibercept 2 mg every 8 weeks. The study found that OTX-TKI was well tolerated, with no reports of drug-related ocular or systemic serious adverse events. Best corrected visual acuity and central subfield thickness remained stable for at least 7 months, with minimal changes from baseline. At Month 7, mean changes in best corrected visual acuity and central subfield thickness were comparable between groups. Notably, 80 % of OTX-TKI subjects did not require rescue therapy for up to 7 months. The study is ongoing, with follow-up continuing to Month 12 (Wong et al., 2021).

A study aimed to assess the effectiveness and safety of a netilmicin/dexamethasone ophthalmic hydrogel formulation containing xanthan gum, administered twice daily, compared to the eye drops of the same combination given four times daily for managing inflammation and preventing infection following cataract surgery. Netildex ophthalmic gel (containing Dexamethasone 0.1 % netilmicin 0.3 %) was administered twice daily to Group 1 of patients, whereas same combination Netildex eye drops were administered four times daily to Group 2. Following surgery, both therapies were continued for 14 days. Seven days following surgery, the evaluation of anterior chamber cellularity and flare using slit-lamp biomicroscopy served as the main effectiveness goal. Monitoring the frequency of infection and assessing the signs and symptoms of postoperative ocular inflammation were secondary objectives. Results showed that the twice-daily hydrogel formulation was non-inferior to the four-times-daily eye drops. Both treatments demonstrated similar patient tolerability and symptom profiles, with no microbial load or safety concerns observed. The study concluded that the twice-daily hydrogel formulation is equally effective and well-tolerated as the four-times-daily eye drops, offering a more convenient dosing regimen (Mencucci et al., 2022).

Asmofilcon A, a third-generation silicone hydrogel contact lens, was tested in a clinical experiment over a 6-month period with 6-night extended usage. Sixty participants who were daily soft contact lens users were randomly assigned to wear either asmofilcon A or senofilcon A lenses for six months. Assessments were conducted at lens delivery and after 1 week, 4 weeks, 3 months, and 6 months of extended wear. Fifty participants (83 %) completed the study successfully, with two reporting adverse events. No significant differences in high or low contrast distance visual acuity were found between the two lens types, though low contrast acuity decreased slightly over time for both. Both lenses received high ratings for overall comfort and satisfaction, with median scores of 95 for asmofilcon A and 90 for senofilcon A at the 6-month mark. The study concluded that asmofilcon A's hydrogel formulation offers excellent comfort and consistent performance, making it a promising option for extended-wear contact lenses (Lakkis and Vincent 2009).

Additionally, a study assessed how well chitosan-N-acetylcysteine (Lacrimera®) works as a daily treatment for dry eye illness. Eighteen patients aged 25–86 years with moderate to severe dry eye disease and superficial punctate keratitis were assessed after a trial of Lacrimera® drops. All patients had been using other artificial tears before starting Lacrimera®. Slit-lamp examinations and images were taken before and at 1- and 3-weeks post-treatment. Both subjective and objective assessments were documented, and the data was analyzed using a paired student's *t*-test. According to the results, patients with dry eye illness who were not responding to traditional lubricant treatment experienced an improvement in signs and symptoms after a five-day instillation of chitosan-N-acetylcysteine. Lacrimera® is a good choice for patients with moderate to severe dry eye disease because of its positive posology, lack of adverse effects, and notable outcomes (Efficacy of Different Treatment Regimens With Chitosan-N- Acetylcysteine in Moderate-to-severe Dry Eye Disease,2025).

A study led by Puente *et al.* aimed to assess the subjective and non-invasive effects of Lehfilcon A water gradient silicone hydrogel contact lenses, which feature lipid and bacterial resistance technology. The research involved silicone hydrogel contact lens users in a prospective, longitudinal, single-center, self-controlled trial. The Cobra® HD infrared meibographer was used to evaluate the meibomian glands, while the Integrated Clinical Platform Ocular Surface Analyzer enabled non-

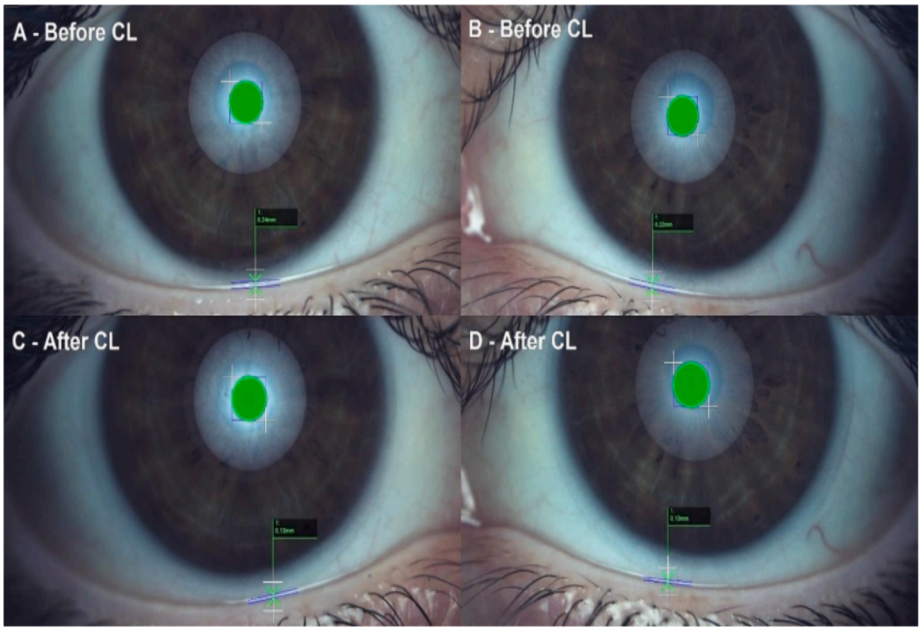

Fig. 5. Illustrates a reduction in tear meniscus height from the baseline measurement to the one-month follow-up. specifically. **(A)** shows the baseline measurement for the right eye at 0.24 mm.; **(B)** presents the baseline for the left eye at 0.22 mm; **(C)** indicates the measurement for the right eye after one month at 0.13 mm; **(D)** reflects the left eye measurement at one month, also at 0.13 mm. This figure represents data from a single participant (subject 5), encompassing both eyes. Reprinted with permission from Capote-Puente et al., 2023.

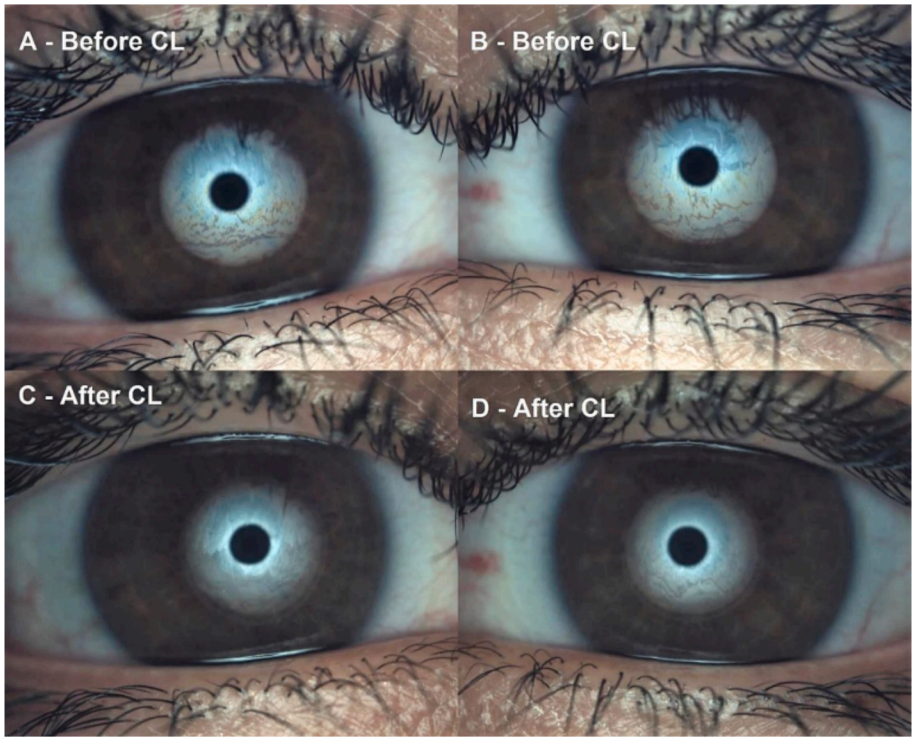

Fig. 6. Illustrates the changes in lipid layer thickness as measured by interferometry, which decreased from grades 5 to 1. **(A)** depicts the Guillon pattern of the right eye at grade 5 prior to the application of a contact lens; **(B)** shows the left eye at grade 5 before contact lens insertion; **(C)** presents the Guillon pattern of the right eye at grade 1 following contact lens use.; **(D)** displays the left eye at grade 1 after the contact lens was applied. This figure represents a specific case involving a single participant (subject 12) with both eyes assessed. Reprinted with permission from Capote-Puente et al., 2023.

invasive analysis of the pre-lens tear film. In order to assess changes in conjunctival redness, subjective dry eye symptoms, tear meniscus height, lipid pattern, and non-invasive break-up time, participants were reassessed after wearing lenses for 30 days. Results showed a reduction in tear meniscus height from 0.21 ± 0.04 to 0.14 ± 0.03 (Fig. 5), alongside a significant decrease in lipid layer thickness from 2.05 ± 1.53 to 0.92 ± 1.09 Guillon patterns (Fig. 6). The average non-invasive pre-lens break-up time improved significantly, increasing from 15.19 ± 9.54 to 25.31 ± 15.81 s. Furthermore, the average score for the Patient Evaluation of Eye Disease dropped from 7.39 ± 4.39 to 5.53 ± 4.83.

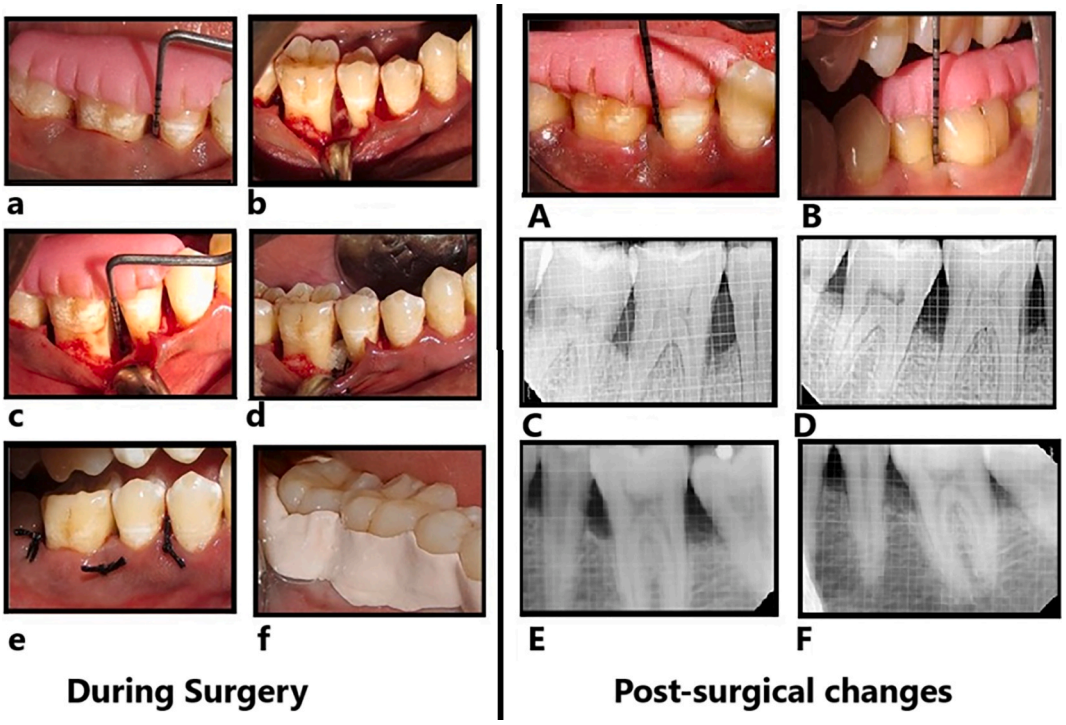

Fig. 7. During Surgery illustrates several key stages: **(a)** measurement of periodontal probing depth and clinical attachment level at 8 mm; **(b)** the process of flap reflection, debridement, and the surgical intervention for the intra-bony defect; **(c)** the intra-surgical assessment of the distance from the cementoenamel junction to the depth of the bony defect; **(d)** the application of fucoidan-chitosan gel into the intra-bony site; **e)** the placement of sutures and the coverage of the intra-bony defect with the flap; **(f)** the application of a periodontal pack.

According to the results, these contact lenses may help people who wear them by lowering the volume of lipid and aqueous tear films, improving the stability of pre-lens tear films, and reducing subjective symptoms of dry eyes (Capote-Puente et al., 2023).

4.6. Dental medicine

Hydrogels are pivotal in dentistry for targeted drug delivery, tissue regeneration, and wound healing. For this reason, they address complex dental conditions like periodontitis, caries, pulpitis, peri-implantitis, and oral malignancies by tackling microbial infections, inflammation, and tissue degeneration (Fratila et al., 2024). Despite dental advancements, existing therapies face limitations such as microleakage in resin composites, tooth fragility in root canal fillings, and side effects in antibiotic dressings. Hydrogels offer solutions by improving treatment delivery, promoting tissue repair, and reducing infection risks. They are exceptional scaffolds for tissue engineering, integrating successfully with stem cells and growth hormones. Chitin hydrogel/nanocomposite scaffolds and shape-recoverable hydrogels for cosmetic applications are examples of innovations that improve periodontal health by increasing treatment effectiveness and application simplicity (Wu et al., 2021). To further validate these promising applications, a number of clinical trials have been conducted to evaluate the effectiveness and safety of hydrogel-based formulations in various dental treatments.

Proanthocyanidins' effectiveness as an adjuvant periodontal therapy in individuals with stage III–IV periodontitis was assessed in a randomized clinical trial. Forty-six patients were split into two groups: one group had minimally invasive nonsurgical therapy in addition to collagen hydrogels containing proanthocyanidins applied subgingivally, and the other group received minimally invasive nonsurgical therapy alone. Before and after treatment, clinical periodontal parameters like as plaque index, bleeding on probing, clinical attachment level, and pocket probing depth were measured. In comparison to minimally invasive nonsurgical therapy alone, the results demonstrated that proanthocyanidins combined with this treatment resulted in a statistically significant decrease in pocket probing depth and an average clinical attachment level gain of 0.5 mL in moderate periodontal pockets. However, the additional use of proanthocyanidins did not significantly improve bleeding on probing or plaque index values. Notably, proanthocyanidins application resulted in a significant reduction of matrix metalloproteinase-3 levels in saliva after eight weeks, demonstrating the potential benefits of hydrogel-based formulations in enhancing periodontal therapy outcomes (Alkimavičienė et al., 2023).

Another study assessed the efficacy of local administration of amino acid-buffered sodium hypochlorite gel in conjunction with minimally invasive nonsurgical therapy for periodontal pockets. Two groups of forty untreated patients with severe or advanced periodontitis were created: one group underwent minimally invasive nonsurgical therapy in addition to the hydrogel-based gel, and the other group received the therapy alone. Gingival recessions, clinical attachment levels, probing depths, full-mouth plaque scores, and full-mouth bleeding scores were measured at baseline and six months following treatment. When compared to the therapy alone, the results demonstrated that the combination of the hydrogel-based gel and the therapy considerably enhanced clinical attachment levels and decreased probing depths. The combination group also saw a significant decrease in the frequency of locations with bleeding on probing and probing depths of 5 mL or more. This study demonstrated how hydrogel-based formulations could improve the results of nonsurgical, minimally invasive treatment for periodontal pockets (Iorio-Siciliano et al., 2021).

Furthermore, a study sought to develop an injectable hydrogel that included chitosan and fucoidan in order to show how successful it is at regenerating periodontal bone. The method known as sol–gel was used to synthesize this hydrogel, and its capacity to promote the production of new bone was evaluated. Forty patients with bone deformities and periodontitis were randomized into two groups, one of which received concentrated growth factor and the other the fucoidan-chitosan hydrogel. While Group 2 received a concentrated growth factor for bone

regeneration, Group 1 participants had their defect sites surgically filled with fucoidan-containing chitosan hydrogel as a bone-regenerative material. Simple interrupted sutures were used to close the original wound, and then a periodontal dressing was placed (Fig. 7). Clinical parameter changes following surgery were assessed at 3, 6, and 9 months. Clinical parameter changes following surgery were assessed at 3, 6, and 9 months. The hydrogel exhibited excellent porosity, water uptake, and biocompatibility with the MG-63 osteoblast cell line. It also resulted in lower probing depth values and greater mean improvement in clinical attachment levels compared to the concentrated growth factor group. Fucoidan's promise in tissue engineering was demonstrated by the hydrogel's considerable improvement in human bone regeneration. A promising biomaterial for the regeneration of bone tissue is fucoidan-chitosan (Eshwar et al., 2023).

Post-surgical observations include: **A)** a decrease in periodontal probing depth within the fucoidan-chitosan group at three months; **B)** a further decrease in periodontal probing depth within the same group at six months; **C)** a radiovisiographic image depicting the intra-bony defect at baseline for the fucoidan-chitosan group; **D)** a radiovisiographic image demonstrating improvement in the intra-bony defect at nine months for the fucoidan-chitosan group; **E)** a radiovisiographic image of the intra-bony defect at baseline for the concentrated growth factor group; **F)** a radiovisiographic image of the intra-bony defect at 9 months for the concentrated growth factor group. Reprinted with permission from Eshwaret al., 2023.

4.7. Drug delivery devices

Drug delivery systems enhance therapeutic efficacy by addressing issues of short half-life, poor bioavailability and solubility, of drugs. Polymer-based hydrogels, the key to a controlled drug delivery system, enable sustained drug release, maintaining therapeutic concentrations and reducing dosing frequency, thereby improving patient compliance. These hydrogels can target specific tissues, minimizing systemic exposure and off-target side effects (Gaharwar et al., 2014; Ye et al., 2016). Hydrogels protect drugs in oral delivery from degradation in the gastrointestinal tract and facilitate transdermal delivery through controlled release when applied to the skin. They are also suitable for implantable systems for chronic diseases and for gene delivery by safeguarding genetic material and directing it to specific cells. Their diverse applications make polymer-based hydrogels a key focus in drug delivery research, promising innovative future developments (Porter et al., 2007).

A clinical trial evaluated the drug delivery rate and safety of the Transderm Scop® hydrogel-based transdermal delivery system in healthy adults. Participants received either a single intravenous dose of 0.4 mg scopolamine hydrobromide or wore a Transderm Scop® patch (1.5 mg) for 3 days, then switched treatments. The primary outcomes measured included maximum serum concentration, clearance, volume of distribution, elimination rate constant, and residual drug analysis in the transdermal system. Secondary outcomes assessed included scopolamine clearance, volume distribution, elimination rate constant, and area under the serum concentration–time curve. Results of the study indicated that Transderm Scop® effectively maintained therapeutic drug levels with minimal systemic side effects, showcasing its potential as a reliable hydrogel-based drug delivery system (Scopolamine Patch Pharmacokinetics in Healthy Adults,2025).

Another clinical study evaluated the effectiveness of combining topical aminolaevulinic acid-photodynamic therapy with hydrogel dressing for treating chronic cutaneous wounds. Sixty-three patients with chronic infectious wounds were divided into three groups: hydrogel dressing changes every three days, aminolaevulinic acid-photodynamic therapy every ten days for four sessions, and a combination of both treatments. Group 3, which combined aminolaevulinic acid-photodynamic therapy with hydrogel dressing, showed the most significant improvement. The hydrogel dressing was key in maintaining a moist wound environment, enhancing the overall effectiveness of the photodynamic therapy. Patients in Group 3 experienced higher wound healing rates, greater total effectiveness, and improved patient satisfaction, with minimal adverse reactions and lower recurrence rates. This study demonstrated the potential of hydrogel dressings in enhancing the therapeutic outcomes of treatments for chronic wounds (Photodynamic Therapy With Hydrogel Dressing for Chronic Wounds, 2025).

A clinical study evaluated the effectiveness of a hydrogel-based microneedle material for minimally invasive monitoring and diagnostic applications in human subjects. The hydrogel was synthesized by crosslinking hydrolyzed poly(methyl-vinyl ether-co-maleic anhydride) with poly(ethylene glycol) (10,000 Da) through esterification. Upon insertion into the skin, these microneedles exhibited swelling properties. During the trial, theophylline and caffeine were analyzed using high-performance liquid chromatography. The findings revealed that the peak mean caffeine concentration in participants reached 91.31 μg/mL within 1 to 2 h after consuming 100 mg Proplus® tablets. Additionally, the highest mean blood glucose level observed was 7.89 nmol/L, recorded 1 h after the ingestion of 75 g of glucose. The maximum mean glucose concentration extracted from the microneedles was 4.29 nmol/L, measured 3 h after skin application. The data indicated that the concentrations obtained from the microneedles closely mirrored blood concentration trends. The study underscored the potential of hydrogel-forming microneedles as a promising tool for non-invasive patient monitoring and diagnostics, offering a minimally invasive alternative for healthcare applications (Donnelly et al., 2014).

4.8. Hearing diseases

A syndrome known as sudden sensorineural hearing loss (SSHL) causes people to rapidly lose their hearing in one ear, usually within three days. Despite being the most common treatment for SSHL, systemic glucocorticoids do not improve the condition for about 20 % of patients. Researchers assessed the efficacy and safety of topical insulin-like growth factor 1 (IGF-1) therapy for SSHL using gelatin hydrogels in a clinical investigation. Patients who had not responded to systemic glucocorticoid treatment were included in this prospective study. 26 patients in all fulfilled the requirements for inclusion; however, one patient was disqualified because they had been diagnosed with functional hearing loss. In the end, 25 patients —13 women and 12 men − were treated in accordance with the study's guidelines. The middle ear was treated with gelatin hydrogels that were impregnated with recombinant human IGF-1. The percentage of patients who experienced improvement in their hearing 12 weeks after treatment was the main goal; the rate of adverse events and the percentage of patients who showed improvement at 24 weeks were secondary endpoints. 48 % (95 % CI 28 % to 69 %; $P = 0.086$) of individuals showed improvement in their hearing at 12 weeks after the test therapy. At 24 weeks, this percentage rose to 56 % (95 % CI 35 % to 76 %; $P = 0.015$). During the study, no significant adverse events were reported. In individuals with SSHL who do not react to systemic glucocorticoids, the researchers found that topical IGF-1 administration using gelatin hydrogels is well tolerated and may be useful in fostering hearing recovery (Nakagawa et al., 2010).

In order to treat abrupt deafness that is not sensitive to systemic corticosteroids, a study examined the safety and efficacy of topical IGF-1 therapy in comparison to intratympanic corticosteroid therapy. Two groups of patients were randomly assigned: 62 individuals received middle ear applications of gelatin hydrogels loaded with IGF-1, while 58 patients received four intratympanic injections of dexamethasone. Eight weeks after treatment, the percentage of patients who experienced hearing improvement − defined as an increase in pure-tone average hearing thresholds of 10 dB or more − was the main outcome that was measured. Adverse occurrences and changes in hearing thresholds over time were examples of secondary outcomes. The findings indicated that while the difference was not statistically significant ($P = 0.109$), 66.7 %

Table 2
Hydrogel-based products on the market.

Product in market	Category	Use	Reference
Ocufilcon D	Contact lenses	These lenses are designed for daily wear and can correct myopia, hyperopia, and astigmatism.	(Ocufilcon D Soft (Hydrophilic) Contact Lenses Daily Wear For Planned Replacement or Daily Disposable, 2025)
Si-Hy (olifilcon B)	Contact lenses	The composition of these colored lenses is 47 % water and 53 % olifilcon B. To prevent UV rays, they have a UV-absorbing monomer.	(510(k) Premarket Notification, 2025)
Maxvue® Airsoft™ Monthly Silicone Hydrogel Contact Lenses	Silicone Hydrogel lenses	Superior oxygen and moisture levels are combined in AirsoftTM Silicone Hydrogel contact lenses to provide outstanding comfort and eye health.	(Experience Cutting-Edge Silicone Hydrogel Technology,2025)
ACUVUE® Abiliti™ Overnight	Orthokeratology lenses	A powerful approach to managing myopia. They enable clear vision during the day without the need for vision correction by temporarily reshaping the cornea.	(ACUVUE® Abiliti™ Overnight, A powerful approach to managing myopia,2025)
Precision7 Multifocal Toric (serafilcon A) Soft Contact Lenses	Soft Contact Lenses	Myopia, or nearsightedness, hyperopia, and astigmatism, or distorted or blurred vision caused by an abnormal curvature of the cornea, or front surface of the eye, are all conditions that can be treated with the lens.	(Precision7, Precision7 for Astigmatism, Precision7 Multifocal, Precision7 Multifocal Toric (serafilcon A) – P220007,2025)
TIMOPTIC-XE®	Timolol maleate ophthalmic gel forming solution	Effective in lowering intraocular pressure.	(Timoptic-XE,2025)
EVO ICL™	Implantable Collamer Lens	People with astigmatism, farsightedness (hyperopia), and nearsightedness (myopia) can correct their vision using this surgically implanted lens inside the eye.	(EVO ICL™, STAAR® Surgical's phakic IOL for myopia and astigmatism,2025)
ACUVUE® OASYS	Contact Lenses	Hydrogel contact lenses for vision correction, specifically for dry eye and comfort.	(ACUVUE® OASYS 1-DAY with HydraLuxe® Technology,2025)
EvoTears® OMEGA	eye drops	Used to treat dry and irritated eyes and eyelids.	(EvoTears® OMEGA: Unique1 in treating dry and irritated eyes or eyelids,2025)
Vistakon®	Contact Lenses	Silicone hydrogel contact lenses for long-lasting comfort and vision correction.	(VISTAKON® Division Of Johnson & Johnson Vision Care, Inc. Sponsors Free Eye Exam Event For World Sight Day,2025)
ACell® MatriStem®	Wound Sheet	Designed to treat a range of wounds, including surgical wounds, tunneled or undermined wounds, venous ulcers, pressure ulcers, diabetic ulcers and full-thickness and partial-thickness wounds.	(ACell MatriStem® Technology Ranks Highest in Constructive Remodeling , 2025)
3 M™ Tegaderm™	Wound dressing	The absorbent clear acrylic dressing is a transparent, absorbent dressing that allows easy monitoring of wounds or surgical sites without removal. Its acrylic polymer pad absorbs low to moderate exudate, creating an optimal healing environment.	(3M™ Tegaderm™ Silicone Foam Non-Bordered Dressing, 90632, 2025)
Aquacel™ Ag + dressings combine Hydrofiber™ Technology	Wound dressing	When this dressing interacts with wound fluid, it forms a soft gel that absorbs moisture, shields the wound from bacteria, and supports healing. The ionic silver helps eliminate harmful microorganisms, reducing the risk of infection.	(Aquacel™ Ag+ dressings, 2025)
PuraPly®AM and PuraPly®XT	matrix scaffold	A cross-linked extracellular matrix scaffold with sustained antimicrobial properties to promote wound healing and enhance granulation tissue formation.	(POWER OF PLUS WITH PURAPLY®AM & PURAPLY®XT, 2025)
Bard CollaMend® Implant	Wound Healing & Tissue Regeneration	The purpose of the Bard CollaMend Implant is to strengthen soft tissue in weak spots, such as in plastic and reconstructive surgery, hernia repair, chest wall abnormalities, and surgical repairs of damaged or ruptured soft tissue membranes.	(510(K) SUMMARY OF SAFETY AN!) EFFECTIVENESS FOR TIlE BARD(®) COL.I AMEND‘‘ IMPLANT,2025)
Mepilex Border	Five-layer all-in-one dressing for wounds	Hydrocolloid dressing promotes moisture balance and enhances wound healing in chronic and post-operative wounds.	(Mepilex® Border, 2025)
Dermagraft®	Wound Healing & Tissue Regeneration	Cryopreserved human dermal fibroblast-based hydrogel dressing for diabetic foot ulcers and chronic wounds.	(Ather et al., 2019)
Regranex®	Wound Healing & Tissue Regeneration	Platelet-derived growth factor hydrogel for chronic diabetic foot ulcers to promote tissue regeneration.	(Jarvis, 2008)
Collagen-Hydrogel Membranes (CollaTape™)	Tissue Regeneration (Dental)	Collagen hydrogel membranes are used in dental tissue engineering, including guided tissue regeneration for periodontics.	(HeliTape® Collagen Wound Dressing, 2025)
PerioPatch™	Wound Healing (Dental)	Hydrogel-based dressing for post-surgical wound healing in dental procedures like extractions and gum surgeries.	(Paquette and Levine, 2015)
Gengigel®	Gum and Soft Tissue Healing	It is used to manage various intra-oral inflammatory and painful conditions, as well as to assist patients with periodontal disease who show poor healing after treatment.	(Gupta et al., 2017)
Restylane	Dermal fillers	It is used for lip enhancement (volume and contouring) and smoothing wrinkles and aging lines, such as nasolabial folds and melomental folds.	(Bagheri and Khan, 2014)
Arthrosamid®	Knee osteoarthritis	It is an injectable hydrogel designed for the treatment of knee osteoarthritis. It provides long-lasting pain relief and improves joint function by acting as a cushion within the knee joint.	(Arthrosamid®,2025)
Aquamid	volume filler	It is used for facial volumizing and deep structural augmentation, enhancing cheeks, lips, folds, and contours.	(Yamauchi, 2014)
Skinvive	Skin hydrator	It is used to improve skin smoothness and hydration, particularly in the cheeks.	(SKINVIVE by JUVÉDERM®, 2025)
Hydrafil	Low back pain	It provides effective pain relief, restores disc height and preserves spinal motion through a minimally invasive procedure.	(Hydrafil™ ,2025)

Table 3
List of key clinical trials ongoing/completed on hydrogels.

Name (sponsor company/ university) and Country	Description	Phase	Status	Results	ClinicalTrials.gov ID
Associazione Infermieristica per lo studio delle Lesioni Cutanee/ Italy	MySkin Patch's effectiveness in healing abrasions and cuts.	Phase 3	2012/ Completed	NRA	NCT01573234
Oystershell NV/ Germany	Assessment of Wound Healing, Cooling Efficacy and Local Tolerability of a Wound Care Hydrogel.	NA	2020/ Completed	NRA	NCT06309446
Teikoku Seiyaku Co., Ltd./ Germany	Esflurbiprofen hydrogel patch's safety and effectiveness in the management of local acute pain.	Phase 2	2021/ Completed	ATP	NCT04908748
B. Braun Ltd. Centre of Excellence Infection Control/ Germany	This study aims to assess how well split-thickness skin grafts heal in patients with partial and full-thickness skin burns after receiving Prontosan® Wound Gel X treatment.	NA	2012/ Completed	NRA	NCT01534858
Contrad Swiss SA/ Italy	The purpose of this post-market confirmatory interventional clinical study is to assess AI500TM SINGLE-DOSE GEL's efficacy and safety in individuals with impaired knee function.	NA	2022/ Completed	NRA	NCT05886608
CooperVision International Limited (CVIL)/Spain	This study was to evaluate the patient's subjective experiences of two daily disposable toric contact lenses.	NA	2023/ Completed	ATP	NCT05805085
Rottapharm Biotech/ Poland	To investigate poly venyl alcohol Hydrogel's effects on patients with osteoarthritis in their knees in comparison to Synvisc-One®	NA	2019/ Completed	NRA	NCT04693104
National Scientific Center of Traumatology and Orthopedics named after academician N.D. Batpenov/ Kazakhstan	The purpose of this study is to compare the efficacy of heparin-conjugated gel and the traditional microfracture approach for treating cartilage lesions in the ankle joint.	Not Applicable	2023/ Recruiting	Waiting	NCT06028763
Assistance Publique – Hôpitaux de Paris/ France	HIV-related lipoatrophy is treated with injections of polyacrylamide hydrogel (LIPOPHILL).	Phase 3	2005/ Completed	NRA	NCT01077765
Wake Forest University Health Sciences/ United States	An oral formulation including a mucoadhesive polymer hydrogel vehicle (MucoLox®) was tested in a phase II randomized trial to reduce mucositis symptoms in patients with head and neck cancer undergoing radiation and chemotherapy.	NA	2018/Active, not recruiting	Terminated	NCT03461354
University Hospital Padova/Italy	Intra-operative air leak management after minimally invasive lung segmental resection: randomized comparison between polymeric hydrogel matrix and standard of care.	NA	2023/ Recruiting	Waiting	NCT06544200
SerenaGroup, Inc./ United States	The purpose of the randomized double-blind controlled clinical trial is to assess the healing rates of chronic lower extremity ulcers between the use of an amorphous gel and normal saline wash and the use of a synergistic antimicrobial cleanser and antimicrobial gel.	NA	2021/Active, not recruiting	Unknown	NCT05107050
CooperVision, Inc./ United States	The purpose of the study is to assess the clinical performance of various hydrogel and silicone hydrogel contact lenses.	NA	2013/ Completed	ATP	NCT01966770
October 6 University /Egypt	The purpose of this randomized clinical trial was to evaluate the clinical efficacy of treating periodontal intrabony deficiencies using chitosan and nano-hydroxyapatite hydrogel.	NA	2023/ Completed	NRA	NCT06373757

Abbreviations: NA: **Not available;** NRA: **No Results Available;** ATP: **Available on the trial platform**.

(95 % CI: 52.9–78.6 %) of patients in the IGF-1 group reported an improvement in their hearing, compared to 53.6 % (95 % CI: 39.7–67.0 %) in the dexamethasone group. The IGF-1 group, however, showed a considerably better change in pure-tone average hearing thresholds over time ($P = 0.003$). Neither group experienced any significant adverse events. Notably, in the dexamethasone group, tympanic membrane perforation remained in 15.5 % (95 % CI: 7.3–27.4 %) of patients, whereas in the IGF-1 group, it vanished entirely ($P = 0.001$). In comparison to intratympanic corticosteroids, the results indicate that topical IGF-1 therapy is a potential treatment for acute deafness, showing both efficacy in improving hearing and a favorable safety profile (Nakagawa et al., 2014).

5. Real-World products and clinical innovations

Hydrogels are currently widely employed in both commercial and medical devices, including medication delivery systems, contact lenses, and wound dressings. Products that preserve moisture and encourage tissue regeneration, such as hydrogel-based dressings, create the ideal conditions for wound healing. The high water content of hydrogels improves oxygen permeability and comfort in contact lenses. The current market for hydrogel-based products is diverse, showcasing their versatility across multiple industries. From healthcare to personal care, hydrogel-based solutions have gained widespread acceptance for their effectiveness and user-friendly nature. Table 2 summarizes some of the most prominent hydrogel-based products currently available on the market, categorized by their application areas.

As evidenced, hydrogels have garnered significant attention in the field of clinical research due to their potential to revolutionize treatments across various medical disciplines. So, numerous clinical trials, both ongoing and completed, are exploring the use of hydrogels for conditions such as wound healing, osteoarthritis, tissue regeneration, and dental problems, among others. For a more objective perception, Table 3 provides an overview of key clinical trials involving hydrogels, highlighting their focus areas, and current status.

6. Challenges and opportunities for hydrogel applications

Hydrogels hold immense potential across various fields but face well-documented challenges that limit their clinical translation. One of the main drawbacks is their low mechanical strength, which hinders their application in load-bearing tissues such as cartilage or bone. This issue has been widely reported and addressed through strategies such as the incorporation of nanomaterials and optimized crosslinking methods (Fang et al., 2023). Ensuring biocompatibility, long-term safety and biodegradability also remains a key concern, since degradation by-products can trigger immune responses or compromise therapeutic performance.

Stability under physiological conditions is another critical challenge, particularly for formulations intended for prolonged or highly sensitive applications, such as controlled drug release. In addition, stringent regulatory requirements and the need for cost-effective and

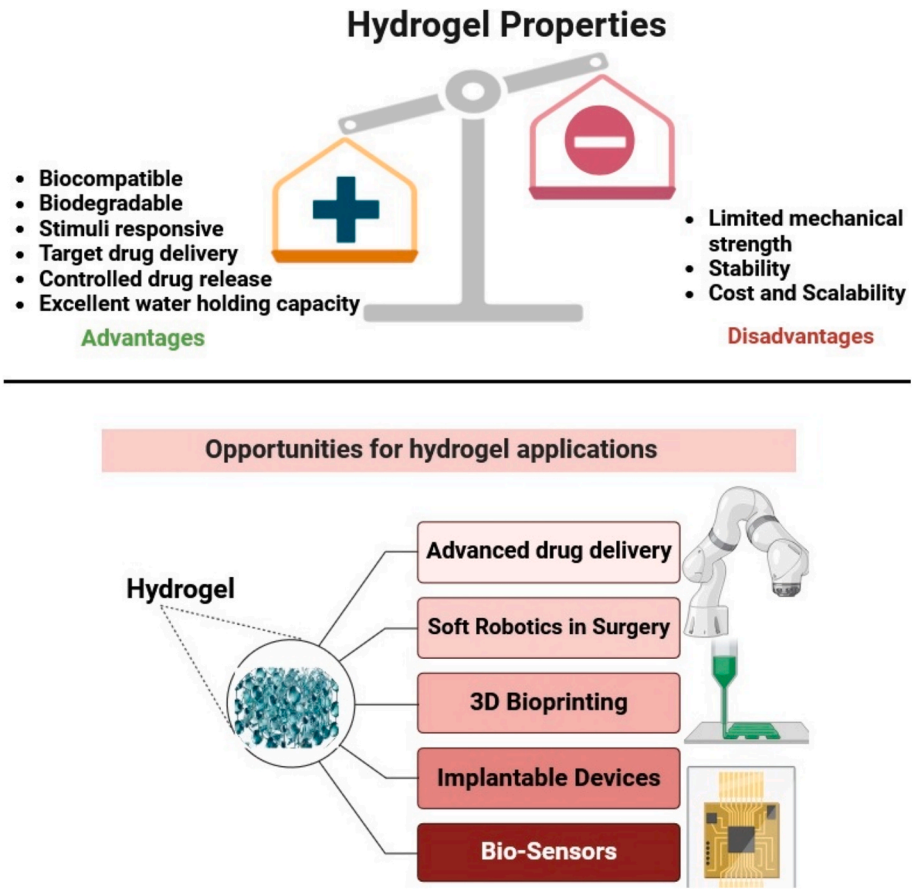

Fig. 8. Advantages, disadvantages, and future opportunities for hydrogel applications.

reproducible manufacturing processes further complicate clinical development (Fang et al., 2023). Many hydrogels perform well in vitro but cannot be transposed to preclinical and clinical models due to scalability limitations and inconsistent performance.

Despite these challenges, hydrogels remain very attractive materials due to their versatility and tunable properties, allowing them to be used in advanced therapeutic strategies. Emerging systems are increasingly stimuli-responsive, capable of reacting to pH, temperature, or biological signals, thus providing precise and regulated therapeutic delivery. These smart systems minimize side effects and increase therapeutic efficiency, addressing the limitations of conventional drug delivery methods.

In tissue engineering, hydrogels function as scaffolds that mimic the extracellular matrix, supporting cell proliferation and tissue regeneration, particularly in cartilage repair and wound healing. However, accurately replicating the biomechanical and biochemical properties of specific tissues remains a significant challenge. Additionally, in 3D bioprinting, combining hydrogels with living cells and biomolecules requires careful balancing of rheological properties and cell viability to maintain structural integrity and function in engineered tissues (Fang et al., 2023).

Hydrogels with tunable features such as softness, elasticity, and environmental responsiveness are also being explored for use in soft robotics, where materials that simulate biological tissues are needed. These systems, often enhanced with nanomaterials, represent promising platforms for biosensors and wearable medical devices (Barhoum et al., 2023; Tai et al., 2024; Völlmecke et al., 2022).

Thus, while hydrogels show broad biomedical potential, overcoming challenges such as mechanical fragility, physiological stability, scalability, and regulatory compliance demands ongoing interdisciplinary research. As advances in material science and biotechnology progress, hydrogels are set to transform healthcare by offering innovative solutions to complex medical problems, allowing an evolution towards increasingly effective and personalized therapeutic platforms. Fig. 8 summarizes the main advantages, disadvantages and opportunities for future hydrogel applications.

7. Conclusions

Polymeric hydrogels have emerged as a cornerstone of modern biomedical innovation, owing to their unique combination of biocompability, tunable properties, and structural similarity to native tissues. As discussed throughout this review, their versatility enables a wide spectrum of clinical applications, from controlled drug delivery systems and renegerative medicine to wound healing, joint therapy, and ophthalmology. Their adaptability has been further enhanced by the integration of smart functionalities, such as stimuli-responsiveness and bioactive modification, making them increasingly suitable for personalized and precision medicine.

However, the successful clinical translation of hydrogels depends on more than their biological promise. It requires overcoming specific barriers, including mechanical fragility, physiological instability, and manufacturing scalability. Building upon the limitations and opportunities previously discussed, future research should prioritize advanced crosslinking strategies, biocompability optimization, and reproducible production methods to enhance afety and performance in clinical settings.

It is important to note that clinical efficacy must remain at the center of hydrogel development. Demonstrating therapeutic efficacy not only speeds up regulatory approval, but also promotes wider adoption in real-world healthcare. Ongoing interdisciplinary collaboration between materials scientists, biomedical engineers and clinicians is vital to bridging the gap between laboratory research and patient-centered

outcomes.

Ultimately, hydrogels are not just promising materials, they are dynamic platforms capable of transforming therapeutic paradigms. With targeted innovations and robust translational strategies, they are well placed to become key drivers of next-generation healthcare solutions.

Informed Consent Statement

Not applicable.

CRediT authorship contribution statement

Alka Lohani: Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Ritika Saxena:** Writing – original draft, Investigation. **Joana Galvão Duarte:** Writing – original draft, Investigation. **Shahbaz Khan:** Writing – original draft, Investigation. **Ana Figueiras:** Validation, Supervision. **Filipa Mascarenhas-Melo:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Funding

This research received no external funding.

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.

Acknowledgment

The authors acknowledge the support from the BRIDGES - Biotechnology Research, Innovation and Design for Health Products, Polytechnic University of Guarda, Portugal and Amity University Uttar Pradesh, Noida, India.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2025.125818.

Data availability

No data was used for the research described in the article.

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