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Historical Perspective

Innovations in hydrogel-based manufacturing: A comprehensive review of direct ink writing technique for biomedical applications

Hossein Baniasadi [a,*], Roozbeh Abidnejad [b], Mahyar Fazeli [b], Juha Lipponen [b], Jukka Niskanen [a], Eero Kontturi [b], Jukka Seppälä [a], Orlando J. Rojas [b,c]

[a] Polymer Technology, School of Chemical Engineering, Aalto University, Espoo, Finland
[b] Department of Bioproducts and Biosystems, School of Chemical Engineering, Aalto University, Aalto FI-00076, Finland
[c] Bioproducts Institute, Department of Chemical & Biological Engineering, Department of Chemistry, Department of Wood Science, 2360 East Mall, The University of British Columbia, Vancouver, BC V6T 1Z3, Canada

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ABSTRACT

Direct ink writing (DIW) stands as a pioneering additive manufacturing technique that holds transformative potential in the field of hydrogel fabrication. This innovative approach allows for the precise deposition of hydrogel inks layer by layer, creating complex three-dimensional structures with tailored shapes, sizes, and functionalities. By harnessing the versatility of hydrogels, DIW opens up possibilities for applications spanning from tissue engineering to soft robotics and wearable devices. This comprehensive review investigates DIW as applied to hydrogels and its multifaceted applications. The paper introduces a diverse range of printing techniques while providing a thorough exploration of DIW for hydrogel-based printing. The investigation aims to explain the progress made, challenges faced, and potential trajectories that lie ahead for DIW in hydrogel-based manufacturing. The fundamental principles underlying DIW are carefully examined, specifically focusing on rheological attributes and printing parameters, prompting a comprehensive survey of the wide variety of hydrogel materials. These encompass both natural and synthetic variations, all of which can be effectively harnessed for this purpose. Furthermore, the review explores the latest applications of DIW for hydrogels in biomedical areas, with a primary focus on tissue engineering, wound dressing, and drug delivery systems. The document not only consolidates the existing state of DIW within the context of hydrogel-based manufacturing but also charts potential avenues for further research and innovative breakthroughs.

List of abbreviations

3D	Three-dimensional
CMC	Carboxymethyl cellulose
CNCs	Cellulose nanocrystals
CNFs	Cellulose nanofibrils
DIW	Direct ink writing
DPL	Digital light processing
EBM	Electron beam melting
ECM	Extracellular matrix
FDM	Fused deposition modeling
GelMA	Gelatin methacrylate
GG	Gellan gum
GMA	Glycidyl methacrylate
GO	Graphene oxide
hBMSCs	human bone mesenchymal stem cells
ME	Materials extrusion
PAAm	Polyacrylamide
PCL	Polycaprolactone
PEG	Polyethylene glycol
PEGDMA	Poly(ethylene glycol) dimethacrylate
PEO	Poly(ethylene oxide)
pHEMA	Poly(2-hydroxyethyl methacrylate)
PNIPAAm	Poly(N-isopropylacrylamide)
PPy	Polypyrrole
PU	Polyurethane
PVA	Polyvinyl alcohol
QSM	Quince seed mucilage
SLA	Stereolithography
SLM	Selective laser melting
SLS	Selective laser sintering
TOCNF	TEMPO-oxidized cellulose nanofibrils
XG	Xanthan gum

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* Corresponding author.
E-mail address: hossein.baniasadi@aalto.fi (H. Baniasadi).

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1. Introduction

Hydrogel, an intricate three-dimensional (3D) polymeric network, is synthesized through chemical and/or physical crosslinking processes. This network structure imparts remarkable hydrophilic characteristics, enabling the hydrogel to absorb and retain substantial amounts of water while maintaining its structural integrity. The unique properties of hydrogels have boosted them to the forefront of scientific exploration and industrial application over the past several decades. This interest can also be attributed to the remarkable versatility and adaptability of hydrogels, as well as the relatively straightforward methods available for their preparation. Furthermore, researchers can manipulate and tailor the physical, chemical, and mechanical characteristics of hydrogels to suit a wide array of applications [1–5]. Consequently, hydrogels are becoming interesting materials in various biotechnological and engineering disciplines. Drug-delivery systems [6,7], tissue engineering scaffolds [8–10], anti-fogging films [11,12], antifouling coatings [13,14], self-healing materials [15,16], soft robotics [17,18], and cutting-edge 3D printing [19–21] technologies are some examples.

3D printing, also known as additive manufacturing, has revolutionized various industries by enabling the creation of intricate 3D objects through a layer-by-layer deposition process. This technology has gained widespread attention and adoption due to its remarkable benefits. One of the key advantages of 3D printing is its efficient use of materials. Traditional subtractive manufacturing methods often result in significant material wastage, whereas 3D printing adds material only where needed, reducing waste and conserving resources. This not only benefits the environment but also contributes to cost savings for manufacturers. Furthermore, the ability to customize the geometry of objects is a major strength of 3D printing. Complex shapes and intricate designs that were once challenging or impossible to produce using conventional methods can now be easily manufactured using 3D printing techniques [22–25].

Direct ink writing (DIW) is a specialized 3D printing technique that holds significant promise, especially in hydrogel printing. DIW offers several advantages that make it particularly well-suited for hydrogel printing. Firstly, DIW allows for precise control over the deposition of hydrogel ink. This control stems from the digital nature of the process, enabling the customization of print patterns with high accuracy. Secondly, the low ink consumption and efficient use of material align well with the resource-efficient nature of 3D printing [26–28]. Additionally, DIW's flexibility in changing print patterns simplifies the process of creating intricate structures, making it an ideal choice for complex hydrogel constructs [29,30]. However, DIW is limited by its focus on the viscoelastic characteristics of the ink. For 3D printing with hydrogels, it's essential that they possess a suitable level of fluidity to pass through the printing nozzle while also exhibiting viscosity during printing to maintain 3D patterns and uphold structural integrity post-printing. Additionally, these hydrogels need to demonstrate properties like shear-thinning or responsiveness to external stimuli to enable successful 3D printing. Shear-thinning hydrogels can be extruded under the influence of shear force and regain their mechanical properties after extrusion. As a result, various natural and synthetic hydrogels such as nanocellulose, sodium alginate, gelatin, gelatin methacrylate (GelMA), silk, polycaprolactone (PCL), and polyvinyl alcohol (PVA) have been employed in the development of 3D objects using the DIW technique [19,31–33].

In this review, we provide a comprehensive exploration of the direct ink writing of hydrogels and their multifaceted applications. With a focus on both the technical aspects and the diverse applications encompassed within this field, we embark on a journey to elucidate the advancements, challenges, and potential future directions of DIW in hydrogel-based manufacturing. The review explores the fundamental tenets of DIW, emphasizing rheological attributes and printing parameters. An essential facet of DIW resides in the choice and formulation of hydrogel inks. Consequently, we traverse the diverse spectrum of hydrogel materials, encompassing both natural and synthetic variants, which can be employed for DIW. In the following, the review explores how DIW has revolutionized different biomedical fields, from creating intricate scaffolds for tissue regeneration to drug delivery systems and wound dressing.

2. Hydrogel potential in direct ink writing

Hydrogels hold immense potential within DIW, a cutting-edge 3D printing technique facilitating precise layer-by-layer material deposition to craft intricate structures [18,19,22]. In this exploration, we delve into the exceptional possibilities that hydrogels offer within the context of DIW. With the flexibility of their rheological properties, hydrogels can be tailored to encompass a diverse spectrum of viscosities and shear-thinning characteristics. This adaptability allows them to be extruded through fine nozzles during DIW, enabling the fabrication of intricate and personalized 3D structures that faithfully emulate biological tissues and desired configurations. Notably, numerous hydrogels possess inherent biocompatibility and share affinities with the extracellular matrix (ECM) of biological tissues [3,34,35]. Thus, when integrated into DIW processes, these hydrogels serve as ideal scaffolds for advancing tissue engineering by fostering the creation of implants, grafts, and constructs that seamlessly engage with living cells and tissues.

Hydrogels possess the capacity to encapsulate bioactive molecules, growth factors, pharmaceuticals, or even living cells. This distinctive property facilitates the direct integration of therapeutic agents into the hydrogel structures, endowing them with capabilities for targeted drug delivery, localized therapy, and enhanced tissue regeneration [36,37]. Moreover, hydrogels demonstrate biodegradability, orchestrated to degrade in a controlled manner over time. This attribute proves particularly valuable for temporary implants and drug release systems, as the material gradually dissipates in tandem with the formation of new tissue, thereby mitigating the necessity for additional surgical interventions. Additionally, hydrogels are amenable to multifunctional design within a solitary structure, encompassing gradients of mechanical properties, porosity, and even the sequential release of multiple bioactive agents. Such multifaceted hydrogel constructs considerably expand their potential for diverse applications.

Through the synergy of advanced hydrogel formulations and DIW techniques, exceptional spatial resolution and precision are attainable. This capability empowers the creation of intricate structures replete with intricate details, a pivotal aspect for applications such as organ-on-a-chip devices, microfluidic systems, and other precision engineering constructs. Furthermore, the convergence of DIW and hydrogels holds promise within regenerative medicine. Tailor-made hydrogel scaffolds can be 3D printed directly at sites of injury or defects, effectively promoting tissue regeneration and potentially diminishing the necessity for invasive surgical interventions. Additionally, hydrogels fabricated *via* DIW act as foundational platforms for an array of endeavors, including drug screening, disease modeling, and pharmaceutical research. These hydrogels adeptly replicate tissue microenvironments, facilitating the systematic study of drug responses and the progression of diseases in a controlled and reproducible manner [20,23,29].

Within the landscape of hydrogel applications, two distinct categories emerge: natural and synthetic hydrogels. Each category boasts its own unique properties and applications, setting the stage for an in-depth exploration of their roles in the context of DIW in the ensuing sections.

2.1. Natural hydrogels in direct ink writing

Natural hydrogels, which frequently stem from materials such as collagen [38], gelatin [39], chitosan [40], alginate [41], and hyaluronic acid [42], exhibit inherent biocompatibility. These hydrogels are readily accepted by living tissues, with a negligible proclivity for eliciting unfavorable reactions when deployed in medical or biological contexts.

Moreover, they often furnish an environment more conducive to cell adhesion, proliferation, and differentiation [43]. By mimicking the architecture of the ECM, they facilitate cellular interactions and growth within an environment that closely approximates native conditions [3]. In addition to their biocompatibility, natural hydrogels possess intrinsic bioactive attributes, including the facilitation of tissue regeneration, acceleration of wound healing, and provocation of anti-inflammatory responses. These multifaceted properties render them highly appealing for utilization in domains such as wound management [44], controlled drug delivery [45], and tissue engineering [46]. For instance, composite hydrogels consisting of alginate, gelatin, and hyaluronic acid were effectively printed to regenerate full-thickness cartilage defects (see Fig. 1).

Another salient feature of natural hydrogels is their inherent biodegradability, characterized by gradual decomposition over time in a meticulously regulated manner. This biodegradability is particularly advantageous in situations necessitating transient support, with the eventual substitution by newly formed tissue being a desirable outcome [48]. Nonetheless, it is worth noting that natural hydrogels often exhibit diminished mechanical strength when juxtaposed with their synthetic counterparts [49]. As such, their utility may be somewhat constrained in applications demanding structural reinforcement, such as load-bearing implants. Various types of hydrogels have been employed in DIW for different purposes. A diverse array of natural hydrogel types has found application in DIW for a range of specific objectives. Tables 1 to 3 encapsulate the latest research endeavors that delve into the DIW of these hydrogels, highlighting their distinct roles and contributions in tissue engineering, wound dressing, and drug delivery, respectively. Moreover, in the subsequent sections, we introduce the most prevalent ones that exhibit promising applications in DIW technology.

2.1.1. *Cellulose hydrogels*

Derived from a primary component of plant cell walls, cellulose has emerged as a highly versatile and promising class of biomaterials. Through various chemical modifications and processing techniques, cellulose can be tailored to yield hydrogels with a wide range of customizable properties. This adaptability makes cellulose hydrogels particularly attractive for a diverse array of biomedical applications, including wound healing, drug delivery, and tissue engineering. One of the standout features of cellulose hydrogels is their exceptional biocompatibility. These hydrogels are well-tolerated by the human body and exhibit minimal cytotoxicity, making them ideal candidates for use in various medical applications. This biocompatibility is essential, especially in wound healing and tissue engineering, where the materials must interact harmoniously with the body's cells and tissues [88,89]. Moreover, cellulose hydrogels have gained recognition for their

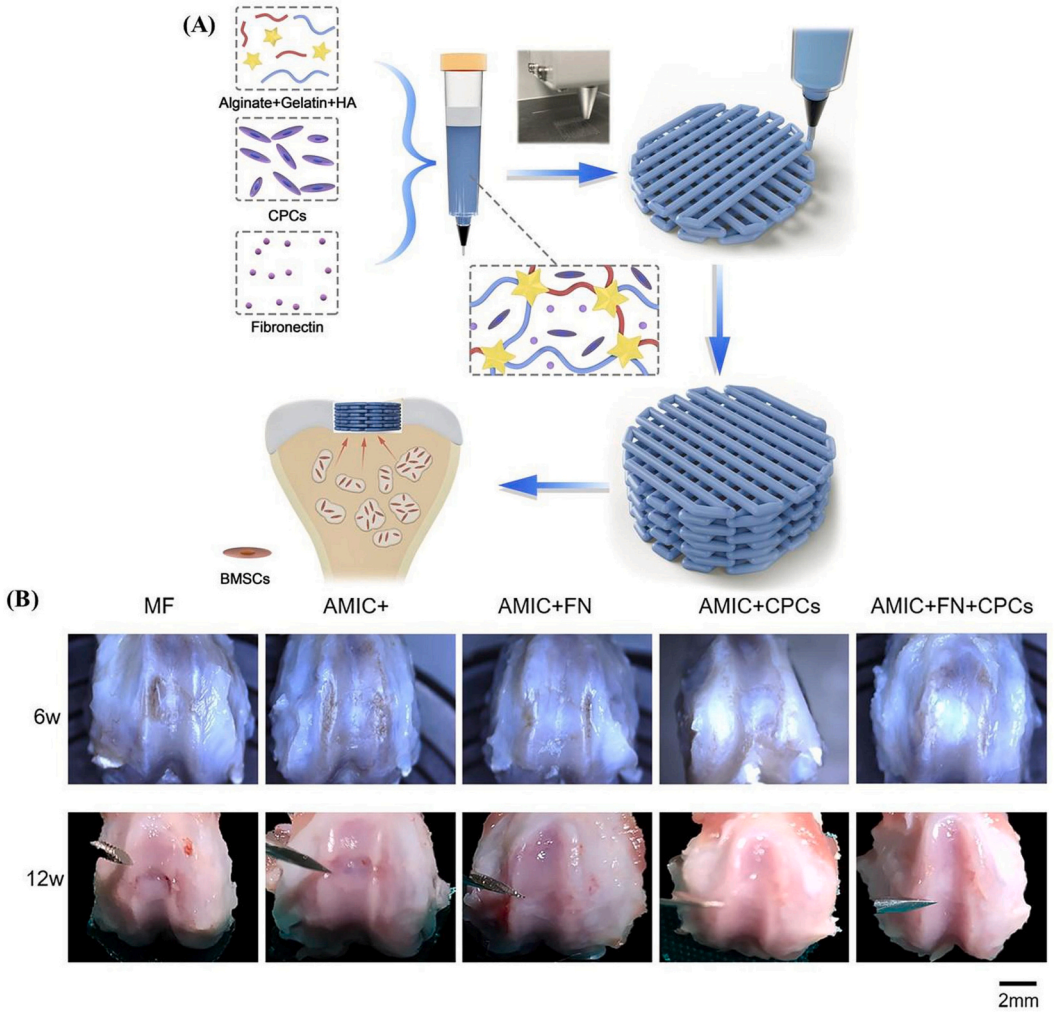

Fig. 1. Schematic illustration of a 3D-printed composite hydrogel of alginate, gelatin, and hyaluronic acid infused with CPC and FN. (B) Macroscopic appearance of regenerated cartilage at 6 and 12 weeks post-surgery in Sprague Dawley rats. The experimental groups include microfracture only (MF), 3D-printed alginate/gelatin/hyaluronic acid scaffold with microfracture (AMIC +), AMIC + with FN (AMIC + FN), AMIC + with CPC (AMIC + CPCs), and AMIC + with FN and CPC (AMIC + FN + CPCs) [47]. AMIC stands for autologous matrix-induced chondrogenesis, CPC for chondrogenic progenitor cells, FN for fibronectin, and HA for hyaluronic acid. With permission from Zhou, 2021, Copyright © 2021, Elsevier Ltd.

Table 1
Hydrogels employed in DIW, along with their applications in tissue engineering and printing parameters.

Hydrogel materials	Nozzle size (Gauge/mm)	Printing speed (mm/s)	Printing pressure (kPa)	Number of layers	Ref.
Cellulose nanocrystals (CNCs), polyethylene glycol	1.29 mm	10	–	3	[50]
Carboxymethyl cellulose (CMC)	0.120 mm	1 - 3	45 psi	11	[51]
CMC	0.260 mm	5	–	–	[52]
Cellulose nanofibrils (CNFs)	0.63	7.5	–	–	[53]
CNCs	0.33 mm	6 - 15	1.5 - 5 atm	40	[54]
CNFs, gelatin	25 G	20 - 25	150 - 170	10	[55]
Cellulose nanoribbons	0.25 mm	20	20 - 50	20	[56]
GelMA, xanthan gum (XG)	25 G	3 - 30	20 - 80	10	[57]
Tragacanth gum, CNFs	20 G	10	30 - 130	–	[58]
Chitosan	0.21, 0.26, 0.311 mm	–	60 psi	25	[59]
PVA, chitosan	22, 25 G	–	30 - 90	–	[60]
Chitosan, alginate	19 G	5	–	–	[61]
Gelatin, CMC, bacterial nanocellulose	0.6 mm	50	180	9	[62]
Oxidized alginate, gelatine	0.41 mm	2	110 - 180	50	[63]
GelMA	22 G	2 - 8	50	35	[64]
Acetylated nanocellulose, TEMPO-oxidized cellulose nanofibrils	19 G, 20 G, and 25 G	5, 8, 12	35, 43, 55	20 mm (layer height)	[65]
CNFs, gellan gum	0.2, 0.25, 0.41 mm	–	50 - 150	6	[66]
Alginate dialdehyde, gelatin	25 G	15	50 -120	4	[67]
GelMA, hyaluronic acid	22, 25, 27 G	5 -7	40 - 100	–	[68]
Pluronic F-127	0.838 mm	10	–	–	[69]
Pluronic F-127, alginate	22, 25, 27 G	15 - 35	45 - 75	–	[70]

Table 2
Hydrogels employed in DIW, along with their applications in wound dressing and printing parameters.

Hydrogel materials	Nozzle size (Gauge/mm)	Printing speed (mm/s)	Printing pressure (kPa)	Number of layers	Ref.
Quince seed mucilage (QCM), CNFs	0.84 mm	–	14 - 18	5	[1]
CNFs, *aloe vera*	0.63 mm	–	40	5	[19]
XG, CNCs	0.25 mm	20	70 - 90	9	[21]
CNFs, CNCs	0.41, 0.84 mm	10	100 - 350	32	[71]
CNFs	0.58 mm	3	–	4	[72]
GelMA, XG	0.3 mm	30	300 - 500	6	[73]
CMC, ε-polylysine	2 mm	6	60	–	[74]
Gelatin	25, 27 G	30	25 psi	3	[75]
CMC	0.41 mm	–	–	2	[76]
Egg white	0.565 mm	13 - 23	75 psi	2	[77]
Alginate, methylcellulose	0.25 mm	–	–	–	[78]
Acrylamide, sodium alginate	0.33 mm	–	–	–	[79]
Chitosan, CNF, polyurethane	0.63 mm	–	–	4	[80]

Table 3
Hydrogels employed in DIW, along with their applications in drug delivery systems and printing parameters.

Hydrogel materials	Nozzle size (Gauge/mm)	Printing speed (mm/s)	Printing pressure (kPa)	Number of layers	Ref.
CNFs, PVA	0.84 mm	–	40	5	[20]
GelMA	0.164 mm	10	345	6	[81]
CMC	0.25 mm	5	–	–	[82]
Alginate, polydopamine	15/20 G, 16/22 G, 18/25 G	5	300 - 400	8	[83]
Hyaluronic acid, chitosan	22, 25 G	5, 10, 13.3	25 - 45	4	[84]
Zein organogels	21 G	3	240 - 320	0.375 mm (layer height)	[85]
CNCs, poly (glycerol sebacate)	18 G	–	–	–	[86]
PVA, κ-carrageenan	–	2 - 7	–	–	[87]

potential in controlled drug release. Their porous structure and tunable properties allow for the encapsulation and sustained release of therapeutic agents. This controlled release capability is instrumental in optimizing drug delivery strategies, ensuring that medications are administered at the right time and in the right place, ultimately enhancing treatment efficacy and patient comfort [90,91].

2.1.2. Chitosan hydrogels

Chitosan hydrogels, stemming from the derivative chitin found abundantly in crustacean shells, have garnered significant attention and utilization in a variety of biomedical applications due to their unique properties. One of the notable characteristics of chitosan is its inherent antimicrobial activity. This feature is particularly advantageous in applications related to wound healing, where preventing or managing infections is critical. The antimicrobial properties of chitosan make it an effective agent for promoting a hygienic environment conducive to the natural healing processes of the body. Beyond its antimicrobial capabilities, chitosan plays a pivotal role in tissue regeneration. It has the ability to stimulate the growth and development of new tissue, making it highly valuable in the field of regenerative medicine [92,93]. Whether it's promoting the regeneration of damaged skin, bone, or cartilage, chitosan hydrogels offer a supportive matrix for tissue growth, facilitating functional tissue restoration in various clinical scenarios. Chitosan's versatility extends to drug delivery as well. These hydrogels can be tailored to encapsulate and release therapeutic agents in a controlled and sustained manner. This controlled drug release is crucial in optimizing the efficacy and safety of medications, making chitosan hydrogels a preferred choice for drug delivery systems. Furthermore, chitosan hydrogels are prized for their biodegradability and biocompatibility, two factors of paramount significance in the biomedical field. Their biodegradable nature ensures that, over time, the hydrogel will naturally break down into non-toxic byproducts, reducing the need for invasive removal procedures. Meanwhile, their biocompatibility ensures that chitosan-based constructs are well-tolerated by the body, minimizing the risk of adverse reactions or immune responses [40,94,95].

2.1.3. Alginate hydrogels

Alginate hydrogels, mainly derived from the abundant source of brown seaweed, have solidified their position as a fundamental and highly favored material in the context of DIW 3D printing. Their popularity is largely due to remarkable features like biocompatibility, adaptable mechanical properties, and rapid gelation behavior. First and foremost, alginate hydrogels exhibit exceptional biocompatibility, making them a preferred option for a wide range of biomedical applications. This biocompatibility ensures that alginate-based constructs can seamlessly interact with living tissues and biological systems, minimizing the risk of adverse reactions or immune responses, and thus, they are well-suited for use in regenerative medicine, tissue engineering, and drug delivery. Another distinctive feature of alginate hydrogels lies in their adaptable mechanical properties. These hydrogels offer engineers and researchers a significant degree of control over their mechanical traits. Whether the need is for a rigid structure to serve as a scaffold for tissue regeneration or a more pliable construct for drug delivery, alginate hydrogels can be tailored to meet the specific requirements of the intended application [41,96]. This versatility makes them an invaluable asset in the creation of custom-designed 3D-printed objects that cater to diverse needs in the biomedical field. Furthermore, alginate hydrogels are renowned for their rapid gelation in the presence of calcium ions. This characteristic is of paramount importance in 3D printing processes like DIW, where precise control over the deposition and solidification of material is critical for achieving intricate and accurate structures. The ability to quickly transition from a liquid to a gel state enables the creation of complex 3D-printed constructs with remarkable precision [97,98].

2.1.4. Hyaluronic acid hydrogels

Hyaluronic acid hydrogels, owing to their natural occurrence in various tissues, notably in the skin and joints, have garnered significant attention in the field of biomaterials. These hydrogels are characterized by their exceptional water retention properties and viscoelastic behavior. One of their most prominent features is their ability to retain large volumes of water, making them highly effective in maintaining hydration levels in tissues. In the context of skin regeneration, this property is invaluable, as it promotes a moist and conducive environment for wound healing, reduces scarring, and enhances tissue regeneration. In addition to their application in skin regeneration, hyaluronic acid hydrogels have been found to be useful in the treatment of conditions such as osteoarthritis [68,99]. Osteoarthritis, characterized by the degradation of joint cartilage, can lead to pain and reduced joint mobility. Hyaluronic acid-based hydrogels can be injected into affected joints to provide lubrication and cushioning. This helps alleviate pain and discomfort, improving joint function and the overall quality of life for individuals suffering from this condition. The versatility of hyaluronic acid hydrogels extends further, making them suitable for various other biomedical applications. Their biocompatibility and ability to mimic the ECM of tissues contribute to their broad utility. Researchers and medical professionals continue to explore new avenues for hyaluronic acid hydrogels, ranging from tissue engineering to drug delivery, owing to their unique combination of properties [42,100].

2.1.5. Gum-based hydrogels

Gum-based hydrogels, a captivating category of materials derived from natural sources such as plant exudates and microbial fermentation, are emerging as a highly promising avenue for DIW applications. What sets these hydrogels apart is their exceptional combination of attributes, including biocompatibility, sustainability, and the capacity for precise property tuning, rendering them exceptionally well-suited for a wide range of additive manufacturing applications. Their innate ability to absorb and retain water and the potential for mechanical property modifications present compelling propositions for DIW technology [58,101]. Researchers have been actively exploring the capabilities of gum-based hydrogels, harnessing their potential to create intricate structures, ranging from tissue engineering constructs to advanced drug delivery systems. Additionally, their renewable nature and ability to incorporate bioactive agents place them at the forefront of efforts to develop environmentally friendly and functional materials for DIW, aligning with the broader goals of sustainable and innovative manufacturing practices [102].

2.1.6. Starch hydrogels

Starch hydrogels, hailing from readily available natural polysaccharides, have emerged as a versatile and eco-friendly biomaterial that finds applications across a spectrum of biomedical fields [103]. One of their standout features is their exceptional biocompatibility, making them well-suited for use in various medical applications. Their compatibility with living tissues ensures minimal cytotoxicity and inflammation, making them ideal candidates for biologically interactive applications. Moreover, starch hydrogels exhibit impressive water absorption capabilities thanks to their hydrophilic nature and the ability to form a robust 3D network. This property makes them prime candidates for use in intricate DIW structures. The hydrogels readily absorb water, swelling to accommodate a significant amount of fluid, while maintaining their structural integrity. This swelling behavior is advantageous in DIW, as it facilitates the precise deposition of material while minimizing deformation during the printing process. The tunable attributes and responsiveness of starch hydrogels are additional strengths [104,105]. Researchers can modify their properties to achieve specific characteristics tailored to the demands of diverse applications. This adaptability is particularly valuable when engineering materials with bespoke properties, whether it's designing tissue scaffolds with precise mechanical properties for tissue engineering or creating drug delivery systems with controlled release profiles. Research involving starch hydrogels extends across a wide array of fields, including tissue engineering, drug delivery, and beyond. Their potential to foster sustainable and functional DIW approaches is increasingly evident. The use of these hydrogels in 3D printing not only enables the creation of intricate and customized structures but also aligns with the growing emphasis on environmentally friendly and biocompatible materials in the biomedical field [106,107].

2.1.7. Gelatin hydrogels

Gelatin hydrogels, arising from the denaturation of collagen, have risen to prominence as a versatile biomaterial with a wide array of applications, particularly in the domains of cell culture, tissue engineering, and 3D printing. One of the standout features of gelatin hydrogels is their capacity to serve as an excellent matrix for cell culture and tissue growth. Their similarity to collagen, a fundamental component of the ECM, makes them highly biocompatible and conducive to cellular adhesion, proliferation, and differentiation. This biocompatibility is essential in tissue engineering, where gelatin hydrogels provide a nurturing environment for the development of functional tissue constructs. Another compelling aspect of gelatin hydrogels lies in their ease of functionalization with bioactive agents. Researchers can readily incorporate growth factors, drugs, or other bioactive molecules into the hydrogel matrix, allowing for precise control over the cellular microenvironment. This property is particularly valuable when tailoring hydrogels to mimic specific tissue niches or deliver therapeutic agents in a controlled manner. Furthermore, gelatin hydrogels excel in the creation of intricate 3D structures with complex geometries. Their moldability and ability to hold shape during printing processes make them an invaluable material for scaffold design in tissue engineering. Whether it's crafting intricate vascular networks or replicating the architecture of native tissues, gelatin hydrogels provide the versatility needed to create biomimetic structures that support tissue regeneration [108,109].

2.1.8. Collagen hydrogels

Collagen hydrogels, derived from one of the pivotal proteins found in the ECM, represent a foundational building block for a wide range of

biomedical applications. The prominence of collagen in the ECM of various tissues underscores its importance in providing a supportive environment for cell adhesion, proliferation, and growth. As such, collagen hydrogels are highly prized for their exceptional biocompatibility, which makes them exceptionally well-suited for cell-mediated tissue regeneration. The remarkable biocompatibility of collagen hydrogels translates into their ability to interact harmoniously with living cells and biological systems, minimizing the risk of adverse reactions or immune responses. This property is particularly valuable in areas of healthcare where fostering a close and constructive relationship between biomaterials and the body's natural processes is paramount. One of the most compelling features of collagen hydrogels is their striking resemblance to native tissue. Their composition closely mimics that of the ECM, providing an environment that mirrors the natural surroundings of cells in the body. This biomimicry accentuates their value in numerous clinical applications, ranging from wound healing to cartilage repair. In the context of wound healing, collagen hydrogels offer a supportive scaffold for cells to migrate, proliferate, and synthesize ECM components, expediting the healing process. The structural and chemical cues provided by these hydrogels promote tissue regeneration while minimizing scarring, making them particularly advantageous in dermatology and plastic surgery [38,110]. Furthermore, collagen hydrogels have demonstrated their efficacy in cartilage repair. Given their compatibility with chondrocytes, the cells responsible for cartilage maintenance, collagen hydrogels have been employed in strategies to treat cartilage injuries and degenerative conditions like osteoarthritis. Their ability to provide a conducive environment for cartilage cell growth and matrix deposition positions them as a valuable tool in regenerative orthopedics. A pivotal protein within the ECM, collagen offers a foundation for cell adhesion and growth. Collagen hydrogels boast high biocompatibility, endorsing cell-mediated tissue regeneration. Their resemblance to native tissue accentuates their value in areas such as wound healing and cartilage repair [111,112].

2.2. Synthetic hydrogels in direct ink writing

Synthetic hydrogels, on the other hand, present a distinctive set of attributes, affording a heightened level of manipulation over their characteristics encompassing mechanical robustness, swelling dynamics, degradation kinetics, and bioactive attributes. This inherent modifiability empowers their customization for precise applications. Additionally, synthetic hydrogels can be precisely engineered to exhibit elevated mechanical potency when juxtaposed with natural counterparts, rendering them exceptionally well-suited for scenarios necessitating structural reinforcement, such as load-bearing implants [113–115]. As an example, a synthetic hydrogel ink comprising polycaprolactone and polyethylene oxide was tailored for DIW to produce 3D objects, demonstrating considerable promise for biomedical applications (see Fig. 2) [116].

However, it is noteworthy that select synthetic hydrogels may cause apprehensions regarding biocompatibility due to the potential for evoking immune reactions or toxic responses. As a consequence,

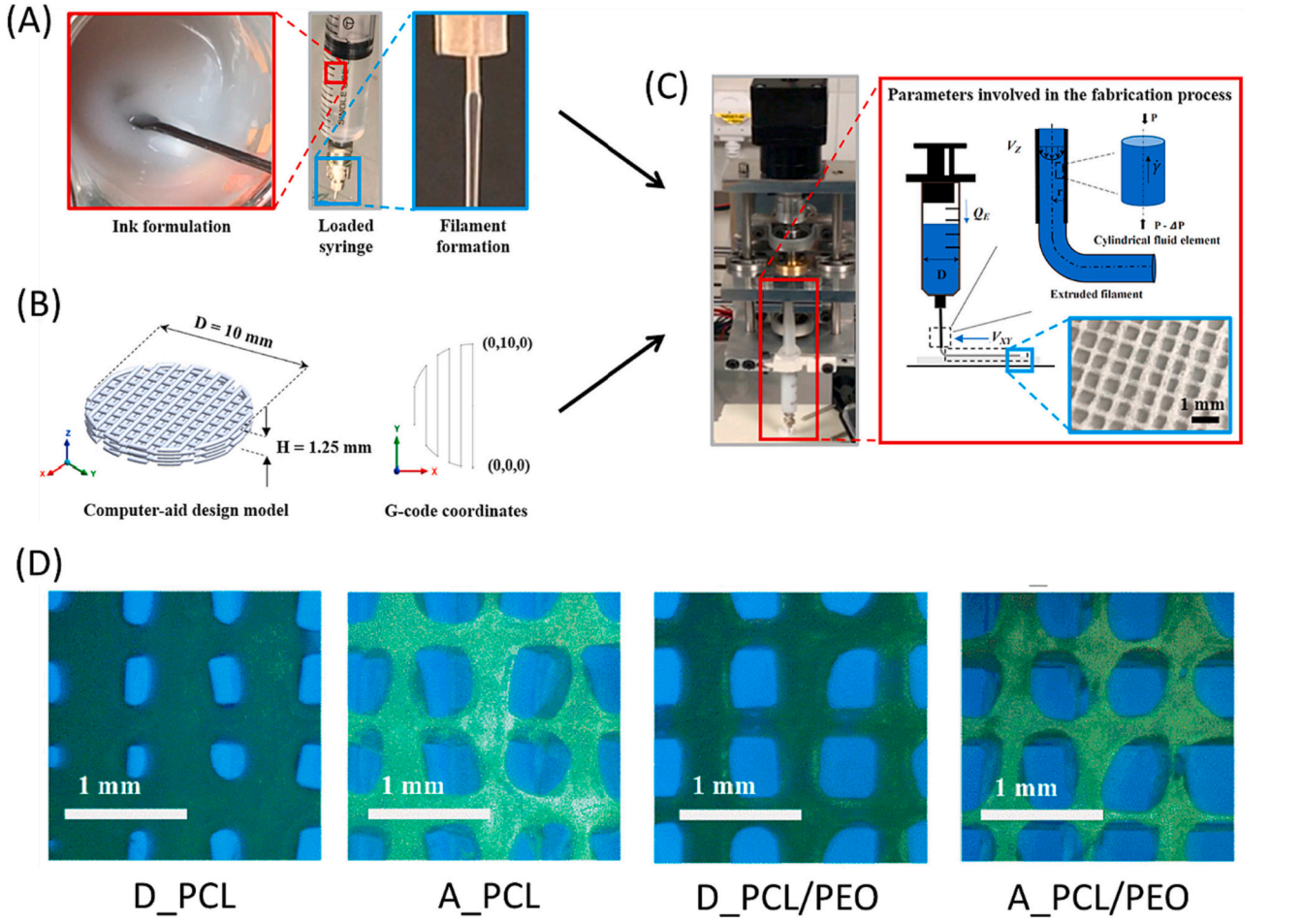

Fig. 2. Illustration of the DIW printer and outlines the fabrication process: (A) Material preparation system - inks were formulated to assess manual dispensing and ink rheological behavior. (B) Data processing system - appropriate G-code was generated using the pre-designed CAD model. (C) Computer control system - the construct was printed following investigations into printing process parameters. (D) Microscopic images of the printed objects are presented [116]. D_PCL and A_PCL stand for dichloromethane-based and acetone-based inks, respectively. With permission from Zhang, 2021, Copyright © 2021, Elsevier Ltd.

exhaustive evaluations of biocompatibility are commonly imperative to ascertain their suitability for deployment in medical contexts. Moreover, while synthetic hydrogels can be functionally augmented to incorporate bioactive compounds, their intrinsic bioactivity might not inherently parallel that of natural hydrogels. Furthermore, a subset of synthetic hydrogels could be characterized by non-degradability, leading to enduring presence within the organism if not meticulously designed [117–119]. This protracted persistence could precipitate challenges in applications mandating requisite biodegradability. To date, a diverse array of synthetic hydrogels has found applications in DIW. A summary of synthetically developed hydrogels that have prominently featured in recent DIW endeavors is provided in Tables 1 to 3. Additionally, a brief introduction to these hydrogels is presented below.

2.2.1. Polyethylene glycol (PEG) hydrogels

PEG hydrogels stand as a pivotal choice in the context of DIW, primarily due to their remarkable versatility and the ease with which they can be functionalized with bioactive molecules. One of the standout features of PEG hydrogels is their ability to offer finely tunable mechanical properties and controlled degradation rates. This intrinsic flexibility allows researchers and engineers to tailor these hydrogels to specific requirements within a spectrum of applications. In tissue engineering, for instance, PEG hydrogels serve as a robust scaffold material that can mimic the ECM, providing structural support for cell growth and tissue regeneration [120]. Moreover, in drug delivery systems, their controlled degradation characteristics enable the sustained release of therapeutic agents, ensuring precise dosing and enhancing the therapeutic effectiveness of pharmaceutical compounds. As such, the adaptability and biocompatibility of PEG hydrogels make them a cornerstone material for advancing innovative solutions in regenerative medicine, pharmaceuticals, and beyond [121].

2.2.2. Poly(N-isopropylacrylamide) (PNIPAAm) hydrogels

PNIPAAm hydrogels represent an intriguing class of materials due to their unique temperature-responsive characteristics. At physiological temperatures, PNIPAAm hydrogels undergo a reversible phase transition, typically collapsing or swelling in response to changes in temperature [31]. This remarkable property has found application in DIW, where it enables the creation of stimuli-responsive structures with a wide range of potential applications. In the field of smart drug delivery, PNIPAAm hydrogels have been harnessed to design innovative drug delivery systems. These hydrogels can respond to variations in body temperature, releasing drugs when and where they are needed most. This precise control over drug release kinetics enhances therapeutic outcomes and minimizes side effects, promising a more effective and patient-centric approach to healthcare [122]. Furthermore, PNIPAAm hydrogels have emerged as a valuable tool for designing scaffolds and constructs in tissue engineering. Their ability to undergo volume changes in response to temperature fluctuations allows for the creation of dynamic tissue engineering platforms. These hydrogels can support cell growth and tissue regeneration in a controlled environment, making them particularly suited for applications where spatial and temporal control of the cellular microenvironment is essential [123]. The utilization of PNIPAAm hydrogels in DIW thus exemplifies the potential of this responsive material in advancing both drug delivery strategies and tissue engineering solutions, offering exciting prospects for the development of innovative biomedical technologies.

2.2.3. Poly(ethylene oxide) (PEO) hydrogels

PEO hydrogels have garnered attention in the field of DIW due to their notable biocompatibility and resistance to protein adsorption, making them a valuable material for various biomedical applications. PEO hydrogels, characterized by their excellent biocompatibility, provide an ideal platform for interacting with biological systems without causing adverse reactions or immune responses. This property is particularly advantageous in drug delivery applications, where maintaining the biocompatibility of the carrier material is essential to ensure the safe and effective delivery of therapeutic agents [124]. One of the key strengths of PEO hydrogels in DIW lies in their ability to create hydrogel structures with precise control over release properties. This is crucial in drug delivery systems, where drug controlled release is essential to achieve therapeutic efficacy while minimizing side effects. PEO hydrogels can be tailored to modulate drug release kinetics, enabling sustained and targeted delivery of pharmaceutical compounds. This controlled release capability is of paramount importance in the development of personalized medicine and therapies for chronic conditions [116].

2.2.4. Polyvinyl alcohol (PVA) hydrogels

PVA hydrogels, characterized by their water-soluble nature, have gained significant traction in the field of DIW, primarily for their utility in constructing scaffolds tailored for tissue engineering applications [20,87]. These hydrogels are notable for several key attributes that make them well-suited for these endeavors. One of the standout features of PVA hydrogels is their ability to dissolve readily in water, which is advantageous in DIW as it facilitates the printing process. PVA-based inks can be easily extruded and deposited to create complex 3D scaffolds that closely mimic the intricate architecture of native tissues. This capability is of paramount importance in tissue engineering, where the goal is to provide a suitable microenvironment for cell growth and tissue regeneration. Moreover, PVA hydrogels exhibit commendable mechanical properties, offering the requisite structural integrity and stability needed for tissue scaffolds. Their ability to maintain their shape and support mechanical loads ensures that the printed structures can withstand the demands of *in vitro* and *in vivo* environments. This mechanical robustness is crucial for the long-term success of tissue engineering applications. Biocompatibility is another pivotal aspect of PVA hydrogels. Their low cytotoxicity and compatibility with biological systems make them a preferred choice for creating scaffolds intended for cellular growth and tissue regeneration. This biocompatibility is essential for fostering cell adhesion, proliferation, and differentiation, all of which are critical processes in tissue engineering [125].

2.2.5. Polycaprolactone (PCL)-based hydrogels

Hydrogels that incorporate PCL with hydrophilic components represent a compelling innovation in DIW due to their ability to merge the advantageous mechanical properties of PCL with enhanced biocompatibility, resulting in versatile materials for various applications. The blending of PCL with hydrophilic components addresses a common challenge in tissue engineering and drug delivery, where achieving a balance between mechanical integrity and biocompatibility is crucial. These hydrogels achieve a harmonious synergy of properties by combining the hydrophobic characteristics of PCL with hydrophilic components, such as natural or synthetic polymers like PEG or PVA [126,127]. This strategic combination not only improves the overall mechanical strength and stability of the hydrogel but also imparts a greater affinity for aqueous environments, enhancing their suitability for biological applications. In DIW, these PCL-based hydrogels have proven invaluable for the creation of complex, multi-material structures tailored for tissue engineering. The improved mechanical properties enable the fabrication of scaffolds that can withstand physiological conditions while providing the necessary support for cellular growth and tissue regeneration. Furthermore, their enhanced biocompatibility fosters an environment conducive to cell adhesion, proliferation, and differentiation, making them an attractive choice for regenerative medicine. Additionally, the versatility of these hydrogels extends to drug delivery applications. Their controlled release properties, tunable through the precise composition of hydrophilic and hydrophobic components, enable the sustained and localized delivery of therapeutic agents [116,128].

2.2.6. Polyurethane (PU) hydrogels

PU hydrogels stand as a notable class of materials, renowned for their exceptional mechanical properties and biocompatibility. Within the domain of DIW, they have emerged as a versatile and highly sought-after choice for crafting a diverse array of structures, with applications spanning tissue engineering, wound healing, and even fascinating shape memory composites. The outstanding mechanical properties of PU hydrogels make them particularly attractive for DIW. These hydrogels possess a unique combination of toughness and resilience, allowing them to withstand mechanical stresses and maintain structural integrity over time. In tissue engineering, this durability ensures that the printed scaffolds can support cell growth and tissue regeneration, even in load-bearing applications [129,130]. Moreover, the biocompatibility of PU hydrogels is a key asset, rendering them suitable for use in a biological milieu without causing adverse reactions. This biocompatibility is a crucial factor in both tissue engineering and wound healing applications, where the materials must seamlessly integrate with the host tissue while promoting the healing process.

2.2.7. Methacrylate hydrogels

Methacrylate hydrogels, stemming from methacrylate monomers, represent a noteworthy category of hydrogels that have gained prominence in DIW. Notably, poly(ethylene glycol) dimethacrylate (PEGDMA) is a prime example of a methacrylate-derived hydrogel that has garnered significant attention. What sets these hydrogels apart is their capacity for achieving high crosslinking densities and precise control over mechanical properties, rendering them invaluable for a wide range of applications, with a particular focus on tissue engineering and cartilage regeneration. The high crosslinking density characteristic of methacrylate hydrogels contributes to their remarkable mechanical strength and stability. This feature is particularly advantageous in DIW, where the ability to create structures with excellent mechanical properties is essential, especially when the goal is to mimic the structural integrity of native tissues. In tissue engineering, these hydrogels serve as robust scaffolds that can support cell attachment, growth, and differentiation, ultimately facilitating the regeneration of functional tissues. Furthermore, the ability to fine-tune mechanical properties within these hydrogels allows researchers to tailor the materials to match specific tissue requirements [131,132]. For instance, in cartilage regeneration, where both structural integrity and compressibility are crucial, the flexibility to control mechanical attributes becomes paramount. In the context of DIW, these hydrogels are not only limited to tissue engineering and cartilage regeneration but also extend their reach into a variety of other applications where controlled mechanical properties are essential. Their adaptability and biocompatibility make them a versatile choice for producing intricate 3D structures for diverse applications within the biomedical and materials science fields [81,132].

3. 3D printing and direct ink writing

3D printing, also known as additive manufacturing, is a revolutionary technology that allows the creation of 3D objects from digital designs by adding material layer by layer. This process offers numerous advantages, including increased design freedom, reduced waste, and the ability to produce complex geometries that would be challenging or impossible to create using traditional manufacturing methods. So far, various printing techniques have emerged for different materials and applications. These techniques are categorized into contact and non-contact methods, each with its advantages and suitability for specific contexts. Non-contact 3D printing methods involve creating objects without direct physical contact between the printing material and the work surface. A few examples of non-contact 3D printing methods are selective laser sintering (SLS) [133], selective laser melting (SLM) [134], inkjet 3D printing [135], and electron beam melting (EBM) [136,137]. Contact-based 3D printing methods, on the other hand, involve the physical contact of the printing material with the work surface. A few examples of contact-based 3D printing include material extrusion (ME), stereolithography (SLA) [138,139], and digital light processing (DLP) [140] [141]. These techniques are often used for their precision, repeatability, and ability to work with a variety of materials, including flexible substrates like plastics and textiles. Among these, inkjet-based, laser-assisted, stereolithography, acoustic, microvalve, needle array bioprinters, and extrusion-based materials (see Fig. 3) have emerged for biomedical applications [142], each possessing distinct advantages and limitations.

Materials extrusion (ME) is a category of contact-based 3D printing techniques that involves depositing material in a controlled manner to build up objects layer by layer. In this process, a nozzle or extrusion head dispenses material onto a build platform, following a predefined path to create the desired shape. ME techniques are versatile and can be used with a wide range of materials, including plastics, metals, ceramics, composites, and even biological materials in certain cases. However, the materials are typically in a semi-liquid, paste, or filament form, depending on the specific technique being used. The primary principle behind ME is additive layering, where each layer of material fuses with the layer below it, gradually building up the final object. This approach contrasts with traditional subtractive manufacturing methods, where the material is removed from a larger piece to achieve the desired shape [138,143,144]. Several common 3D printing techniques fall under the ME category, including fused deposition modeling (FDM), DIW, pellet extrusion, and paste extrusion. These techniques offer advantages such as relatively low equipment costs, the ability to create functional prototypes, and the capability to produce large-scale objects. However, ME methods might have limitations in terms of surface finish and resolution compared to some other 3D printing techniques like SLA or SLS. Nevertheless, advancements in technology continue to improve the quality and capabilities of ME-based 3D printing, making it a valuable tool in various industries [145–147].

DIW involves extruding liquid or paste-like inks to create objects. It's particularly useful for printing materials that are not in solid filament form. DIW is employed in applications requiring precise control over material properties and complex geometries [148]. DIW of hydrogels is an advanced 3D printing technique that has gained significant attention in recent years due to its potential applications in various fields. DIW allows for the precise deposition of hydrogel-based inks, enabling the creation of complex and functional structures. DIW of hydrogels involves extruding hydrogel-based inks through a nozzle onto a substrate to build up 3D structures layer by layer. Fig. 4 schematically illustrates the DIW of hydrogels. The hydrogel inks used in this process often consist of a combination of polymers, water, and sometimes bioactive components such as growth factors or cells. The ink must have appropriate viscosity and rheological properties to ensure accurate deposition and structural integrity during printing [149–151].

DIW of hydrogels has a wide range of potential applications. Tissue engineering [55,152], organ-on-a-chip devices [153], soft robotics [154], drug delivery [20], and bioprinting [31,155] are well-known examples. DIW can create intricate and complex structures, which is essential for fabricating biomimetic tissues and structures with high fidelity. Consequently, researchers are exploring DIW to create functional tissue constructs, such as cartilage, bone, skin, and blood vessels [23,156]. Likewise, DIW plays a significant role in the emerging field of bioprinting, where researchers aim to create functional living tissues using 3D printing technologies. The ability to incorporate cells into hydrogel constructs is essential for fostering tissue growth and regeneration [57,157]. Furthermore, hydrogel-based DIW has been used to create microfluidic devices that simulate the function of organs in the human body, providing platforms for drug testing, disease modeling, and personalized medicine [158]. Additionally, hydrogel-based structures created through DIW have been employed to develop soft and flexible robotic components that interact with biological systems more naturally [159].

Despite its promise, DIW of hydrogels also presents challenges.

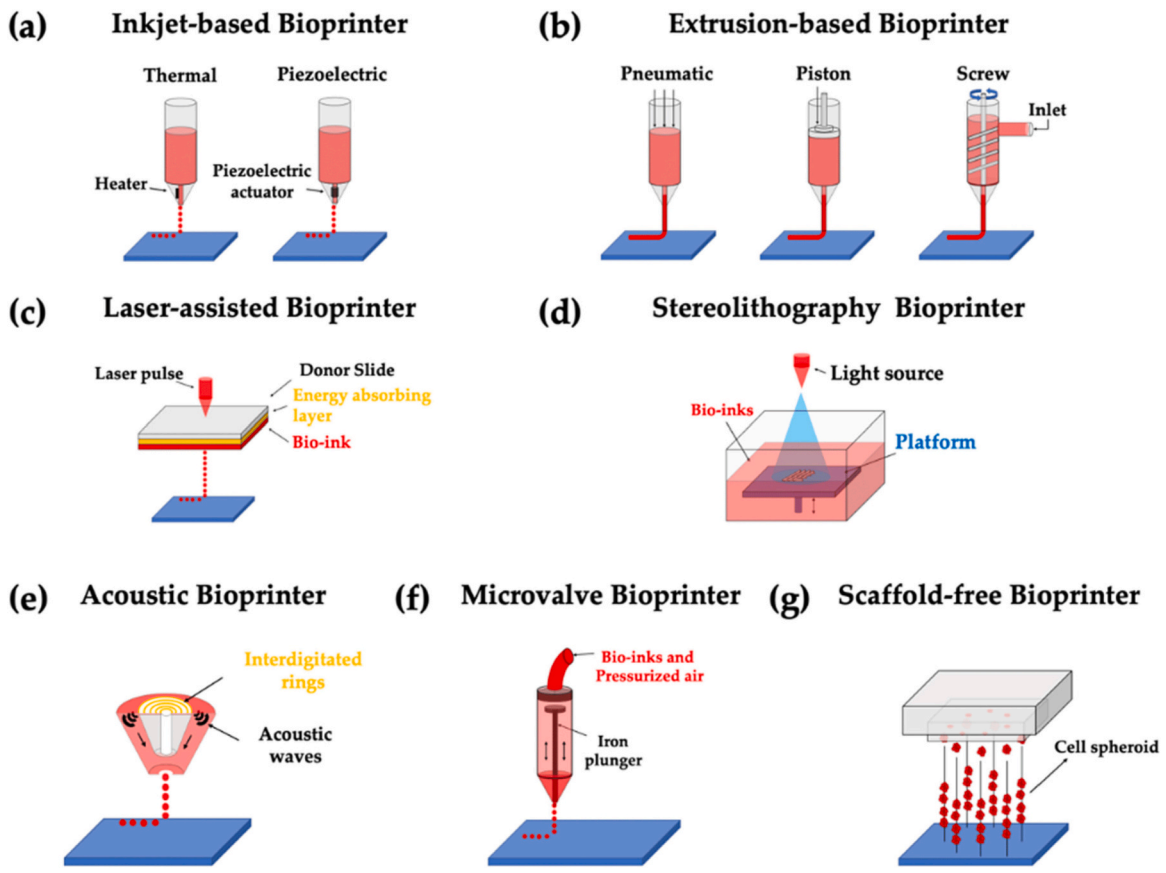

Fig. 3. Schematic illustrations depict various strategies employed in current 3D bioprinting techniques. (a) Inkjet-based printer, (b) extrusion-based printer, (c) laser-assisted printer, (d) stereolithography-based printer, acoustic printer, and (f) microvalve printer [142]. With permission from Yu, 2020 MPDI publication.

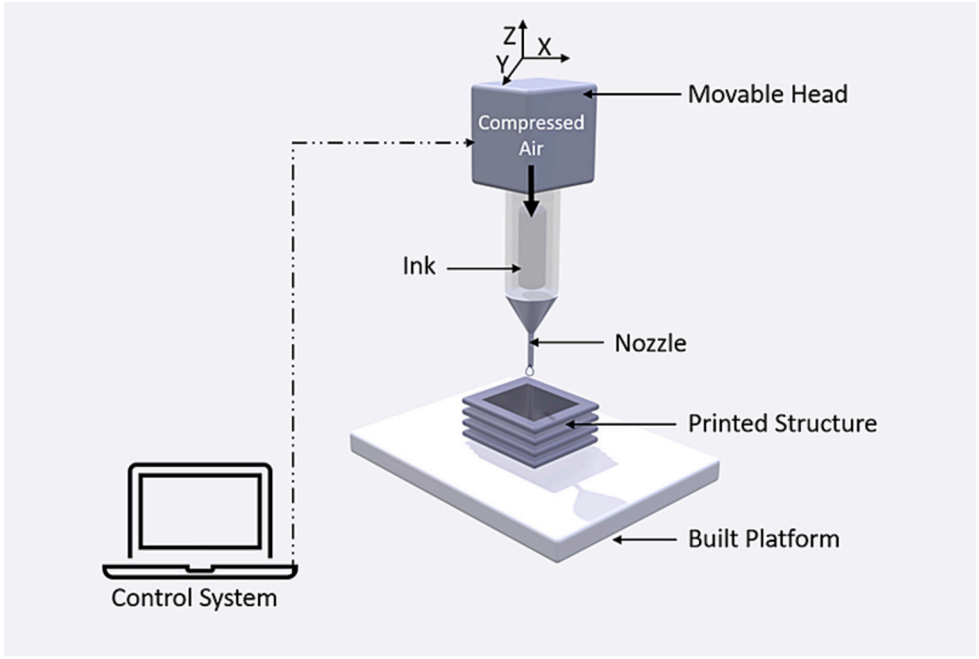

Fig. 4. Schematic illustration of DIW of hydrogels.

Choosing the suitable hydrogel formulation with the desired properties can be complex and depends on the intended application. Furthermore, achieving high-resolution prints while maintaining the structural integrity of hydrogel-based constructs can be challenging [19,55,87]. And ensuring high cell viability after printing is crucial for tissue engineering applications [160].

3.1. Printing parameters in direct ink writing

As previously highlighted, DIW is a versatile additive manufacturing technique that has gained significant attention in recent years due to its ability to create complex and intricate structures using hydrogel materials. The success of DIW relies not only on the formulation of hydrogel inks but also on the precise control of various printing parameters. These parameters play a crucial role in determining the final structural integrity, resolution, and mechanical properties of the printed hydrogel constructs [161,162]. Successful DIW of hydrogels relies on a comprehensive understanding and careful control of various printing parameters. Each parameter interplays with others to influence the quality of the final printed structure, mechanical properties, and functional characteristics. Iterative experimentation and optimization are key to achieving the desired results and advancing the capabilities of hydrogel-based 3D printing for various applications. Tables 1 to 3 present a list of DIW parameters utilized by various researchers in the context of biomedical applications. These parameters include nozzle diameter, printing speed, printing pressure, and the number of printed layers, offering insights into the various approaches adopted in hydrogel-based 3D printing in the biomedical field. Presented herewith are key printing parameters of prominence in DIW, along with their respective significance.

3.1.1. Nozzle diameter and geometry

Nozzle diameter and geometry are critical factors in the 3D printing process, significantly influencing the precision and quality of printed structures. The dimensions of the nozzle, particularly its diameter, play a crucial role in determining the level of detail that can be achieved in the printed object. Smaller nozzle diameters allow for the creation of finer and more intricate features, resulting in higher-resolution prints. However, it's important to note that using very small nozzle diameters may increase the risk of nozzle clogging, disrupting the printing process and necessitating maintenance [163]. Additionally, the geometry of the nozzle has a substantial impact on ink flow and deposition during printing. The shape of the nozzle can affect the way ink is extruded onto the print bed or previous layers. Different nozzle geometries can be optimized for specific printing tasks, such as creating support structures or achieving specific surface finishes [52,164]. Therefore, selecting the appropriate nozzle geometry is pivotal for achieving the desired print quality, ensuring consistent ink flow, and preventing issues like over-extrusion or under-extrusion.

3.1.2. Layer height

Layer height is a fundamental parameter in 3D printing that directly influences the quality, speed, and efficiency of the printing process. Essentially, layer height determines the thickness of each individual layer deposited to build the final 3D object. When selecting the appropriate layer height, there is a trade-off between achieving finer resolution and minimizing printing time [165,166]. Lower layer heights result in finer resolution because they allow for the creation of more detailed and intricate features in the printed object. This is particularly important when precision and aesthetics are critical, such as in the production of intricate prototypes, intricate art pieces, or intricate mechanical parts. Smaller layers can capture fine details and complex geometries with greater accuracy, enhancing the overall visual and functional quality of the print [167,168]. However, it's essential to consider that using lower layer heights increases the number of layers needed to build the entire object. As a consequence, the printing time can be significantly extended, especially for complex or large-scale prints.

3.1.3. Printing speed

Printing speed is a crucial aspect of 3D printing that directly influences the rate at which material is deposited to create each layer of the printed object. It plays a significant role in determining the overall efficiency and quality of the printing process. The speed at which the printer's nozzle moves affects the ink deposition rate, and finding the right balance between layer height and printing speed is essential for achieving accurate and uniform deposition. When the printing speed increases, the printer moves more rapidly, potentially reducing the overall printing time for a given object. However, higher printing speeds can come at a cost in terms of print quality [169,170]. If the printer moves too quickly, it may not give the ink sufficient time to properly adhere to the previous layer or may result in uneven deposition. This can lead to issues like layer misalignment, poor bonding between layers, and a loss of overall print accuracy. Conversely, reducing the printing speed allows for more precise control over ink deposition. Slower printing speeds can result in smoother, more uniform layers, which is especially important when producing intricate or complex objects that require high levels of detail and precision [167,171].

3.1.4. Printing temperature

Printing temperature plays a pivotal role in the 3D printing of hydrogel-based materials, exerting a profound influence on various aspects of the printing process and the resulting printed objects. The temperature at which the hydrogel ink is extruded affects its rheological properties, which dictate how it flows and behaves. It also impacts the ink's viscosity, which can determine how easily it is extruded through the printer nozzle. Additionally, printing temperature influences the gelation behavior of the hydrogel, affecting how quickly it solidifies or sets after deposition. Optimizing the printing temperature is crucial for several reasons. First and foremost, it ensures the stability of the hydrogel ink throughout the printing process [163,167]. Maintaining a consistent temperature helps prevent issues such as nozzle clogging or inconsistent flow, which can disrupt the printing process and lead to defects in the printed object. Furthermore, the printing temperature is closely tied to the proper layer adhesion in 3D printing. If the ink is extruded at a temperature that is too high, it may result in excessive spreading or smearing of the material, leading to poor layer adhesion and decreased print quality. Conversely, if the temperature is too low, the ink may not adhere properly to the previous layer, resulting in weak bonds between layers and a structurally compromised final product [172,173].

3.1.5. Material flow and pressure

Material flow and pressure are fundamental considerations in the 3D printing of hydrogel-based materials, as they directly impact the extrusion and deposition process. The precise control of pressure applied to the hydrogel ink is essential for regulating the flow rate and ensuring deposition accuracy during printing. Adjusting the pressure is a critical means of fine-tuning the printer's performance. Too much pressure can result in over-extrusion, where an excessive amount of material is deposited, potentially leading to a loss of detail, smearing, or distortion in the printed object. Over-extrusion can also result in poor layer adhesion and a less structurally sound final product [169,174]. Conversely, insufficient pressure can lead to inconsistent deposition, with material being extruded unevenly or intermittently. This can result in visible gaps, weak bonds between layers, and compromised print quality. Achieving the right balance of material flow and pressure is essential to maintain both the structural integrity and aesthetic quality of the 3D print. Proper pressure control ensures that the hydrogel ink is deposited consistently and accurately, resulting in a high-quality final product that meets the intended design specifications. In practice, the adjustment of material flow and pressure is often part of the fine-tuning process in 3D printing. It may require iterative testing and calibration to find the optimal settings for a specific hydrogel ink and printing application. Ultimately, precise control over material flow and pressure contribute to the successful and reliable production of hydrogel-based 3D prints with the desired properties and characteristics [164,165,169].

3.1.6. Print path and pattern

The print path and deposition pattern are critical elements in the 3D

printing process, particularly when working with hydrogel materials. These factors not only affect the visual appearance of the printed object but also substantially impact its mechanical properties and porosity, which are crucial considerations for functional applications. The print path, or the trajectory followed by the printing nozzle, can significantly influence the structural integrity and strength of the printed hydrogel structure. The direction and order in which the material is deposited affect how individual layers bond with each other [172]. A well-optimized print path can enhance interlayer adhesion, reducing the risk of delamination or weak bonds between layers. This is especially important when printing load-bearing or structurally significant parts. Similarly, the deposition pattern used, such as lines, grids, spirals, or infill patterns, plays a vital role in determining the porosity and mechanical properties of the printed object. Different patterns offer varying degrees of infill density and distribution, which can affect factors like weight, flexibility, and rigidity. The choice of deposition pattern should align with the specific functional requirements of the printed object. By carefully considering the print path and deposition pattern, 3D printing enthusiasts and professionals can optimize the mechanical strength and porosity of hydrogel-based prints [52]. This thoughtful approach ensures that the printed objects meet their intended design and functional specifications, whether it's for biomedical applications, tissue engineering, or other innovative uses of hydrogel materials in 3D printing technology.

3.1.7. Environmental factors

Environmental factors play a significant role in the 3D printing of hydrogel materials, influencing both the properties of the hydrogel ink and the overall printing process. Factors such as humidity, temperature, and air circulation in the printing environment can have a substantial impact on print quality, material behavior, and the reliability of the printing process. Humidity levels are a critical consideration when working with hydrogel inks. High humidity can lead to increased moisture absorption by the hydrogel, altering its rheological properties, such as viscosity and gelation behavior. This can result in unexpected changes in the ink's flow characteristics and may lead to print defects [52]. Conversely, low humidity levels can cause the ink to dry out or become less stable, affecting extrusion and layer adhesion. Temperature also plays a crucial role. It can affect the consistency and viscosity of the hydrogel ink. A controlled temperature environment helps maintain stable ink properties, ensuring that the ink flows predictably and adheres well during printing [30]. Extreme temperature fluctuations can cause issues like nozzle clogging or warping of the printed object. Air circulation is another factor to consider. Adequate ventilation and air circulation can help dissipate heat generated during the printing process, preventing overheating of the printer components and ensuring a more stable printing environment. Additionally, proper ventilation can help disperse any fumes or odors that may be produced during printing. Maintaining a controlled printing environment is essential for achieving reproducible results in 3D printing with hydrogel materials. It helps minimize variations in print quality, material behavior, and printing process reliability [175]. This control is particularly important in research and industrial settings where consistency and precision are critical for consistently producing high-quality hydrogel-based 3D prints.

4. Rheological considerations for successful direct ink writing of hydrogels

Rheology plays a pivotal role in the success of DIW, particularly when dealing with hydrogels. A profound comprehension of the rheological properties of hydrogel inks holds paramount importance in achieving precise and controlled extrusion throughout the 3D printing process. Key rheological traits such as shear-thinning behavior, yield stress, and flowability exert a profound influence on both the DIW procedure and the quality of the resultant printed structures [21,30]. Shear-thinning, also known as pseudoplastic behavior, is a pivotal rheological characteristic that holds great significance in various scientific and industrial applications. It is defined by a material's propensity to exhibit a decrease in viscosity as the shear rate, or the force applied per unit area, increases. The shear-thinning behavior of a material typically arises from a combination of factors, including chain entanglement and extension, as well as interactions between molecular entities like hydrogen bonding or physical cross-linking. In hydrogel inks, for instance, the polymer chains may become disentangled under shear forces, reducing viscosity and making the material flow more readily during extrusion. Additionally, interactions like hydrogen bonding can weaken under shear, further contributing to the material's shear-thinning behavior. These dynamic rheological properties make shear-thinning materials well-suited for applications like 3D printing, where they can maintain structural integrity during deposition while allowing for smooth flow [176,177].

Within the context of DIW, shear-thinning emerges as a particularly advantageous property. This behavior facilitates the smooth flow of hydrogel ink under the influence of shear forces during the extrusion process. As the nozzle moves, the shear-thinning effect transforms the ink into a less viscous state, akin to a fluid, which is instrumental in ensuring a seamless and uniform deposition of material. This dynamic property plays a pivotal role in achieving precision and detail in 3D printing. One of the notable advantages of shear-thinning is its adaptability to varying shear rates. When the extrusion process is active, the ink's reduced viscosity allows it to flow readily, conforming to the intricate patterns and structures being printed. However, once the shear forces cease, such as when the ink is deposited in its designated location, the ink rapidly regains its heightened viscosity. This quick transition from a fluid-like state to a more solid form is instrumental in upholding the shape and structural integrity of the deposited lines and layers, which is crucial for the success of 3D printing processes. The combination of shear-thinning and rapid viscosity recovery makes hydrogel inks particularly well-suited for demanding applications such as tissue engineering, biomedical research, and the creation of intricate prototypes. This unique rheological property enhances the precision and efficiency of DIW, contributing to the production of high-quality 3D-printed objects with intricate designs and fine details [29].

The yield stress emerges as the other pivotal determinant for ink suitability in DIW. Two variants of yield stress warrant consideration: static yield stress, signifying the stress prerequisite for initiating flow from a state of rest, and dynamic yield stress, indicating the minimal stress required to sustain the flow of a fluid in motion. On the one hand, the ink must surmount static yield stress to initiate extrusion from a nozzle. On the other hand, it must exhibit a significant dynamic yield stress to counteract the gravitational forces exerted by the entire printed structure and the capillary forces. The latter aspect ensures the uninterrupted extrusion of filament, minimizes deformation and preserves ink shape post-printing to provide support for subsequent layers [21].

Hydrogels frequently exhibit yield stress behavior, wherein a certain threshold force must be applied before they initiate flowing. This yield stress prevents ink from uncontrollable flow during idle printer phases and contributes to maintaining the integrity of the printed structure by retaining ink shape when not actively being deposited [21,178]. Similarly, flowability pertains to the ease with which a substance flows under an applied force. For hydrogel inks deployed in DIW, flowability must strike a delicate balance, being sufficiently viscous to uphold shape during printing while remaining sufficiently fluid to extrude through the printer nozzle. Attaining optimal flowability guarantees precise ink deposition and the capacity to produce intricate geometries without clogging the nozzle.

An understanding of ink rheology empowers researchers and engineers to meticulously refine ink compositions, attaining desired Shear-thinning, yield stress, and flowability attributes. This, in turn, ensures consistent extrusion, yielding top-tier 3D-printed structures replete with accurate dimensions and geometries. A case in point is the work of

Baniasadi et al. [19], who harnessed CNFs to fine-tune the viscoelastic properties of *aloe vera* gel. The outcome was a shear-thinning ink endowed with enhanced viscoelastic performance. The augmentation of both storage (G') and loss (G") moduli, attributed to the uniform dispersion of high-aspect-ratio nano and microfibril cellulose, conferred reinforcement to the 3D hydrogel structure. Moreover, the blending of *aloe vera* gel with CNFs yielded appropriate yield stress, a critical factor in successful DIW. In a similar vein, Erfanian et al. [29] delved into the viscoelastic behavior of conductive inks comprised of CNF and graphene nanoparticles. They discerned pronounced Shear-thinning behavior across all formulations, manifesting as a viscosity reduction of approximately five orders of magnitude, indicative of smooth nozzle flow. Their investigation also revealed that, for all inks, G' surpassed G" within the entire probed frequency range, underscoring the dominant solid-like behavior of the inks under minimal shear strains. This significant discrepancy of around one order of magnitude between G' and G" further facilitated ink shape retention post-printing and bolstered subsequent deposited layers.

In another notable study by Cianciosi et al. [55], the viscoelastic properties of gelatin were ingeniously tailored through the addition of CNFs. The outcome of this investigation revealed CNF's role as an effective rheology modifier, with optimal printability and shape fidelity achieved at a 1.8 *w/v* % CNF concentration within the inks. Similarly, Baniasadi et al. [21] harnessed the potential of CNCs as a means to enhance the viscoelastic behavior of XG within the DIW process. Notably, the power-law index exhibited a reduction with increased CNC content, indicating the beneficial impact of CNC addition on shear-thinning behavior in hybrid inks. Moreover, the amplification of both G' and G" with higher CNC content illustrated the ink's strengthened properties attributed to hydrogen bonding between CNC's hydroxy groups and XG's hydroxyl and carboxyl groups.

Furthering this line of research, Teixeira Polez [58] successfully enhanced biomaterial inks' rheological properties and printability by fusing tragacanth gum hydrogel with CNFs and lignin nanoparticles. Similarly, Belyaeva et al. [31] delved into the rheological traits of CNCs and poly(N-isopropylacrylamide) hydrogels. Their study underscored the significant shear-thinning behavior of this mixture, a characteristic profoundly advantageous for gels to be employed as inks for DIW or extrusion-based 3D printing. In their work, Baniasadi et al. [20] formulated printable inks by incorporating CNFs into PVA-based hydrogels. Initially, a 10 wt% PVA solution exhibited slight Shear-thinning behavior with a viscosity of approximately 120 mPa.s, which proved unsuitable for DIW. However, the addition of CNFs induced pronounced Shear-thinning behavior, optimizing the ink for DIW. The observed viscosity range within this study was deemed suitable for extruder-based 3D printers. Furthermore, they discerned notable improvement in gel strength as CNF content increased, confirming the reinforcing effect of well-dispersed high-aspect-ratio nano and microfibrils cellulose within the PVA matrix. In a similar vein, the viscoelastic properties of PVA hydrogels were adeptly tailored for DIW applications through the incorporation of κ-carrageenan [87].

Marapureddy et al. [59] embarked on a study involving chitosan/graphene oxide (GO) nanocomposite hydrogels with varying concentrations of GO for 3D structure DIW. The presence of GO significantly ameliorated the viscoelastic properties of the final inks, primarily in terms of storage and loss moduli enhancement. This improvement was attributed to interactions between chitosan chains and GO nanosheets, along with inter-nanosheet interactions. Similarly, the viscosity and yield stress displayed enhancement with increasing GO concentration. CMC was effectively utilized by Nocheseda et al. [52] to devise metallic inks possessing apt viscoelastic properties suitable for DIW. Particularly, the rheological behavior of metallic inks incorporating stainless steel (316 L) was meticulously explored. Given the high metallic powder concentration, interparticle interactions escalated ink viscosity. Nonetheless, the ink exhibited a favorable shear-thinning trend across applied shear rates. Additionally, the ink showcased elastic behavior over a broad strain range, with storage modulus dominance in the stress *vs.* strain curve. However, in a collision regime, inelasticity emerged, with G" prevailing. Frequency exhibited minimal influence on G' and G" values, consistent across tested frequencies.

In another significant contribution by Baniasadi et al. [1], the viscoelastic performance of QSM was notably enhanced by amalgamating it with CNFs for DIW of hydrogels. The inclusion of CNF heightened sample viscosity, indicating the formation of a more robust structure due to inter- and intra-molecular hydrogen bonds within the nanocellulose. Furthermore, the pronounced shear-thinning behavior was consistent across all formulations, coupled with significant enhancements in both G' and G" upon increased CNF content. Importantly, the original QSM exhibited poor printability due to low yield stress, but with CNC addition, yield stress improved significantly, enabling intricate structures with high resolution and shape stability to be printed. A thorough examination of acrylamide, a representative hydrogel precursor, was undertaken to explore the impact of alginate addition in varying amounts of 0, 1.7, 3.3, and 6.5 wt% on rheology tailoring. The addition of alginate transformed the inks from water-like to viscoelastic fluids, indicated by strong shear-thinning behavior resulting in decreased apparent viscosity with increased applied shear rate. The viscosity of the ink reached 15,600 Pa·s at a low shear rate of 0.01 s^{-1}, sharply dropping to 50 Pa·s at a shear rate of 50 s^{-1} (typical during printing) [159]. Similarly, the rheological behavior of Bi2Te3-based inks was adjusted to meet DIW criteria using polyelectrolyte additives, while methylcellulose reinforced the inks to achieve yield stress, structural recovery, stability, and accuracy [179].

5. Direct ink writing of hydrogels for biomedical applications

DIW has emerged as a transformative technique with immense potential across a broad spectrum of biomedical applications. By harnessing precise material deposition, DIW empowers the creation of intricate 3D structures meticulously tailored to meet specific biomedical requirements. Within this innovative approach, bio-inks—often comprising biocompatible and bioactive materials—are systematically layered to craft constructs endowed with desired mechanical, chemical, and biological attributes. The adaptability of DIW transcends various domains, encompassing tissue engineering, drug delivery systems, implantable devices, and biocompatible sensors. This technology not only catalyzes the advancement of cutting-edge medical solutions but also charts a course toward personalized and patient-specific interventions, thereby propelling healthcare progress. Within this section, we explore the pivotal role of DIW in three vital biomedical domains: tissue engineering, wound dressing, and drug delivery systems. Moreover, we survey the latest research endeavors undertaken in this dynamic field.

5.1. Revolutionizing tissue engineering with 3D-printed hydrogels

Hydrogels have emerged as a remarkable class of materials in tissue engineering due to their distinctive properties and compatibility with biological systems [180,181]. Tissue engineering strives to fabricate functional substitutes for damaged or ailing tissues, and hydrogels play a pivotal role in realizing this objective by providing a supportive matrix that emulates the extracellular milieu. This matrix facilitates cell growth, differentiation, and tissue formation. Hydrogels are intricate 3D networks of hydrophilic polymer chains that have the ability to absorb and retain a substantial volume of water. This inherent high water content lends them a soft and pliable consistency reminiscent of natural tissues, rendering them highly suitable for various biomedical applications [182].

The benefits of hydrogels in tissue engineering encompass their capability to replicate the natural extracellular environment, thereby fostering cell attachment, proliferation, and differentiation. They can be engineered to release growth factors, pharmaceuticals, and other

bioactive agents in a controlled manner, thereby augmenting tissue regeneration.

Moreover, their physical characteristics can be customized to align with the requisites of diverse tissues, offering mechanical reinforcement while facilitating the exchange of nutrients and waste products. More importantly, hydrogels are derived from biological sources and are frequently composed of polymers found within the ECM of tissues. Notable examples of these hydrogel materials encompass alginate, cellulose, chitosan, and hyaluronic acid [183–185]. Nonetheless, employing hydrogels in tissue engineering presents certain challenges, including the attainment of optimal mechanical traits, the preservation of long-term stability, and the assurance of seamless integration with surrounding tissues [186,187]. Researchers are actively addressing these hurdles through advancements in materials science, cross-linking techniques, and strategies for biofunctionalization [188–190]. As discussed earlier, synthetic hydrogels are meticulously designed and synthesized in laboratory settings to achieve specific attributes such as mechanical robustness, degradation rate, and bioactivity. Prominent synthetic hydrogel materials include PEG, PNIPAAm, and PVA [191,192].

Regardless of their origin, the advent of 3D-printed hydrogels has revolutionized the field of tissue engineering by endowing precise control over the spatial arrangement of cells and biomaterials, enabling the fabrication of intricate, tailor-made tissue constructs. This pioneering approach amalgamates the strengths of both hydrogels and additive manufacturing techniques, thereby empowering researchers to forge tissues possessing heightened structural integrity, biomimetic architecture, and tailored mechanical traits. The technology of 3D printing confers meticulous control over scaffold geometry, porosity, and internal structure. This personalized framework facilitates the crafting of tissues featuring specific dimensions and contours, particularly pertinent in the context of patient-specific applications [23,193,194].

Furthermore, 3D printing facilitates the direct incorporation of cells within the hydrogel framework at precise locations. This precision placement of cells within the scaffold nurtures appropriate cell-cell interactions, fosters nutrient exchange, and fosters the development of functional tissues [195,196]. Similarly, 3D printers can concurrently manipulate multiple materials, enabling the generation of intricate tissue architectures possessing diverse mechanical traits and biological functionalities. This attribute proves pivotal in simulating the heterogeneous composition of natural tissues [197,198]. Of greater significance, 3D-printed hydrogels enable the integration of growth factors, pharmaceuticals, and other bioactive agents within the scaffold matrix. This calibrated release of biochemical cues amplifies tissue regeneration and the healing process [197,199].

While the potential of 3D-printed hydrogels is vast, there are several challenges that demand attention. One pivotal concern is ensuring the compatibility of 3D-printed hydrogels with cells and tissues. Particularly, some synthetic materials might provoke immune reactions or exhibit cytotoxic tendencies, thus necessitating comprehensive biocompatibility assessments. Furthermore, the pursuit of desired mechanical attributes within 3D-printed hydrogels, including traits like elasticity and strength, remains a formidable task. Striking the right balance between structural robustness and the requisite flexibility for optimal tissue functionality presents a nuanced challenge. Similarly, ensuring the enduring stability of 3D-printed hydrogels over extended durations holds paramount significance in tissue engineering applications. The control of degradation rates must be meticulously calibrated to align with the timeline of tissue regeneration.

In recent years, significant research efforts have been devoted to hydrogel DIW, aimed at the creation of 3D scaffolds for tissue engineering. The depth of this subject warrants a dedicated review paper. However, herein, a selection of the most recent advancements is examined. Notably, Jaing et al. [87] showcased the fabrication of custom hydrogel structures using DIW, employing hybrid hydrogel inks composed of PVA and κ-carrageenan with exceptional rheological properties. Fig. 5 illustrates schematic representations of the fabrication and post-processing steps for these 3D-printed hydrogel structures. Employing a freezing and thawing process subsequent to DIW, they induced the formation of physically crosslinked networks due to PVA's crystallinity. This augmentation of mechanical attributes and resistance to swelling in the printed structures was apparent. The resulting hydrogel not only displayed remarkable cytocompatibility but also supported cell attachment and extension within the grid-like architectures, providing conducive microenvironments for cellular cultivation. Their assertion is that these printed constructs harbor immense potential in fields spanning tissue engineering, drug delivery, bone regeneration, and implant medicine. Another notable endeavor, undertaken by Bhatt et al. [60], sought to develop engineered 3D scaffolds for liver tissue engineering. Their approach involved DIW-printing objects composed of PVA and chitosan. They exhaustively characterized distinct physical properties of the printed structures and assessed their compatibility with HepG2 cells. Their conclusion highlighted the substantial promise of chitosan-PVA cross-linked 3D hydrogels in liver tissue engineering.

Cianciosi et al. [55] made significant strides in biomaterial ink development for DIW, enabling the crafting of 3D structures boasting customizable functional and mechanical gradients. Their ink formulation integrated CNFs, allyl-functionalized gelatin, and PEG. Through azido-group functionalization of CNFs, they achieved spatial distribution of functional groups within the 3D structures. This allowed them to establish mechanical gradients spanning 3 to 6 kPa in indentation strength in conjunction with functional gradients. The addition of an anisotropic photocrosslinking step further enabled the introduction of dual gradients. Their ink formulation's potential lies in the printing of intricate multigradient structures, mirroring the intricate hierarchical organization found in living tissues. Cellulose-based inks were leveraged by Baniasadi et al. [21] to engineer 3D scaffolds using DIW, mimicking the properties of soft tissues. Their formulation exhibited excellent viscoelastic traits, enabling precise control over hydrogel shaping and the printing of intricate lattice structures across up to eleven layers with remarkable fidelity and resolution. The printed objects maintained their form without deformation, as depicted in Fig. 6. Extensive evaluations of the printed objects, including their compatibility with HepG2 cells, underscored the potential applicability of these 3D-printed scaffolds in soft tissue engineering. In a parallel vein, the same research group harnessed cellulose-based hydrogels to print QCM using DIW technology, thereby fashioning suitable 3D scaffolds for soft tissue engineering [1].

Employing DIW, Mohandesnezhad et al. [61] successfully manufactured meticulously structured porous scaffolds composed of chitosan, alginate, and hardystonite, mirroring the properties of bone tissues. Notably, these printed scaffolds exhibited a yield strength of 1.38 MPa and an elastic modulus of 125.71 MPa. Furthermore, their compatibility with MG-63 cells was outstanding. Marapureddy et al. [59] engaged DIW in the development of 3D-printed scaffolds for tissue engineering, focusing on chitosan-based hydrogel. This involved the formulation of printable inks, the printing of 3D scaffolds, and subsequent characterization of the printed samples. Differentiation studies of neuroblastoma cells cultured on the printed scaffolds added another layer of insight to their research.

Recently, Heidarian et al. [62] formulated inks based on gelatin, CMC, and dialdehyde-functionalized bacterial nanocellulose, marked by high thermo-processability, shear-thinning, mechanical strength, self-healing, self-recovery, and biocompatibility. These inks exhibit promise in the domain of additive-manufactured tissue engineering scaffolds. Kreller et al. [63] ventured into the development of gelatin-based inks for DIW, tailored to meet the prerequisites of cartilage tissue engineering. Likewise, Dutta et al. [64] reported intriguing research on the DIW of gelatin-based inks. Their endeavor yielded a remarkably stable and conductive bio-ink founded on polypyrrole (PPy)-grafted GelMA, employing a triple cross-linking strategy (thermo-photo-ionically) for DIW-based 3D printing applications. Fig. 7 illustrates the evaluation of

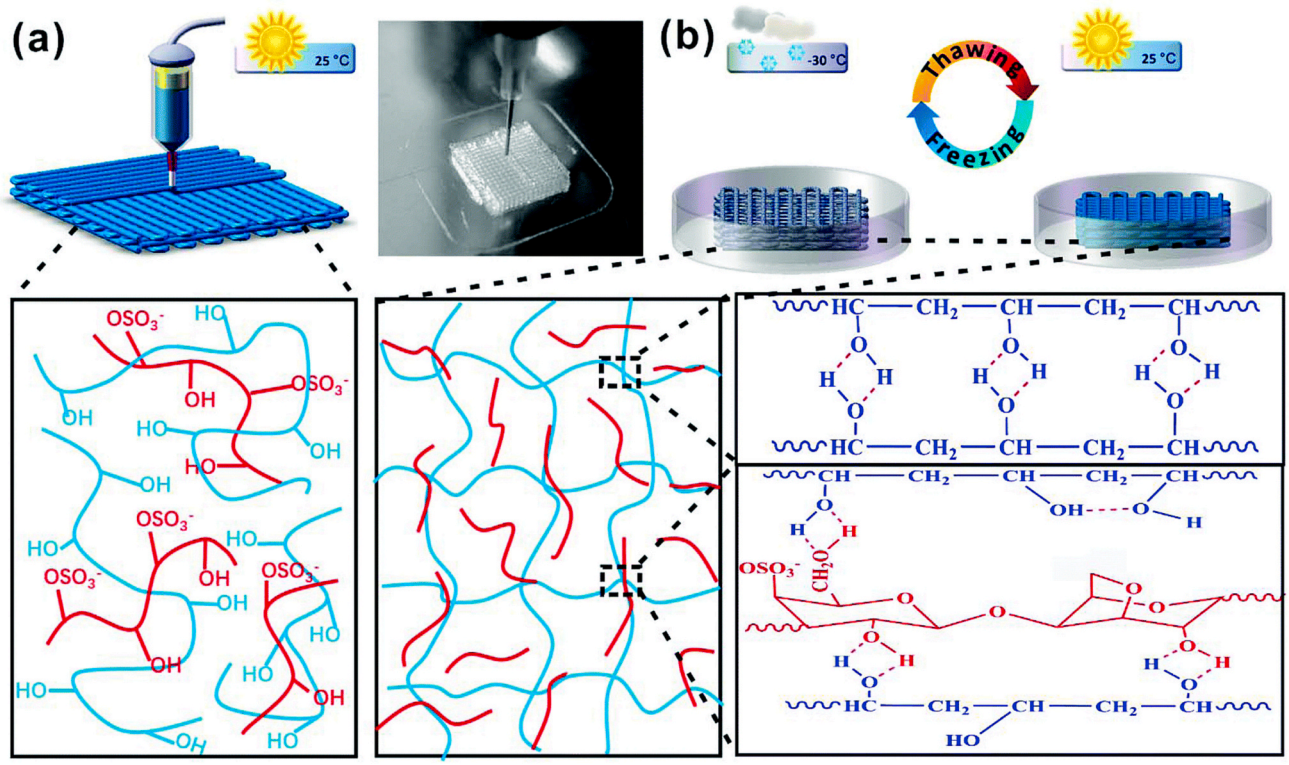

Fig. 5. Illustrative diagrams depicting the production and subsequent processing of 3D-printed hydrogel structures are presented. (a) 3D structures were created using hybrid inks comprising PVA and κ-*CA*. Notable visuals encompass the printing procedure and a woodpile-designed hydrogel scaffold. (b) Performance enhancement of the hydrogels was achieved through freezing and thawing procedures, capitalizing on PVA crystallization [87].

the printability of the GelMA-PPy hydrogel. The bio-ink showcased exceptional shear-thinning characteristics, leading to enhanced shape fidelity and structural stability during 3D printing. The self-supporting nature and tunable mechanical properties of the bio-ink facilitated the high-resolution 3D printing of biological structures. Impressively, the printed structures exhibited a 93% cytocompatibility rate with human bone mesenchymal stem cells (hBMSCs) under microcurrent stimulation. Noteworthy among their achievements, the researchers successfully printed a full-thickness rat bone model, demonstrating the structural integrity of their approach. Transcriptomic analysis of the 3D bioprinted hBMSCs indicated significant expression of gene hallmarks associated with NOTCH/mitogen-activated protein kinase (MAPK)/SMAD signaling, coupled with down-regulation of the Wnt/β-Catenin and epigenetic signaling pathways during osteogenic differentiation over a week-long period. The outcome of this work positions the developed GelMA-PPy bio-ink as an exceptionally stable and non-toxic material for hBMSCs, holding promise as a platform for bone tissue engineering applications.

In the pursuit of a gum-based ink tailored for DIW of engineered scaffolds, Iervolino et al. [57] introduced a versatile blend called GelMA-XG. The incorporation of XG not only enabled the fine-tuning of biodegradability but also improved GelMA's printability. After rheological characterization and printability testing, an optimal concentration of XG was established. This refined blend showcased enhanced printability and superior shape fidelity, and the degradation products were proven non-cytotoxic, thereby laying a robust foundation for cellular applications. Lameirinhas et al. [66] further delved into the development of a printable gum-based ink, combining NFC and gellan gum (GG) in various NFC/GG mass ratios (90:10, 80:20, 70:30, and 60:40). The augmentation of GG content resulted in improved rheological properties, as demonstrated by increased G' and G". Remarkably, the optimized ink formulation, loaded with HaCaT cells, was successfully printed, maintaining elevated cell viability up to day 7 post-bioprinting. To engineer an osteogenic construct, an alginate dialdehyde-gelatin hydrogel was fortified through the incorporation of bioactive glass nanoparticles, specifically mesoporous silica-calcium nanoparticles [67]. This composite hydrogel was DIW-printed into superhydrated composite constructs arranged in a grid pattern. The significant enhancement of mechanical rigidity in these constructs was attributed to the mesoporous silica-calcium nanoparticles, which also catalyzed the formation of an apatite layer upon immersion in simulated body fluid. This augmentation facilitated cell adhesion and proliferation, as evidenced by Fig. 8, showcasing digital images of the printed samples. With the realization of structural and biological advancements, the authors held optimistic expectations for hydrogel nanocomposites in bone tissue engineering.

Simińska-Stanny et al. [68] innovated a highly printable biomaterial ink tailored for 3D printing of shape-sustaining hydrogel scaffolds. This formulation encompassed tyramine-modified hyaluronic acid and GelMA, whose optimization was achieved through Box-Behnken design. The ink exhibited shear-thinning behavior, substantial swelling capacity, ECM-like attributes, and biocompatibility, positioning it as an ideal candidate for soft tissue matrices. Animal trials and chick chorioallantoic membrane assays corroborated the biocompatibility and integration of the printed structure with host tissue. Furthermore, Kachit et al. [69] generated macroporous metallic scaffolds characterized by a 3D macroporous architecture through DIW. Fig. 9 provides a schematic representation of the fabrication process. The formulation centered around a water-based gel infused with Pluronic F-127 and stainless steel powder. The optimization of the printing process balanced 3D extrusion, stiffness, and viscosity, ensuring congruence with design requirements. Pluronic F-127 was also employed to create 3D scaffolds using DIW technology [70].

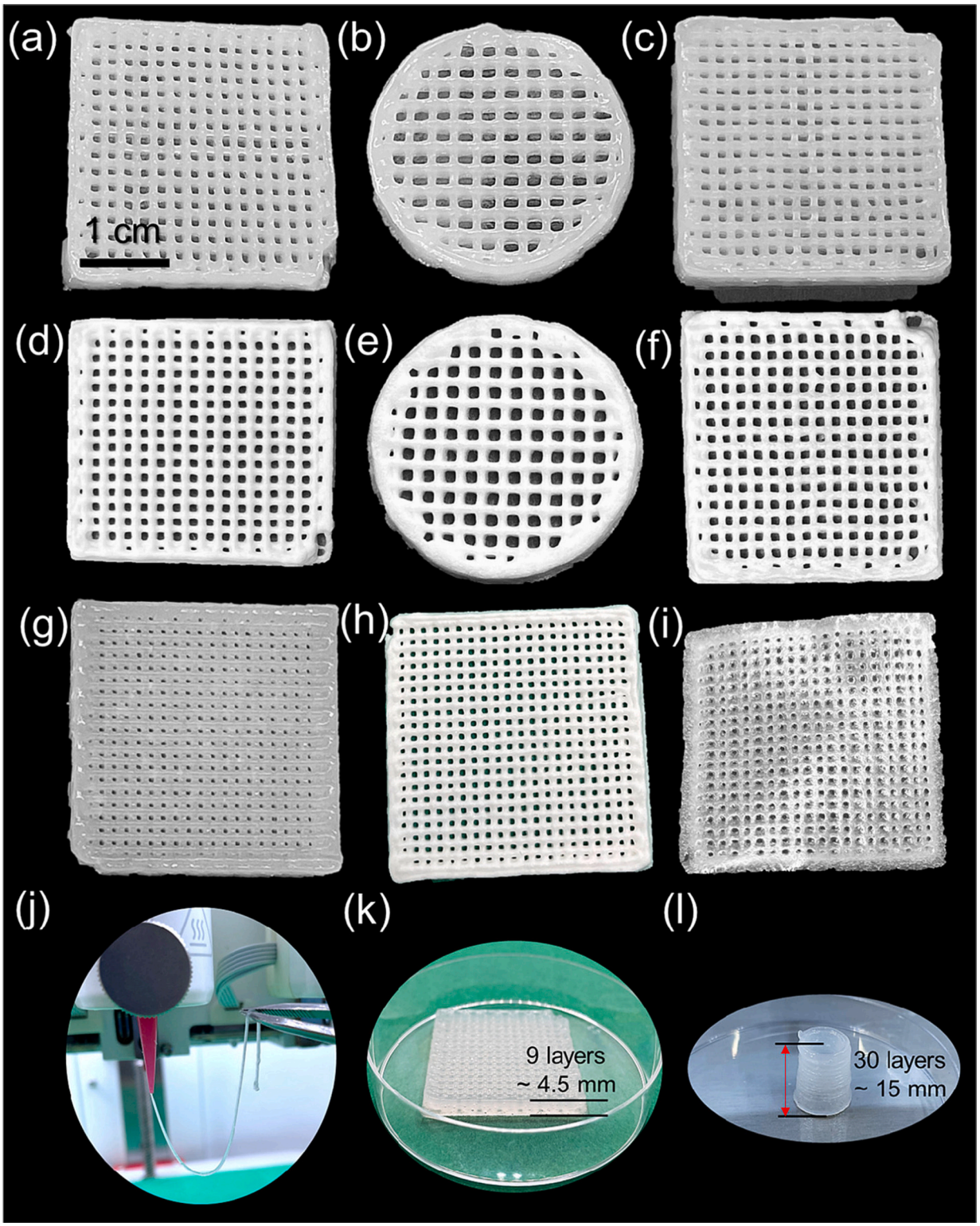

Fig. 6. Photographs showcasing 3D-printed scaffolds: (a) and (d) XG70, (b) and (e) XG60, (c), and (f) XG50 before and after freeze-drying (with a 15% infill density). (g) G50 with a 20% infill density, (h) and (i) XG50 after freeze-drying and air-drying, respectively. (j) Extruded filament, (k) lateral view of XG50, and (l) a hollow cylinder printed using XG50 bio-ink [21]. With permission from Baniasadi, 2022, Copyright © 2022, Elsevier Ltd.

5.2. Advancing wound dressing with 3D-printed hydrogels

Hydrogels have demonstrated significant potential in wound dressing, owing to their capacity to cultivate a conducive environment for wound healing, stimulate tissue regeneration, and facilitate controlled delivery of therapeutic agents [200,201]. Wound dressing plays a pivotal role in the management of diverse wound types, spanning from acute injuries to chronic ulcers, and hydrogel-based materials present innovative solutions to enhance healing outcomes. The high water content of hydrogels aids in maintaining wound hydration. This moist milieu encourages cell migration, fosters angiogenesis (the formation of new blood vessels), and facilitates the creation of granulation tissue.

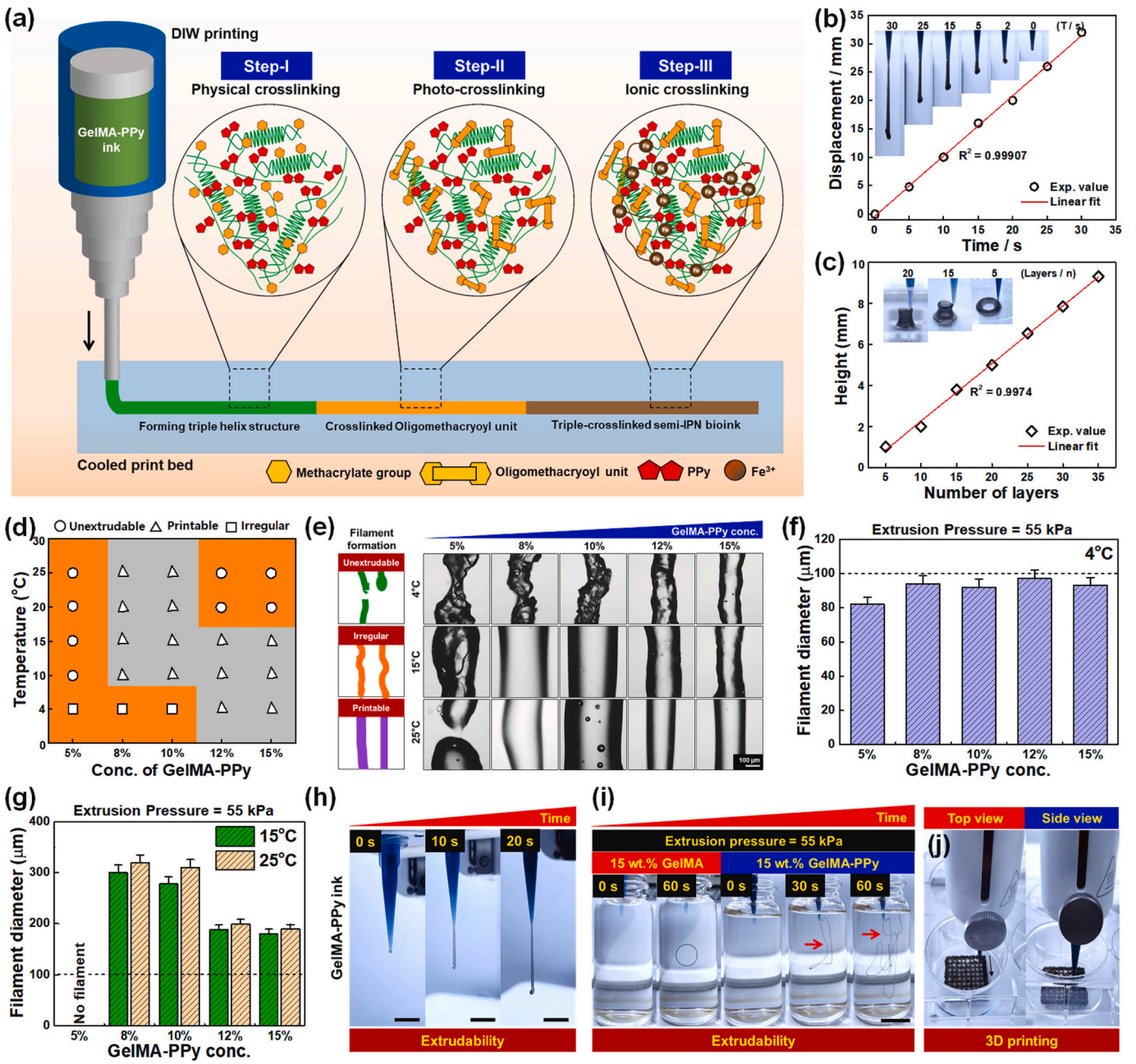

Fig. 7. Assessment of GelMA-PPy Hydrogel Printability: (a) Schematic depiction of the ink deposition process. (b) Steady-state flow curve depicting GelMA-PPy hydrogel ink behavior over time. (c) Relationship between layer height and layer count, illustrating printability variation. (d) Phase diagram showcasing printability based on GelMA-PPy ink concentration and temperature. (e–g) Qualitative and quantitative evaluation of filament formation under diverse temperatures. Scale bar: 100 μm. (h) Sequential digital images capturing shear-thinning behavior of extruded hydrogel. Scale bar: 0.5 mm. (i) Extrudability of GelMA and GelMA-PPy hydrogel inks in PBS over time, showcasing filament stability. The barrel temperature was maintained at 4 °C. The scale bar was 10 mm. (j) There is a visual representation of the 3D printing process with GelMA-PPy hydrogel ink. The black arrowhead indicates the printing direction [64]. With permission from Deb Dutta, 2023, Copyright © 2023, Elsevier Ltd.

Moreover, hydrogels often exhibit permeability to oxygen and moisture while effectively blocking the intrusion of bacteria and contaminants. This duality prevents infection and establishes an optimal habitat for cellular growth [202,203]. Additionally, certain hydrogels encompass cooling attributes that can assuage pain and discomfort at the wound site. Likewise, specific hydrogel formulations contribute to the gentle removal of necrotic tissue and debris from the wound, thereby promoting a clean wound bed. Most importantly, hydrogels are generally biocompatible and non-toxic, thereby minimizing the potential for adverse reactions or allergic responses [204,205].

Analogous to other spheres of biomedicine, 3D-printed hydrogels elevate wound dressing to a new class of customization and efficacy [19,77,206]. For instance, the process of 3D printing facilitates the generation of wound dressings that impeccably conform to the contours of a patient's wound. This tailored fit helps curtail movement and mitigate friction, thereby bolstering the healing process. Furthermore, by incorporating diverse bioactive molecules, growth factors, and antimicrobial agents, 3D-printed hydrogels proffer multiple functionalities within a single dressing. This multifaceted approach can concurrently promote tissue regeneration, regulate inflammation, and stave off infections. Moreover, contingent upon the chosen material and design, 3D-printed hydrogels can provide mechanical reinforcement to delicate or

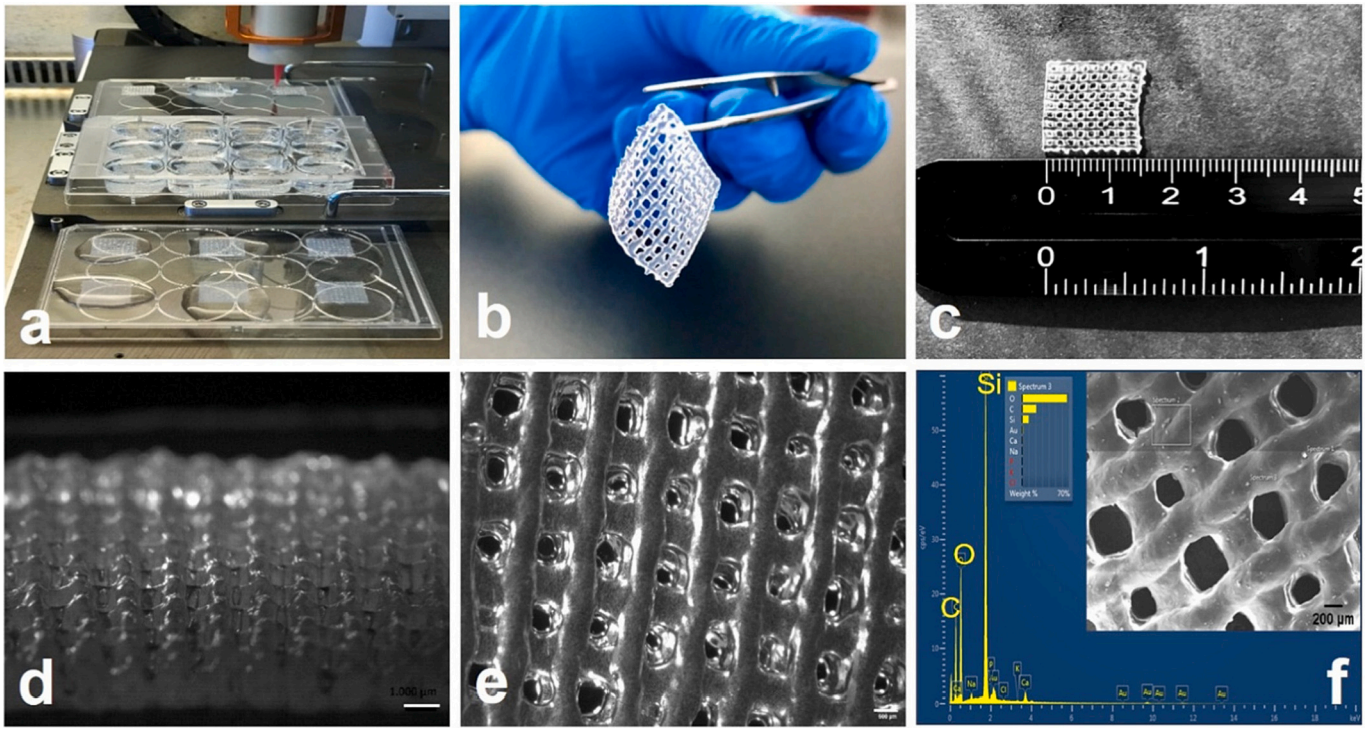

Fig. 8. (a) 3D printing process, (b) & (c) Captured Images Displaying the Quality and Dimensions of a Representative 3D Printed Hydrogel Structure. (d) & (e) Close-Up Views Highlighting Surface Pores and Strut Morphology of the Construct (scale bars: 1000 µm and 500 µm, respectively). (f) Surface Elemental Composition of the MSN-Infused Hydrogel, Corroborated by an SEM Image of the construct [67]. With permission from Monavari, 2021, Copyright © 2021, Elsevier Ltd.

intricate wounds, averting additional damage and ensuring proper recovery. Notably, it is worth highlighting that 3D-printed hydrogels enable the controlled release of therapeutic agents directly to the wound site. This targeted administration enhances the efficacy of treatment while mitigating systemic side effects [207,208].

Notwithstanding the substantial progress, there are challenges to surmount in the utilization of hydrogels and 3D-printed hydrogels for wound dressing. Ensuring the enduring stability of hydrogels or 3D-printed structures over time stands as a fundamental consideration for long-term wound care. Moreover, the rate of hydrogel degradation should align with the timeline of wound healing. Rapid degradation might necessitate frequent dressing changes, whereas slow degradation could potentially impede tissue regeneration. It is pertinent to acknowledge that although 3D printing facilitates customization, the large-scale creation of patient-specific wound dressings may present challenges in terms of time and cost. As of the present moment, numerous researchers have undertaken the task of developing hydrogel-based 3D-printed wound dressings using DIW technology. In the subsequent section, we delve into and discuss some of the most recent endeavors in this field.

Utilizing the beneficial properties of *aloe vera* gel in the healing of burn wounds, Baniasadi et al. [19] engineered 3D structures employing the DIW technique with CNFs and *aloe vera* bio-hydrogels. The resulting hydrogels exhibited exceptional viscoelastic traits, enabling the extrusion of delicate filaments through a 630 µm-diameter nozzle. This precision allowed for the precise fabrication of lattice structures with optimal resolution. These 3D-printed configurations demonstrated notable wet stability, attributed to the elevated aspect ratio of nano- and microfibril cellulose, which reinforced the hydrogels and counteracted substantial shrinkage during drying. Additionally, all printed specimens displayed a porosity exceeding 80%, coupled with a remarkable water absorption capacity, suggesting a promising foundation for 3D wound dressings. Similarly, Chinga-Carrasco et al. [72] explored the potential of cross-linked CNF-alginate inks with Ca^{2+} to design personalized wound dressing devices. These tailor-made constructs can be customized to fit the specific contours of wounds, optimizing the healing process. Notably, the CNF-alginate grids exhibited lateral expansion post-printing, followed by controlled shrinking due to Ca^{2+} cross-linking. Furthermore, Yang et al. [73] pioneered the fabrication of 3D antibacterial wound dressings by incorporating N-halamine/TiO_2 into GelMA and XG (GX). These printed dressings showcased ideal swelling properties and exceptional water uptake efficiency. Remarkably, the dressings exhibited potent antibacterial effects, with complete inactivation of *Escherichia coli* O157:H7 and *Staphylococcus aureus* after a 60-min contact period. Fig. 10 illustrates the outstanding biocompatibility of these printed samples, which also exhibited the capacity to accelerate wound healing in a mouse model, positioning them as promising candidates for wound treatment.

Wang et al. [74] introduced novel printable bionic hydrogels possessing both antibacterial and antioxidant attributes, holding significant potential for inflammation inhibition and accelerated wound healing. The formulation, composed of glycidyl methacrylate (GMA) modified CMC and ε-polylysine (ε-PL), not only exhibited a high compression modulus (238 kPa), stable rheological traits, and effective degradability but also demonstrated a remarkable inhibitory effect (95%) against *Escherichia coli* and *Staphylococcus aureus*. Noteworthy was the hydrogels' ability to counteract excessive reactive oxygen species and safeguard fibroblasts from damage. Compared to commercial dressings (Tegaderm ™ film), CP hydrogels displayed enhanced expression of VEGF and CD31, fostering granulation tissue regeneration and expediting wound healing. Likewise, for the enhancement of dermal fibroblast cell wound healing, conductive inks containing GelMa, poly(3,4-ethylenedioxythiophene), and polystyrene sulfonate were developed, printed, and characterized [208].

In recent research, antibacterial Manuka honey-gelatin 3D wound dressings were crafted *via* a DIW process featuring controlled porosity, high shape fidelity, and structural stability. These dressings exhibited antibacterial efficacy against both gram-positive (*Staphylococcus epidermidis* and *Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria commonly associated with wound infections. Additionally, the

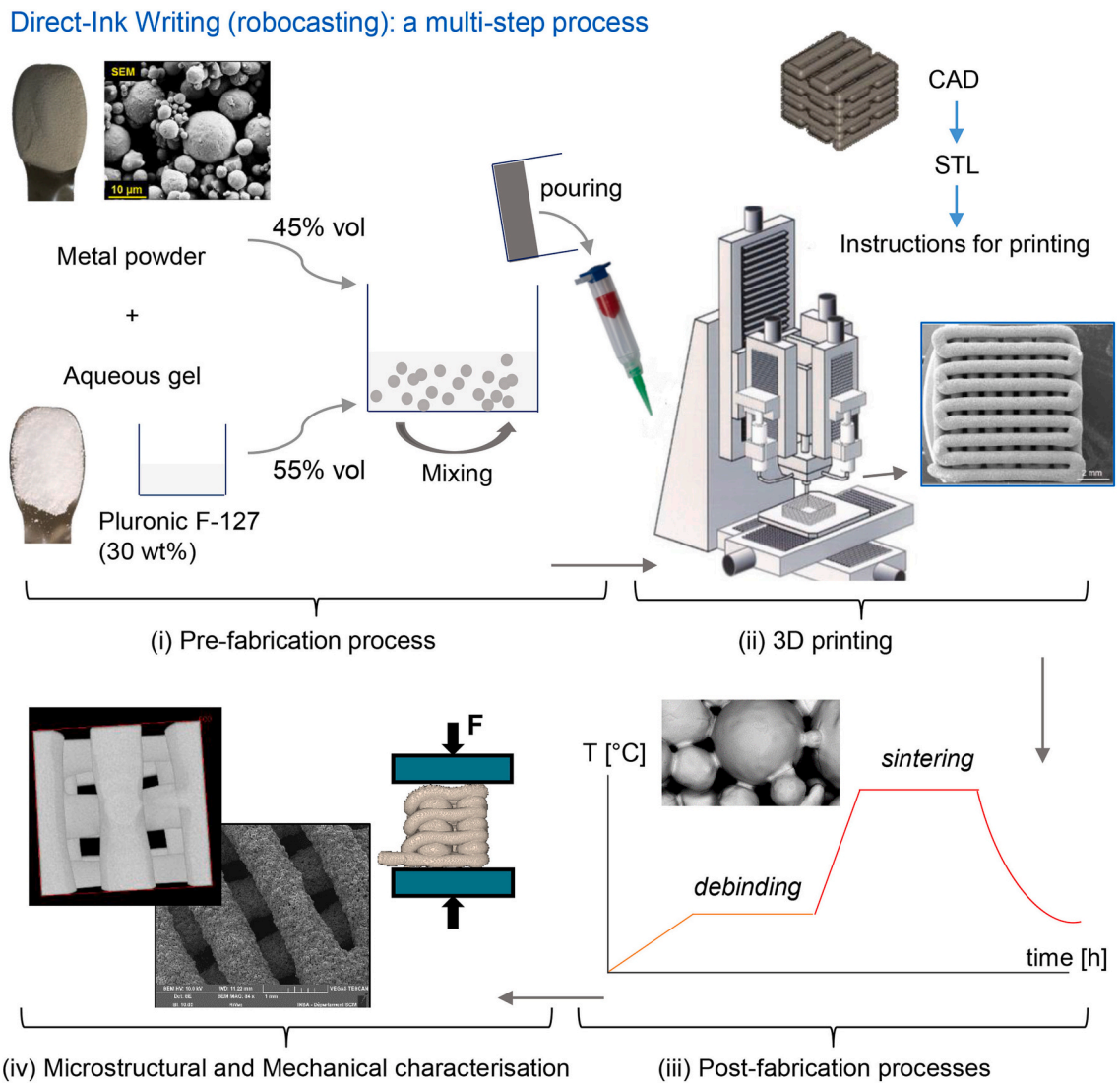

Fig. 9. DIW strategy and characterization of macroporous metallic scaffolds [69]. With permission from Kachit, 2022, Copyright © 2022, Elsevier Ltd.

printed samples demonstrated the capacity to enhance the proliferation of human dermal fibroblasts and human epidermal keratinocytes, as well as promote angiogenesis, rendering these 3D dressings as promising contenders for wound healing applications [75]. In a similar vein, Diaz-Gomez et al. [76] produced 3D wound dressings using CMC-citric acid ink. This formulation showcased remarkable self-healing rheological characteristics and stability during storage, along with the sustained release of pertinent growth factors. The printed samples promoted angiogenesis *in vitro*, stem cell migration *in vitro*, and wound healing in a diabetic model *in vivo*, establishing them as integral components of active dressings for diabetic wounds. In recent developments, hydrogels designed specifically for biomedical applications, such as wound healing films, have emerged. These hydrogels are both biocompatible and 3D printable, achieved through the integration of antibacterial double-quaternized chitosan with cystamine-based non-isocyanate polyurethane. Additionally, CNFs were introduced into the formulations to enhance rheological behavior, swelling attributes, and printability. The resulting hydrogels, fabricated using a DIW technique, exhibit a porous structure and possess biocompatible properties. These hydrogels offer valuable attributes, making them well-suited for diverse wound-healing applications [80].

With the objective of harnessing the abundant protein content and physical crosslinking, Guo et al. [77] created a well-defined architecture through the 3D printing of egg white hydrogel for chronic wound healing. This hydrogel harbored innate bioactive elements that stimulated fibroblasts and adipose tissue-derived stem cells, fostering proliferation, migration, and functions without inducing cytotoxicity. Moreover, the resulting 3D-printed hydrogels induced a proangiogenic effect and augmented collagen deposition *in vivo*, promoting the recuperation of normal and diabetic chronic wounds without the requirement of exogenous growth factors. Employing nickel–copper (NiCu) nanoparticles within polysaccharide hydrogels comprised of methylcellulose, CNFs, and alginate, a range of printable inks were formulated. These inks were then employed to construct customizable dressings with tailored attributes for melanoma treatment. The dressings were assessed in terms of their physicochemical characteristics and their potential application, particularly in melanoma cell cytotoxicity. While all dressings exhibited consistent degradation profiles regardless of composition, the inclusion of NiCu nanoparticles influenced hydrophilicity, swelling rates, and surface properties. Furthermore, all formulations demonstrated compatibility with skin-derived cells; however, dressings loaded with nanoparticles demonstrated promising anti-melanoma activity [78]. Aiming to create wound dressings for diabetic wound healing, Chen et al. [79] printed novel cerium-based metal-organic frameworks (MOFs) nanozyme hydrogel. This hydrogel displayed specific catalytic activity toward various oxygen free radicals and

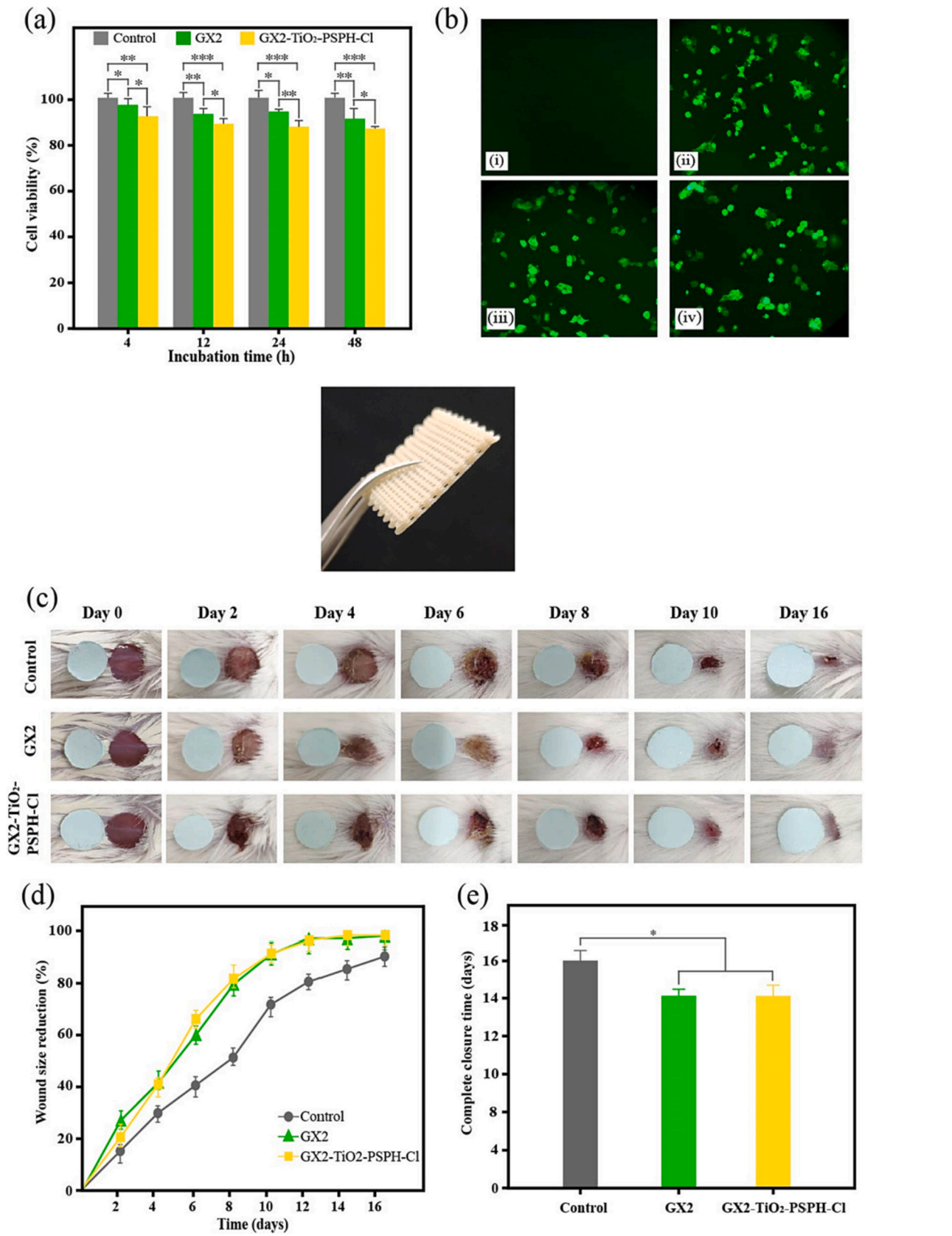

Fig. 10. Cell viability and wound healing assessment: (a) Cell viability of GX2 and GX2-TiO_2-PSPH-Cl dressings after 4, 12, 24, and 48 h of incubation (*$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$). (b) Cell morphology images following 24-h incubation (negative control group (i), control (ii), GX2 (iii), and GX2-TiO_2-PSPH-Cl (iv) dressings). (c) Representative photographs (c) showcasing wound treatment outcomes with gauze, GX2, and GX2-TiO_2-PSPH-Cl dressings spanning 0 to 16 days, accompanied by corresponding quantitative measurements of wound area reduction (d) and complete closure time (e) (*$p < 0.05$) [73]. With permission from Yang, 2021, Copyright © 2021, Elsevier Ltd.

underwent glucose concentration-dependent color changes due to interconversion between different valence cerium ions. This characteristic enabled indirect monitoring of glucose content around the wound. Furthermore, the hydrogel exhibited potent antibacterial properties and biocompatibility. In animal experiments, rats with diabetic wounds of 1 cm2 fully healed within 21 days (as depicted in Fig. 11), attributed to the synergistic effects of the cerium-based MOF nanozyme hydrogel's anti-inflammatory and hyperglycemia capabilities.

5.3. Revolutionizing drug delivery systems with 3D-printed hydrogels

Hydrogels have emerged as a versatile and promising platform for drug delivery due to their remarkable ability to encapsulate and release therapeutic agents in a controlled and targeted manner. Whether intended for localized treatment or systemic distribution, hydrogels possess a multitude of advantages that render them exceptionally appealing in drug delivery [45,209,210]. To begin, hydrogels are inherently biocompatible and well-tolerated by living tissues, thereby mitigating the potential for adverse reactions. Furthermore, their water-rich composition facilitates the dissolution and dispersion of a broad spectrum of hydrophilic and hydrophobic drugs. Additionally, the engineering of hydrogels empowers the modulation of drug release kinetics. This adjustability enables the attainment of sustained, pulsatile, or triggered drug delivery, thereby augmenting treatment effectiveness while minimizing undesirable side effects. Most notably, hydrogels offer the capability for localized drug delivery to specific tissues or sites, thereby curtailing the necessity for systemic administration and the associated systemic side effects [211–213].

Hydrogels play a multifaceted role in drug delivery, acting as protective carriers that shield enclosed drugs from various detrimental factors, including degradation, enzymatic activity, and harsh environmental conditions. This protective function ensures the prolonged stability and bioactivity of therapeutic agents, which is crucial for their efficacy. Beyond this fundamental role, certain hydrogels exhibit the remarkable capability of responding to changes in environmental factors, such as alterations in pH, temperature, or enzymatic activity. This responsiveness allows for precise control over the release of drugs, enabling [177] targeted and on-demand drug delivery. This feature is particularly valuable in optimizing therapeutic outcomes and minimizing potential side effects. Moreover, hydrogels offer versatility in drug delivery strategies. They can be engineered to accommodate the loading of multiple drugs or diverse types of therapeutics within their 3D network. This capability facilitates combination therapy, where different drugs or therapeutic agents can be delivered simultaneously or sequentially. Combination therapy is advantageous in tackling complex diseases or simultaneously addressing multiple facets of a disease, such as targeting both the primary source and associated symptoms [115,214,215].

Similar to their impact in other biomedical domains, 3D-printed hydrogels have emerged as a groundbreaking approach in the field of drug delivery. This innovation combines the advantages of precise structural control with the capability to incorporate diverse bioactive

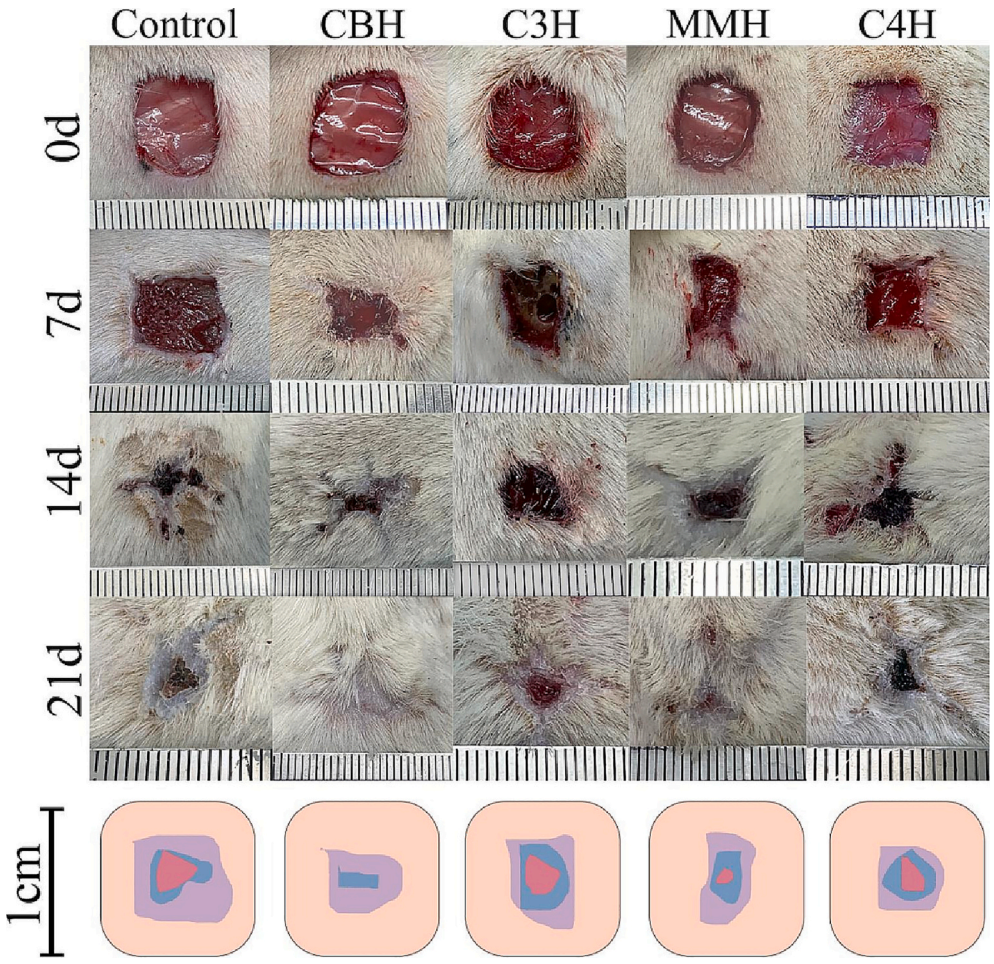

Fig. 11. Providing an overview and schematic illustration of wound healing in animals treated with the printed structures over the course of 0, 7, 14, and 21 days. As depicted in the diagram, flesh-color signifies the wound area at 0 days, purple symbolizes the wound area at 7 days, blue corresponds to the wound area at 14 days, and red denotes the wound area at 21 days [79]. With permission from Chen, 2023, Copyright © 2023, Elsevier Ltd. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

agents. The technology holds the potential to revolutionize drug delivery strategies by enabling customized, patient-centric treatments. Specifically, 3D printing facilitates the creation of intricate structures with meticulous control over the arrangement of drug-loaded compartments or channels. This precision permits targeted drug delivery to specific areas within the body. Furthermore, each 3D-printed hydrogel can be tailored to align with the patient's unique requirements or the specifics of the treatment regimen, thereby optimizing therapeutic outcomes and enhancing patient comfort. An equally significant aspect in the design of 3D-printed hydrogels for drug delivery pertains to fine-tuning release kinetics. The architecture of these hydrogels can be meticulously crafted to regulate the rate and pattern of drug release, thereby facilitating sustained or pulsatile delivery as necessitated [20,81,151,216].

Despite the exciting potential of 3D-printed hydrogels for drug delivery, several challenges persist. Ensuring the biocompatibility and safety of these hydrogels for patient health remains paramount. Technically, achieving the necessary print resolution for micro-scale drug compartments and channels is crucial for precise drug release. Prolonged stability poses another challenge, requiring the maintenance of structural integrity and drug release kinetics over extended periods. The task of patient-specific production presents its own set of hurdles, as scaling up 3D printing for personalized applications while upholding quality and efficiency proves to be a logistical challenge. Thus far, the 3D-printed hydrogels have witnessed substantial utilization in drug delivery, prompting a wealth of research endeavors focused on integrating drugs within 3D-printed architectures. Herein, we present a comprehensive review of some of the most pertinent studies in this domain.

To exemplify, ascorbic acid was seamlessly incorporated into PVA/CNF 3D structures, unveiling a controlled and efficient release within PBS buffer media at 23 °C [20]. Furthermore, Mirek et al. [81] introduced a novel bio-ink consisting of GelMA and gelatin modified with PCL or polyethersulfone microspheres to serve as carriers of bioactive substances. The matrices were subsequently loaded with ampicillin, with the release of the antibiotic corroborated by its antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. In addition, the release profile of rhodamine 640, serving as an active substance marker, was meticulously examined, culminating in a sustained release spanning 7 h (as illustrated in Fig. 12).

Noteworthy contributions came from Diaz-Gomez et al. [76], who introduced 3D-printed constructs constituted of CMC-citric acid inks as vehicles for the controlled release of growth factors, particularly proteins. An initial burst release occurred within the first 6 h of incubation, succeeded by a more regulated release rate. The cumulative protein release reached 232 ± 41 μg per mg of scaffold after 72 h of incubation. By day 7, the scaffolds had fully disintegrated, leading to the deduction that the encapsulated growth factors were entirely released. This time frame of release was deduced to align well with the requisites of wound dressings, which typically undergo examination or replacement on a weekly basis to circumvent hindrances in the healing process. Mesoporous silica with nanostructured pores, known as SBA-15, was employed as a carrier for the hydrophobic drug triamcinolone acetonide. This formulation aimed to incorporate the drug within a hydrophilic printable ink composed of CMC. Evidenced by reduced surface area and pore volume, along with enhanced aqueous solubility of triamcinolone acetonide through *in vitro* release studies, the drug was successfully adsorbed into SBA-15 pores [82].

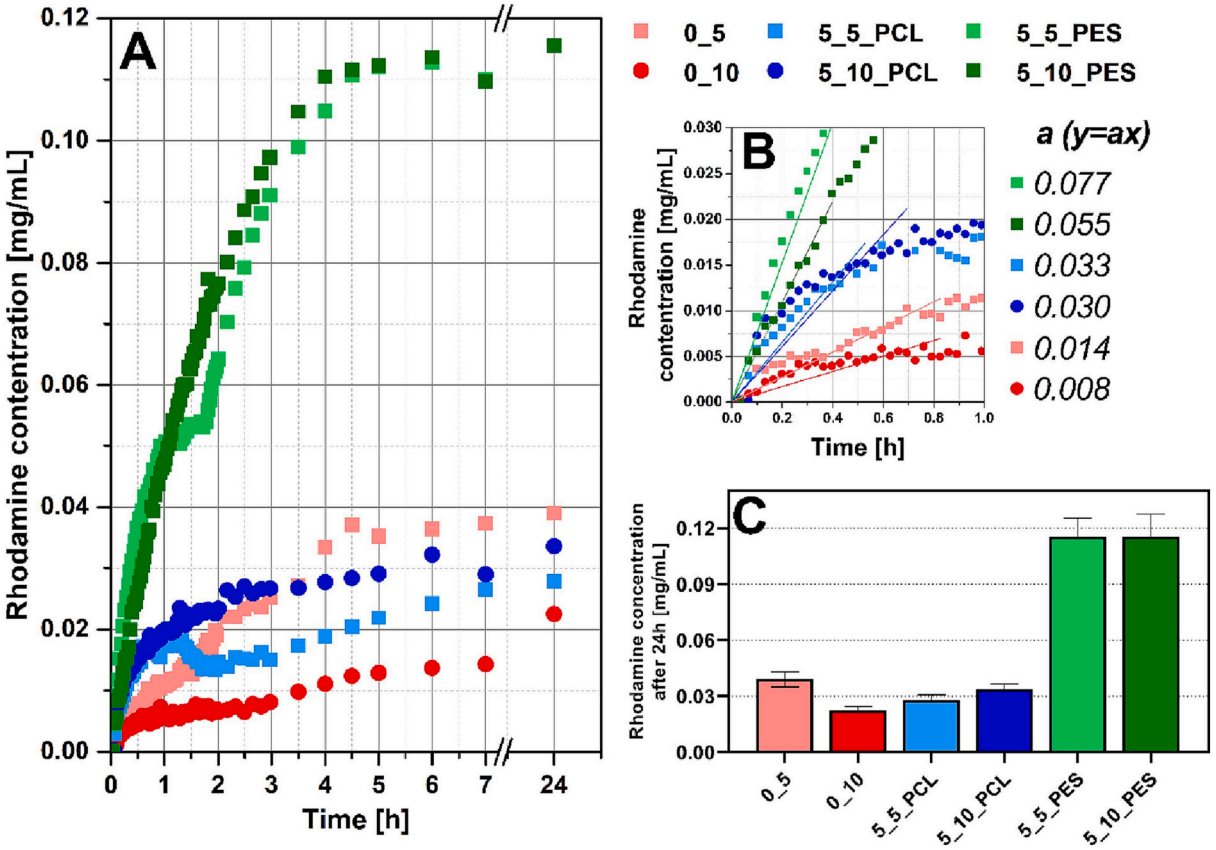

Fig. 12. Findings from investigations on rhodamine release from GelMA/Gelatin matrices, influenced by microsphere content and UV-cross-linking duration: (A) Profiles depicting marker release trends within a 24-h span. (B) In-depth analysis of the initial release phase (first hour), alongside linear model fit (y = ax), with corresponding parameter values listed adjacent to the graph. (C) Rhodamine concentration following 24 h of release from UV-cross-linked GelMA/gelatin matrices, considering the inclusion of microspheres laden with substances, contingent upon microsphere type and cross-linking duration [81]. With permission from Mirek, 2023, Copyright © 2023, Elsevier Ltd.

Wei et al. [83] introduced a facile method for crafting core-shell hydrogel fibers/scaffolds with controlled drug release and structural design tailored for residual breast cancer treatment and the prevention of local recurrence post-surgery. This involved *co*-injecting mixtures of polydopamine (PDA) and concentrated alginate inks for the shell layer alongside drug-loaded temperature-sensitive hydrogels for the core. Coaxial 3D printing yielded core-shell hydrogel fibers and scaffolds. Under near-infrared irradiation, PDA exerted a remarkable photothermal effect, raising the temperature of core-shell fibers and prompting the gel-sol transition of the core gels. Consequently, the drug was released from the relaxed hydrogel network, with the combined photothermal effect and drug release effectively combating cancer. Maiz-Fernández et al. [84] ventured into the creation of 3D-printed structures incorporating chitosan and hyaluronic acid, equipped with customizable attributes, including self-healing and controlled drug release. These structures showcased the ability to modulate and encourage the controlled release of various drugs, including the anionic anti-inflammatory sodium diclofenac and the neutral antibiotic rifampicin. In a recent exploration, Raza et al. [85] delved into the potential of printable self-assembled zein organo-gels in crafting drug delivery systems. Ciprofloxacin served as the model drug, and the release rate, contingent on solvent exchange pace, was meticulously tracked. *In situ* implants in agarose gel sustained antibacterial efficacy against *Staphylococcus aureus* for over 14 days.

6. Conclusions and outlook

Direct Ink Writing (DIW) presents itself as a revolutionary additive manufacturing technique poised to redefine the landscape of hydrogel fabrication. The method's precision in layer-by-layer deposition of hydrogel inks has been conducted in a new era of crafting intricate 3D structures with customizable shapes, sizes, and functionalities. Capitalizing on the inherent versatility of hydrogels – renowned for their biocompatibility and biomimetic properties – DIW opens up a spectrum of applications ranging from tissue engineering and drug delivery to soft robotics and wearable devices. This comprehensive review delved into the world of DIW as it applies to hydrogels and their multifaceted applications. The manuscript introduced a spectrum of printing techniques coupled with a comprehensive exploration of DIW's application in hydrogel-based printing. The intention of this investigation was to explain the progress achieved, challenges encountered, and potential trajectories awaiting DIW of hydrogel-based manufacturing. The underlying principles of DIW were thoroughly explored, with specific emphasis on rheological attributes and printing parameters. This detailed review facilitated a thorough survey of the broad spectrum of hydrogel materials, encompassing both natural and synthetic variants, all of which can be harnessed effectively. Furthermore, this review probed the most recent biomedical applications of DIW for hydrogels, particularly in tissue engineering, wound care, and drug delivery systems. The approach presented here not only consolidates the present state of DIW within hydrogel-based manufacturing but also sets the stage for potential avenues of future exploration, innovative research, and groundbreaking discoveries. The future holds exciting prospects for DIW in hydrogel fabrication. The continued maturity of printing techniques, alongside advances in material science, holds the promise of expanding the horizons of applications in both medical and non-medical domains. Further interdisciplinary collaborations will likely enhance the precision, speed, and scale of DIW technology, enabling it to address challenges and create solutions in fields as diverse as regenerative medicine, advanced materials, and even consumer products.

CRediT authorship contribution statement

Hossein Baniasadi: Conceptualization, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Roozbeh Abidnejad:** Methodology, Visualization, Writing – original draft. **Mahyar Fazeli:** Visualization, Writing – original draft. **Juha Lipponen:** Funding acquisition, Supervision, Writing – review & editing. **Jukka Niskanen:** Funding acquisition, Supervision, Writing – review & editing. **Eero Kontturi:** Funding acquisition, Supervision, Writing – review & editing. **Jukka Seppälä:** Funding acquisition, Supervision, Writing – review & editing. **Orlando J. Rojas:** Funding acquisition, Supervision, Writing – review & editing.

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.

Data availability

Data will be made available on request.

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