Shen and Shen
BioMedical Engineering OnLine (2025) 24:5
https://doi.org/10.1186/s12938-025-01334-3

BioMedical Engineering OnLine

REVIEW

4D printing: innovative solutions and technological advances in orthopedic repair and reconstruction, personalized treatment and drug delivery

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Abstract
With precise control of smart materials deformation in time dimension, doctors can customize orthopedic implants. This review focuses on the advances of 4D printing technology in orthopedics, including its applications in bone repair and reconstruction, personalized treatment, and drug delivery. 4D printing enables the creation of bionic scaffolds and fixation devices for bone repair, customized implants matching patients' conditions for personalized treatment, and specific carriers for accurate drug release and delivery, which together contribute to accelerating bone healing, providing exclusive treatments, enhancing therapeutic effects and reducing side effects, thus helping improve orthopedic medicine. It offers comprehensive reference materials for relevant medical personnel.

Keywords: 4D printing, Bone repair and reconstruction, Personalized orthopedic treatment, Drug delivery

Introduction

Bone repair and reconstruction, personalized orthopedic treatment, and efficient orthopedic drug delivery systems all hold extremely important positions in treatment of orthopedic-related diseases [1–3]. Bone tissue has a unique structure and physiological function. In the process of repair and reconstruction, not only must the mechanical support function be restored, but also biocompatibility and integration with surrounding tissues need to be ensured, among which the technical difficulty is quite high [4–6]. Due to significant differences in bone structure and physiological function among individual patients in personalized orthopedic treatment, there are many obstacles to achieving precision medicine [7]. In the aspect of orthopedic drug delivery, how to ensure that drugs accurately reach the lesion site and maintain an effective drug concentration has always been a difficult problem to be overcome [8, 9].

The 4D printing technology belongs to new additive manufacturing approach [10], which is a further extension of traditional 3D printing, and its uniqueness lies in integrating a new dimension-time (Fig. 1). Through pre-set stimulus shape memory effect (SME), under specific external stimulus conditions, it can accurately change the shape, properties, and functions of materials, showing remarkable characteristics, such as self-assembly, multi-functionality and self-repair [11]. Adaptable materials play a central role in this technology and can react actively to different environmental stimulus factors like temperature, humidity, and light. With its unique performance and potential advantages, 4D printing also shows broad applications in many areas, such as biomedicine, architecture and robotics [12]. However, challenges like regulatory issues, cost barriers, and scalability also exist. For example, the complex regulatory approval process may delay its clinical application, and the relatively high cost of materials and equipment restricts its wider adoption. The scalability in mass production is also a concern that needs to be addressed.

The core purpose of this work is to systematically summarize cutting-edge progress of 4D printing in the fields of bone repair and reconstruction, personalized orthopedic treatment, and orthopedic drug delivery [13]. The combination of 4D fabrication technique and adaptable materials applied in orthopedic treatment brings unprecedented unique advantages for the manufacturing of products, such as smart tissue engineering scaffolds and smart orthopedic implants [14]. These intelligent products can perform intelligent adaptive adjustments according to external stimuli and dynamic changes in the individual physiological environment, thereby greatly improving treatment effectiveness and patients' quality of life [15]. For diseases like bone cancer, the efficient drug delivery system of 4D additive manufacturing plays an irreplaceable key role [16]. Personalized orthopedic implant manufacturing can be accurately designed and produced according to the individual characteristics of patients, which helps significantly improve the adaptability and comfort of implants and effectively reduce the occurrence rate of complications [17, 18]. In general, 4D printing possess and important potential and value for orthopedic treatment[19, 20]. Future research and application will focus on overcoming challenges in material selection, biocompatibility, precision, and cost control to further promote the innovation and development process of the field of orthopedic treatment [21].

4D printing technology principle and key materials

The principle and challenge of 4D printing

4D printing, encompasses several elements [22], including the 3D printing process, stimulation mechanisms, stimuli-responsive materials. The basic principle lies in printing using intelligent materials that react to different stimuli (like., pH, magnetic field,

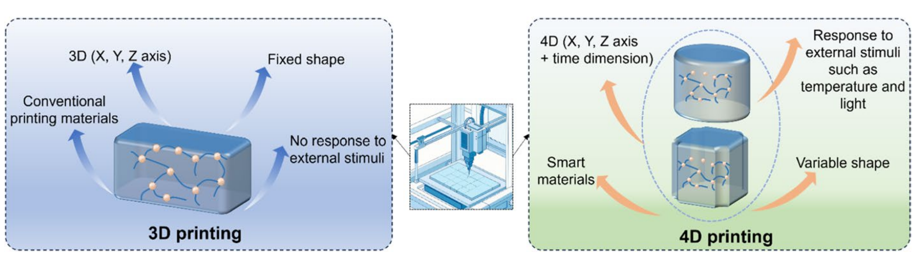

Fig. 1 Illustration of comparison of 3D and 4D printing technology

humidity, heat, and light) and adapt to the extracellular microenvironment by adjusting their shape or other properties. 4D printing uses the same additive manufacturing system compared to traditional 3D printing techniques, but the main difference between the two is the properties of the materials applied [23]. For 4D printed products, the 3D printed structure should exhibit at least one type of intelligent behavior, such as "self-drive" or "shape memory" [24]. Self-drive: refers to the ability of the 3D printed structure of a 4D printed product to spontaneously generate some form of motion or deformation without external continuous force. Shape memory: is a property of the 3D printed structure of a 4D printed product, that is, the material can remember a pre-set shape. Under certain external stimuli, such as temperature changes (thermal shape memory), light (photoinduced shape memory), etc., the material can recover from a temporary shape to its original preset shape.

Traditional 3D printing only focuses the initial stiffness and static state of the printed item, which cannot be deformed to adapt to the dynamic environment of living things [25]. However, with the increasing demand for therapeutic precision, conventional 3D printing has considerable limitations in adapting to dynamic biological environments. In contrast, 4D fabrication technique uses multi-material printing or customized material systems, which not only allows for explicit and complex structural designs, but also gives the printing device the ability to change over time, with changes spontaneously initiated by internal and external stimuli [26]. After leaving the print bed, the printed product can transform from one shape to another, enabling precise regulation of space and time dimensions of the product, and thus production of dynamic and living structures. These features give 4D printing great potential for developing intelligent structures.

The selection and design of intelligent materials is a complex endeavor that needs to be considered the mechanical properties [27], biocompatibility, and stimulus response properties of the materials as well as their utility for specific applications [28]. Another challenge is the accuracy and resolution of 4D fabrication technique. Since 4D printing involves complex shape changes, only high-precision and high-resolution printing devices can realize fine structural designs [29]. In addition, the control of temperature, humidity, and other environmental factors, which may has influence on the stimulus response of the materials, also poses a challenge [30]. One strategy to address these challenges is through research and development of new intelligent materials and printing technologies [31]. Joshi et al. [32] developed an inkjet printing based 4D printing platform capable of printing Clostridium perfringens natto cells, which would alter their shape with the change of relative humidity. In addition, Patdiya et al.[33] developed an open-source smart material printer capable of printing shape-changing materials with various stimulus responses. Another solution strategy is to use software tools to assist the design and manufacturing process of 4D printing. Software like Project Cyborg, and Kinematics can help designers to be able to visualize 4D printed products at the development stage to better realize product design [34].

Key materials for 4D printing

Common materials utilized in bone repair and reconstruction chiefly comprise biodegradable and bioactive substances. Polylactic acid (PLA) [35, 36], poly(glycolic acid) and its copolymers (PGA, PLGA) [37–39] display excellent biocompatibility and biodegradability. The degradation products, like lactic acid or glycolic acid, are capable of being assimilated into the body's metabolic processes. By adjusting parameters like molecular weight and copolymer ratio, the mechanical properties can be precisely customized to meet diverse bone repair requirements [40, 41]. In addition, their ability to change shape in response to external stimuli such as temperature or humidity can also be adjusted, which is crucial for 4D printing. They can be employed to create bone nails, bone plates, and other fixation materials, as well as tissue engineering scaffolds (Table 1).

Among natural polymer materials, chitosan exhibits remarkable biocompatibility, biodegradability, and antibacterial properties [42–44]. It can enhance cell adherence, proliferation, and development, which is beneficial for bone tissue repair. It can be fabricated into sponge-like or gel-like forms to fill bone defects. In addition, chitosan can be modified to have shape memory properties, allowing it to change its structure in a preset manner when subjected to specific stimuli, which is critical for 4D printing applications in the orthopedic field. Collagen, a key component of human bone tissue, has favorable biocompatibility and biological activity. It can serve as a scaffold material, providing an environment conducive to cell growth and differentiation. In addition, collagen can be designed to self-assemble and repair under specific conditions, which are valuable for 4D printed orthopedic materials, because they can adapt and repair themselves in the body over time.

Bioactive materials, such as hydroxyapatite (HA), possess inorganic constituents analogous to those of human bone tissue and possess good bioactivity and biocompatibility [45, 46]. They can form chemical bonds with bone tissue to promote bone regeneration. They can be divided into natural and synthetic hydroxyapatite, and the purity and performance of synthetic hydroxyapatite can be regulated according to needs. Their surface properties can be adjusted in response to external stimuli, allowing for the controlled release of bioactive ions or drugs, which is beneficial for orthopedic 4D printing applications that require dynamic functionality. They can be used to produce bone filling materials, coating materials, etc. Bioactive glass has good bioactivity and biocompatibility and can form a firm bond with bone tissue. It can release ions beneficial to bone regeneration, such as silicon and calcium ions, to stimulate cell proliferation and differentiation. It can be made into granular or block forms for bone defect repair and regeneration. Its structure can be designed to change in response to physiological signals, such as pH or enzyme concentration, which is important for 4D printing, where materials need to adapt to changing environments in the body over time. Tricalcium phosphate (TCP) is biocompatible, biodegradable, and can be designed with adaptive porosity. It can be processed into a variety of forms, for example, beta-tricalcium phosphate has a relatively slow degradation rate and is more suitable for bone repair. It establishes stable connections to bone tissue and promotes bone regeneration. Its porosity can be adjusted in response to external stimuli, resulting in better cell infiltration and nutrient transport over time. This is a key feature of 4D printed orthopedic scaffolds [47, 48].

The materials used for personalized orthopedic treatment have the following characteristics: The material must have high compatibility with human tissue and not cause immune rejection, inflammation, or other adverse reactions. For example, as biodegradable materials degrade gradually in the body, their degradation products should be metabolized or excreted by the body without causing harm. At the same time, bioactive

Table 1 Comparison of typical 4D printing technologies and materials

Categories	Material type	Advantages	Disadvantages	Applicable scene	Refs.
Biodegradable materials	Polylactic acid (PLA) and its copolymers	Adjustable degradation rate, mechanical properties, good biocompatibility, easy to process	Degradation products may cause local acidic environment and insufficient toughness	Non-load-bearing bone defect repair, tissue engineering scaffold	[35, 36]
	Polyglycolic acid (PGA) and its copolymers	Fast degradation, high strength and good processability	Brittleness and strong acidity of degradation products	Temporary fixation assistance for fractures, controlled drug release	[37–39]
	Polycaprolactone (PCL)	Fast degradation, high strength and good processability	Weak biological activity and relatively low strength	Long-term implantation of non-load-bearing site-assisted repair	[40, 41]
Polymer materials	Chitosan	Good biocompatibility, antibacterial, can promote cell adhesion	Poor mechanical properties	Bone defect filling (with risk of infection), drug carrier	[42–44]
	Collagen	High biological activity, similar to human bone tissue composition	Mechanical properties need to be enhanced	Bone tissue engineering scaffolds (provide an environment for cell growth)	[49]
Bioactive materials	Hydroxyapatite (HA)	Inorganic components similar to bone tissue, with strong biological activity and can promote osseointegration	Brittle, difficult to process	Bone filling and coating to enhance osseointegration	[45, 46, 49]
	Bioactive glass	Can release beneficial ions to promote cell proliferation and differentiation, good biological activity	Poor mechanical properties and complex molding process	Complex bone defect repair	[50]
Composite materials	HA/PLA composite material	Both HA biological activity and PLA processing and degradation properties	The preparation process is complex and the cost is high	Bone tissue engineering scaffold, bone repair and filling	[47, 48]
	Collagen/HA composite material	Good biocompatibility and strong osteoinduction	Mechanical properties to be improved	Bone defect repair with high biocompatibility requirements	[51, 52]

materials can form stable bonds with bone tissue and promote bone regeneration without triggering a foreign body response. Personalized orthopedic treatment requires that the material be customized according to the specific condition and anatomical structure of the patient. Through 3D printing technology, the implant can be precisely manufactured to be in accordance with the shape of the patient's bone defect, improving the treatment effect. In addition, the mechanical and porosity properties, etc. of the material can also be changed according to the patient's needs to meet the mechanical requirements and biological function needs of different parts of the bone tissue.

Orthopedic materials need to have appropriate mechanical properties to support and protect damaged bone tissue. For different parts of bone damage, the mechanical parameters such as strength, stiffness, and flexibility of the material should match those of the normal bone tissue around it. For example, in the repair of load-bearing bone, the material needs to have high strength and stiffness to support the body's weight; in non-load-bearing areas, materials with lower mechanical properties but higher biological activity can be selected. The materials used for personalized orthopedic treatment should have the capability to promote bone regeneration. Materials with biological activity can release beneficial ions, growth factors, etc. to promote bone tissue repair and regeneration. Meanwhile, the surface structure and porosity of the material can also affect cell adhesion, proliferation, and differentiation, providing an optimal environment for bone regeneration.

Implanted orthopedic materials need to have certain long-term stability to ensure the sustainability of the treatment effect. The material should retain its shape, mechanical properties, or biological activity in the body without deforming, degrading too quickly, or losing biological activity over time. In addition, the material should have good corrosion resistance to avoid chemical reactions with body fluids. To monitor the treatment effect and the state of materials in the body, it is preferable for materials for personalized orthopedic treatment to have monitoring capabilities.

Common 4D printing materials also have certain advantages in orthopedic drug delivery. Biodegradable materials have good biocompatibility and degradability, and the degradation rate can be regulated. Adjusting polymer parameters can control the drug release rate and time. It can be made into multiple dosage forms, facilitating drug encapsulation and delivery. For example, PLGA microspheres can encapsulate drugs such as antibiotics for the treatment of orthopedic infections. As the material degrades, the drugs are slowly released, continuously exerting the antibacterial effect. Chitosan has antibacterial and tissue repair-promoting functions and can be used as a drug carrier to play an adjuvant therapeutic role. Collagen, similar to bone tissue components, can provide a good binding site for drugs and can be gradually degraded and absorbed in vivo. Thermosensitive hydrogels can undergo sol–gel transformation at a specific temperature, facilitating the loading and injection administration of drugs. At room temperature, they are in a liquid state, which is convenient for mixing with drugs. After being injected into the body, they form a gel at body temperature, and the drugs are fixed locally to achieve local drug sustained release. They can be used for intra-articular drug delivery and the treatment of diseases such as arthritis. Self-healing hydrogels have the ability to self-repair and can automatically restore structural integrity after being damaged by external forces. This property allows the hydrogel to maintain stable drug release performance in the body and is not easily broken even under certain mechanical stress. At the same time, the softness and high-water content of the hydrogel make it adhere well to tissues, reducing the irritation to surrounding tissues.

Applications of 4D printing for bone repair and reconstruction

Variety of tissues and organs with regenerative capacity exist in our body. Although bones have the ability to self-heal, for small-scale bone injuries, the body's bone tissues are usually able to regenerate on their own. However, for large-scale bone defects, relying on the body's self-healing mechanisms alone is not sufficient. Currently, the mainstream clinical approach to address such large-scale bone defects is to use bone grafts from one's own body or from a different individual to fill the defects to rehabilitate their function and structure. However, the efficacy of this approach is limited by the morbidity and bone supply at the donor site. The application of bone grafts and biomaterials involves a variety of complex factors in the actual treatment, such as the location of the bone defect in anatomy, blood flow status, injury to neighboring tissues, infection, the status of the organism, and whether it is accompanied by other diseases. For bone defects treatment, scaffolds act as a crucial function, which not only offer a connection for the growth of newly formed bone tissue, but also provide a platform for the physiological action of cells and growth factors. In recent years, 4D printing has offered new potentialities for manufacturing implantable scaffolds. This technology enables the production of scaffolds that vary with time and are able to adapt to the geometry of bone defects and complex physiological environments, thus more accurately mimicking the dynamics of natural bone tissue. In addition, the functional transformation of 4Dprinted scaffolds after printing can be harmonized with natural healing mechanisms, further facilitating the dynamic reconstruction of bone.

By using 4D fabrication technique, a multi-response bilayer deformable film consisting of SMP layer and a hydrogel layer was fabricated by You et al. [53], which holds a reactive surface micro-structure is capable of precisely toggling the phase between proliferation and differentiation, consequently facilitating bone formation. Zhou and co-authors [54] announced that the SMP stent fabricated in this research can be configured to take on a transient small-sized form and subsequently be returned to the working size and shape under alternating magnetic fields for filling bone defects. The 4D printed scaffold that has been prepared with bioactive filler and Col–Dex coating will present an efficacious avenue for individualized bone tissue repair and strengthened bone tissue regeneration.

Du et al. [55] used four-dimensional fusion deposition modeling of biodegradable polyester copolymers to fabricate bone scaffolds with bioactivity and shape memory (Fig. 2a). In addition, Liu et al. [56] used 4D fabrication technique for the first time to insert aligned cell sheets on deformable hydrogel, and maintain the bone reconstruction microenvironment by introducing adjustable shapes, so as to build personalized bionic periosteum with anisotropic microstructure. This approach can be expanded to mend complex bone defects. By employing 4D printable cross-linked shape memory linear copolyesters via fused deposition modeling (FDM), a workable strategy has been formulated for crafting scaffolds boasting exquisite architecture. The developed composite scaffolds are capable of being utilized for minimally invasive soft tissue repair [57] (Fig. 2b). By probing the potential of heat-induced radial gradient shape

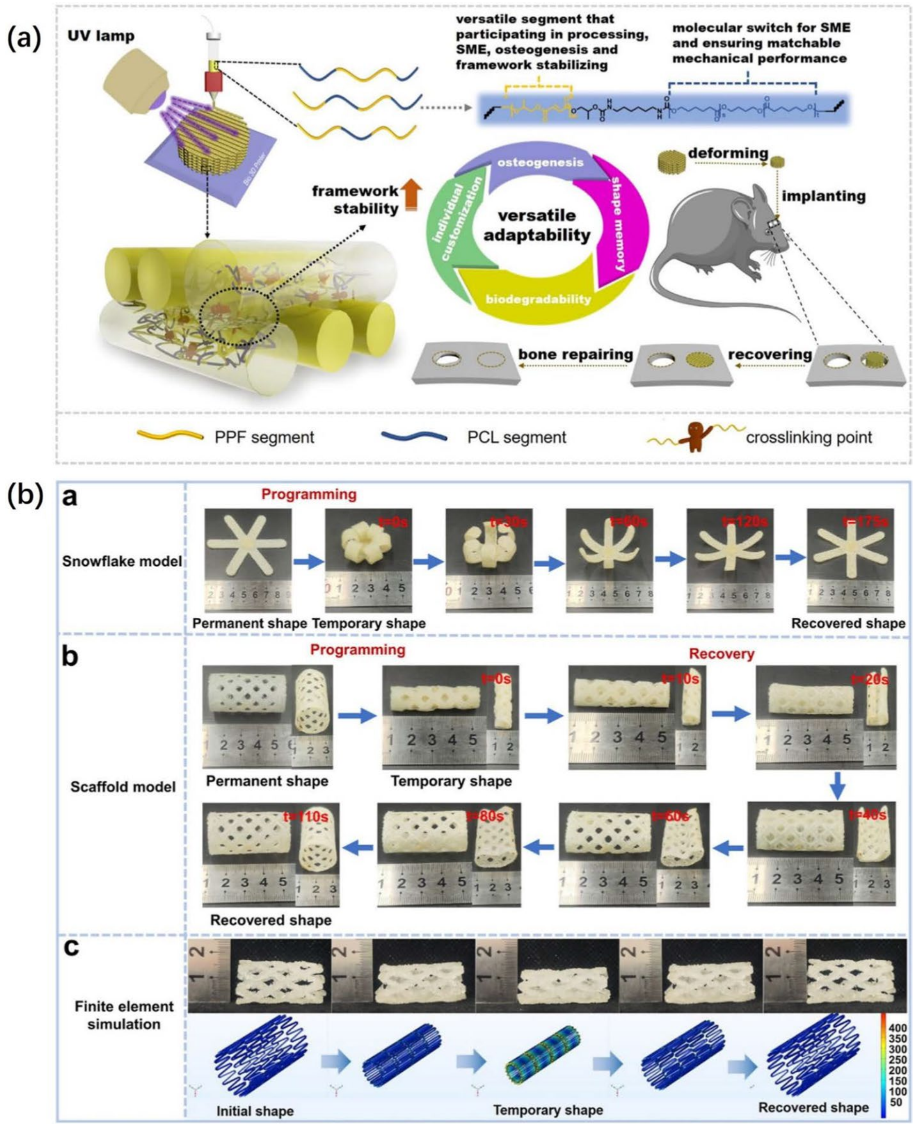

Fig. 2 **a** Fabrication of bone scaffolds by four-dimensional fusion deposition. Reproduced with permission from ref. [55]. Copyright 2023, American Chemical Society. **b** Fabrication of fine structure scaffolds using FDM. Reproduced with permission from ref. [57]. Copyright 2023, American Chemical Society

memory (RGSM) scaffolds for minimally invasive bone repair, it is found that these scaffolds can effectively replicate the natural bone structure, potentially boosting bone integration and regeneration. The outcomes validate the feasibility of RGSM scaffolds for bone tissue engineering, presenting hope for advancing minimally invasive surgical techniques and ameliorating the treatment of bone defects [58]. By examining the viability of 4D printing for polylactic acid (PLA)-based composite scaffolds, it is found that the inclusion of calcium phosphate can boost mechanical strength and shape memory capabilities. Nevertheless, surface integrity is detrimentally impacted. This research holds potential in the creation of self-fitting biomedical stents with high shape recovery for bone repair applications [59].

For example, Shakibania et al. [60] employed 4D printing to produce a smart bone repair scaffold composed of biodegradable materials embedded with shape memory polymers. It was shown that this scaffold was able to adaptively adjust its morphology and release growth factors according to body temperature and the process of fracture healing, thus effectively promoting fracture healing and bone tissue regeneration. Thus, 4D printed scaffolds are expected to realize precision medicine in orthopedics [61].

Cartilage is another important part of the bone system. When osteochondral tissue is damaged, joints, bones and their connecting parts may be affected. Unlike bone, cartilage lacks a vascular supply and has a limited number of its cells, making its self-repair capacity relatively weak. For cartilage tissue engineering, scaffolding materials are considered as key components for repairing osteochondral defects. Several studies have further indicated that combining chondro-forming cells and growth factors may be the optimal cartilage repair strategy [62], which offers the possibility of modulating the parameters of scaffold biomaterials to optimize the microenvironment of regenerated tissues. Considering the properties of cartilage and its healing patterns, hydrogel materials have been considered for potential applications on account of their mechanical traits, biocompatibility, and printability and biodegradability[63]. Tamay et al. [14] also explored the utilization of 4D printing for tissue engineering, which can be used to regenerate organs and tissues employing self-healing hydrogels. These tissues are highly foldable and controllable, and can replace marred tissues drug delivery and during surgery to provide more precise and effective treatment options for patients. Nevertheless, according to existing studies, the ability of 4D printed materials to fully mimic the structure and function of natural cartilage remains a challenge, especially in adjusting the balance between the biodegradation rate of hydrogels and the rate of cartilage recovery. Currently, 3D printing has been widely reported in the field of cartilage repair, but relatively only a limited number of studies have been carried out on 4D printing, so there is still plenty of room for preclinical studies and clinical trials in this field.

In bone tissue engineering, in addition to the need to utilize adaptable materials to construct bone graft substitutes, the synergistic development of microvascular and neural networks is crucial to achieve complex bone regeneration scaffolds [64]. Especially in large and thick bone defects, the regeneration of blood vessels and nerves becomes a major challenge due to limited diffusion of oxygen and nutrients [49]. Bioprinting technology, although showing great potential in biomedical manufacturing, still faces many difficulties in printing hollow tubular forms with complex layered structures [65]. To repair bone defects along nerve pathways, researchers have employed conductive biomaterials, such as graphene, to construct 4Dprinted hybrid architectures, which provide for the regeneration of intricate neural tissues [66]. Compared to neutralized scaffolds, vascularized scaffolds have been more intensively studied in bone tissue engineering. To imitate the structure and function of the natural vascular system, the printed vascular constructs should possess a certain degree of complexity. Cui et al. [67] reported a photo-crosslinked bioink based on gelatin derivatives, which was used for 4D printing to drive the expansion of self-folding scaffolds. It was found that HUVECs (human umbilical vein endothelial cells) exhibited good adhesion and multiplication properties in these self-folding microtubules and successfully integrated into the inner wall of the vessel, a process that provides a new perspective to mimic the formation of natural micro-vessels.

4D fabrication technique holds tremendous potential in bone repair and reconstruction. It uses biodegradable materials for personalized treatment via customization and performance regulation, facilitating bone regeneration and having drug delivery advantages. However, challenges remain, including optimizing material properties, controlling degradation rate, complex preparation, high cost, and improving long-term stability and monitoring accuracy (Table 2).

Applications of 4D printing in personalized orthopedic treatment

4D fabrication technique has brought about a revolutionary change in the field of orthopedics, showing great potential especially in personalized therapy. The goal of personalized therapy is to custom design and manufacture medical devices according to each patient's specific situation and needs to provide more precise and effective treatment options [68]. In addition, this technology allows physicians to precisely customize the form and dimension. of implants based on the patient's bone structure, degree of injury and treatment needs using the patient's CT scan data to provide the most appropriate orthopedic implants and scaffolds for each patient. The Shin's adaptable materials 4D prints scaffolds that mimic the dynamic response of tissues to adjust to alterations in their properties. The technique uses smart nano-bioinks to efficiently fabricate scaffolds. Provides feasibility to stimulate neural stem cell behavior. Capable of creating complex microstructures with 4D variations [69]. The key advantage of 4D printing lies in its capacity to incorporate the properties of smart materials to enable dynamic morphology adjustment of implants and scaffolds within the patient's body to adapt to the physiological and mechanical environments. 4D printing also has great potential for manufacturing highly personalized and functional prosthetic and orthotic devices. The design

Table 2 Applications of 4D printing for bone repair and reconstruction

No	Repair type	Example description	Refs.
1	Fabrication of Responsive Double-layer Deformable Films Using 4D Printing	Consisting of a shape memory polymer layer and a hydrogel layer, the surface microstructure of the SMP layer promotes bone formation	[53]
2	Manufacturing SMP brackets	Restores shape under alternating magnetic fields and fills in bone defects	[54]
3	Fabrication of bone scaffolds by four-dimensional fusion deposition	It has biological activity and shape memory	[55]
4	Manufacturing bionic periosteum	Maintaining the bone reconstruction microenvironment by inserting aligned cell sheets into a deformable hydrogel using 4D printing	[56]
5	Fabrication of Fine Structure Scaffolds Using FDM	For minimally invasive soft tissue repair	[57]
6	Fabrication of thermally induced radial layer shape memory stent	Mimics natural bone structure to enhance osseointegration and regeneration	[58]
7	4D printing PLA composite bracket	Introducing calcium phosphate to improve performance exerts an important function in bone repair	[59]
8	Manufacturing Smart Bone Repair Scaffolds	Composed of degradable materials and shape memory polymers, it adaptively adjusts to promote healing	[60]
9	Building Hybrid Architectures Using Conductive Biomaterials	For nerve tissue regeneration	[66]
10	4D printing self-folding bracket	HUVECs have good adhesion and proliferation properties	[67]

and manufacture of these devices can be precisely tailored to individualize them to the patient's specific physiological conditions and daily habits. This not only improves the comfort of the device and reduces the patient's distress in using it, but also enhances the efficiency of the device's use and further improves the patient's quality of life. In addition, 4D additive manufacturing can also realize the intelligence of the device, Grinberg et al. [70] has been through the 4D printed knee prosthesis embedded with sensors, the device can monitor and adjust its status in real time to adapt to the dynamic needs of the patient, and these intelligent prostheses can handle the knee movement in an ideal way and greatly improve the patient's comfort. Schwartz et al. [71] reported on smart spinal implant technology that unlocks new potentialities for treatment of spinal deformities and injuries. Surgeons can use this technology to print customized spinal implants for the treatment of conditions like fractures, degenerative disc disorders, and scoliosis. These personalized implants can restore spinal stability and improve surgical outcomes and patient quality of life. In addition to making breakthroughs in spinal treatment, 4D printing technology also has important applications in the field of hip joint treatment. Wong et al. [72] used 4D printing to successfully fabricate an acetabular cup with superior performance, revolutionizing the traditional approach to treating large pelvic bone defects. The acetabular cups printed through this technology have design freedom, can produce complex porous structures to adapt to the individualized needs of different patients, and can be used for long-term clinical treatment, which greatly improves the therapeutic efficacy and surgical success rate. The future application of 4D printing will undoubtedly unlock new possibilities for design and manufacture of prostheses and orthoses, providing patients with more humanized and efficient services. Although the development of personalized orthopedic treatment is currently facing challenges, such as smart material preparation, cost and stability of 4D printing technology, it is expected that these problems will be solved with the advancement of technology. In summary, 4D additive manufacturing can provide patients with more precise and efficient treatment options in personalized orthopedic treatment, which predicts a broad application prospect and better treatment results.

Moreover, a UV-assisted FDM 4D printing strategy was demonstrated to manufacture an elbow protector model based on a shape memory copolyester network. The photo-crosslinked network can not only enhance the bonding strength of each layer but also ensure that the object has excellent shape memory performance [73] (Fig. 3a). Langford et al. [74] introduced the combining origami and four-dimensional printing to construct a delivery of biomedical scaffolds with high shape recovery capabilities in a minimally invasive way, and the herron-mosaic origami structure is integrated with the internal natural spongy bone core to meet the design demands of collapsible scaffolds.

In addition, 4D printing to manufacture a multi-response bilayer deformable film which is composed of a hydrogel layer and a SMP layer was reported by You et al. [75]. The layer of shape memory polymer has a surface microstructure that is responsive and can precisely toggle between the proliferation and differentiation phases, consequently promoting bone formation. The 4D membrane can preserve the shape of the model of bone defect in a noninvasive mode. Elshazly et al. [76] studied and quantified the forces generated by a three-dimensional-printed orthotic made of a four-dimensional orthotic, which successfully achieved significant tooth movement on typos.

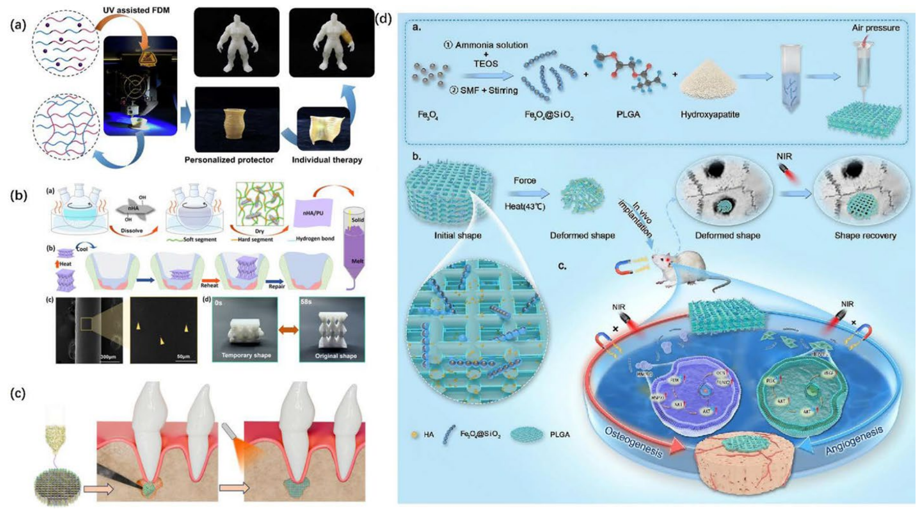

Fig. 3 **a** UV assisted FDM to make elbow protector model. Reproduced with permission from ref.[73]. Copyright 2020, ELSEVIER. **b** Preparation of shape memory composites for cartilage defects. Reproduced with permission from ref.[79]. Copyright 2023, American Chemical Society. **c** Preparation of near-infrared response programmable PLMC stent. Reproduced with permission from ref.[80]. Copyright 2024, American Chemical Society. **d** Development of dual-response bone tissue engineering scaffolds. Reproduced with permission from ref.[81]. Copyright 2024, ELSEVIER

Although 3D printing provides a relatively inexpensive, swift, and less hazardous manufacturing approach, it is rather restricted in crafting more intricate objects. Over the past three decades, additive manufacturing has transformed from an innovative technique to an increasingly accessible instrument in diverse medical domains, including orthopedics. In recent years, stable 3D printed items have been converted into intelligent objects or implants by means of novel 4D printing systems. 4D printing is an advanced procedure in which smart materials are incorporated to create the final product. Human bones have a morphological characteristic of curving along their axis, which augments the mechanical stress induced by external forces. In contrast to the three axes employed in 4D printing, the 5D printing technology utilizes five axes to produce curved and more complex items. Currently, 6D printing technology amalgamates the concepts of 4D and 5D printing to generate objects that alter their shape over time in response to external stimuli. In future research, it is evident that printing technology will comprise a combination of multi-dimensional printing technology and smart materials. Multidimensional additive manufacturing technologies will propel print sizes to higher levels of structural freedom and printing efficiency, presenting promising performance for a variety of orthopedic applications [77].

In addition, Zhou et al. [78] prepared a 4D printed SMP scaffold comprising bioactive fillers, such as hydroxyapatite and alendronate, along with a collagen–dexamethasone (Col–Dex) coating. Biological studies demonstrated the effective bioactivity and osteogenic effects of the 4D printed SMP scaffold. It has potential application prospect in bone tissue regeneration. Deng et al. [79] prepared shape memory composites for cartilage defects by adding nano-hydroxyapatite to matrix of shape memory polyurethane, which showed excellent biocompatibility or mechanical properties. 4D printed cartilage scaffolds can be expanded from convenient insertion shapes to unfold shapes to suit defects (Fig. 3b).

Moreover, Liu et al. [82] used a 4D printing technique to insert aligned cell sheets onto deformable hydrogels. Apart from deforming preset shapes to act as physical barriers, aligned bionic periostees can also actively boost local angiogenesis and early osteogenesis. What's more, Barmouz et al. [83] focuses on the additive manufacturing of hand-shaped memory polymers orthotics for the treatment of cerebral palsy patients. Design and manufacture of new thermal action custom hand orthoses by DLP. The manufactured orthopedic apparatus holds great potential as an alternative treatment option for cerebral palsy. Choudhury et al. [80] produced a near infrared programmable and reactive PLMC scaffold through extrude-based three-dimensional (3D) printing, which, compared to pure PLMC, PLMC–PDA composites showed a markedly higher in vitro osteogenic potential and were able to cope with asymmetrical and complicated tissue imperfections for bone tissue regeneration (Fig. 3c). Guo et al. [84] developed a new type of shape memory polymer reactive to near-infrared radiation, which can entirely blend the shape memory effect of PLLA and the printability, outstanding biological activity and the remarkable photothermal effect of FECL3–TA-modified nanoparticles (MgO). PLLA/(FeCl3–TA/MgO) scaffolds with uniform spongy structure were prepared by 4D printing. Hao et al. [85] reported a millimeter-scale PEGDA micro-patterned micro-scaffold by 3D printed that is self-assembled by Mosaic, the scale of which is relevant for applications in osteochondral reconstruction. This 4D printable injectable technology is promising in future clinical applications of osteochondral tissue engineering. Li et al. [81] developed a framework for bone tissue engineering that is bifunctional-responsive and manufactured using a 4D printing strategy by integrating printing inks comprised of bio-ceramics and biopolymers with particular kind of multifunctional Fe_3O_4@SiO_2) (Fig. 3d). Applications of 4D printing in personalized orthopedic treatment are summarized in Table 3.

Applications of 4D printing in drug delivery system

Drug delivery systems (DDS) capable of providing local, targeted, and continuous drug delivery hold great promise in more effectively managing diseases while reducing toxicity. For orthopedic medicine, orthopedic diseases often involve specific local areas, such as the fracture site, joint cavity, spine, etc. The drug delivery system is able to precisely deliver the drug to these diseased sites, avoiding dilution and metabolism of the drug as it is distributed throughout the body, thus significantly increasing local drug concentration and enhancing the therapeutic effect. Different orthopedic diseases have different requirements for drugs at different stages. The drug delivery system is able to regulate the rate of drug release, and achieve continuous and stable drug supply [86]. Titanium implants are used in improved techniques for drug loading and drug release control [87]. Cui et al. [88] selected ciprofloxacin hydrochloride as the model drug and produced three implants with customized internal structures through) and FDM. 3D printing technologies provide a practical approach and innovative tactic for implant DDS. In addition, metastatic osteopathy is common in patients with advanced cancer. Local carriers composed of poly(methyl methacrylate) and inorganic bone cement for chemotherapy drugs offer the advantage of high local drug concentrations and simultaneously

Table 3 Applications of 4D printing in personalized orthopedic treatment

Examples of personalized orthopedic treatment	Description	Refs.
4D Printing Knee Prosthesis Embedded with Sensors	Real-time monitoring of adjustment status to adapt to patient dynamic needs	[70]
Intelligent Spinal Implant Technology	Printable custom spinal implants to treat spinal disorders	[71]
4D printing acetabular cup	Design freedom and adaptability to individual needs	[72]
UV assisted FDM to make elbow protector model	Optical Crosslinking Network Improves Interlayer Bond Strength and Ensures Shape Memory Performance	[73]
Combining origami and 4D printing to develop biomedical scaffolds with highly restorative shapes	Meet the design requirements of foldable brackets	[74]
Fabrication of multi-response double-layer deformed film	SMP layer promotes bone formation and can preserve the shape of bone defect model non-invasively	[75]
Study the forces generated by 3D-printed orthotics	Achieve significant tooth movement	[76]
Fabrication of 4Dprinted shape memory polymer (SMP) scaffolds incorporating bioactive fillers and coatings	It has effective biological activity and osteogenic effect	[78]
Preparation of shape memory composites for cartilage defects	It has good mechanical properties and biocompatibility	[79]
Insert aligned cell sheets in the deformable hydrogel	Deformable preset shape, promoting local angiogenesis and early osteogenesis	[82]
Manufacturing of shape memory polymer hand orthoses	Design and Manufacture of New Thermal Action Custom Orthotics by DLP	[83]
Preparation of near-infrared response programmable PLMC stent	Higher osteogenic potential for dealing with irregular and complex tissue defects	[80]
Development of shape memory polymer composites responsive to near-infrared light	Combining various advantages, it has potential application in the scaffold field of bone tissue engineering	[84]
Design a 3D-printed millimeter-scale micropatterned PEGDA biomaterial micro-scaffold	It has application prospects in osteochondral reconstruction	[85]
Development of dual-response bone scaffolds for tissue engineering	Easy to implant in irregular bone defects, improving bone formation and angiogenesis	[81]

minimize systemic side effects [89]. Moreover, the controlled release of non-steroidal anti-inflammatory drugs (diclofenac) from the coating was demonstrated, along with their positive effects on osteoblast growth for several days. A variety of cell testing methods showed the suitability of the prepared coatings for potential applications in orthopedics [90]. The acelofenac HP–beta-CD complex may serve together with PVP coatings as an extended DDS for effective management of orthopedic pain and inflammation [91]. Uboldi et al. [92] investigated 4D printing in developing coated expandable DDS designed to deliver drugs for durable retention within and controlled release from hollows. muscle organs (Fig. 4a).

Current 4D printed drug delivery systems have also been reported [94]. Melocchi et al. [95] proposed an indwelling device for intravesical DDS fabricated using hot melt extrusion and fused deposition modeling 3D printing. It remains in the bladder for a certain period by reverting to its original shape and is eliminated through urine after dissolution or erosion, leading to 4D printing. In addition, Melocchi et al. [96] reported an expellable gastric retention that relies on shape memory characteristic exhibited by pharmaceutical-grade substances, (vinylidene alcohols), directly fabricated by molten deposition modeling. Inverardi et al. [93] developed a method that integrates experimental and

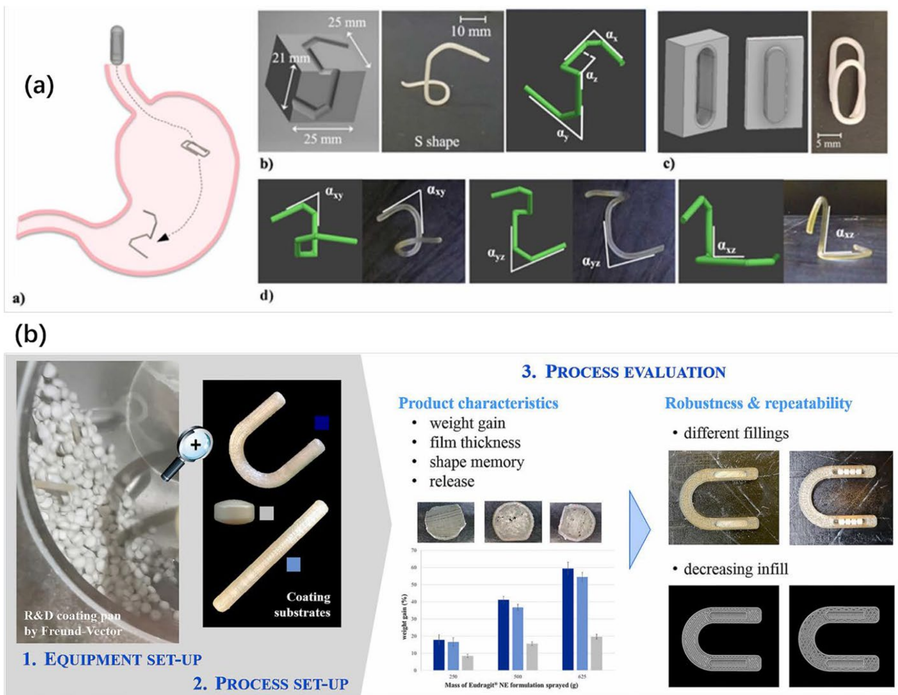

Fig. 4 **a** Researching 4D printing to develop coated expandable drug delivery systems. Reproduced with permission from ref.[92] Copyright 2023, ELSEVIER. **b** Developing shape memory devices for gastric retention drug delivery. Reproduced with permission from ref. [93]. Copyright 2021, ELSEVIER

computational elements used for the design of shape memory devices, manufactured by heat treatment that utilized as gastric retention DDS (Fig. 4b). Uboldi et al. [97] reported that in recent times, the film coating technique has been utilized in the development of a 4D printing slow-release system aimed at retaining organs, evaluating the feasibility of a multifunctional device for rod extrusion and printing prototype film coatings with different cross sections. Uboldi et al. [98] used PVA and SMP to create inflatable organ-holding models created through hot melt extrusion and is an effective material for 4D printing, improving mechanical strength of expandable DDS and decelerating related drug release. Uboldi et al. [99] centers on advances of 4D printed DDS for intravesical drug delivery to combine topical treatment effectiveness with compliance and long-lasting performance. Che et al. [100] proposed an innovative method of manufacturing microneedles, which exhibit 4D properties when exposed to temperature, with needle sizes changing. By increasing resolution, sharpening needles and increasing mechanical strength, these microneedles are capable of loading, delivering, sustainably releasing small molecule drugs and penetrating soft tissue. Oh et al. [101] explored volumetric printing a novel reduction photopolymerization technique, successfully manufactured a scalable drug-eluting 4D device in 7.5 s, and demonstrated drug release ability.

4D printing for orthopedic drug delivery is also an innovative and promising research direction [19]. Compared to traditional drug delivery methods, such as oral administration or injection, these methods may lead to large fluctuations in the concentration of drugs in the body, thus affecting the accuracy of the therapeutic effect. However, 4D additive manufacturing, by combining the properties and morphology modulation

Table 4 Applications of 4D printing technology in drug delivery

No	Example of drug delivery	Describe	Refs.
1	Fabrication of Custom Internal Structural Implants Containing Ciprofloxacin Hydrochloride Using Two Printing Techniques	For drug delivery	[88]
2	Using specific materials as chemotherapy drug carriers	High local concentration and low systemic side effects	[89]
3	Controlled release of nonsteroidal anti-inflammatory drug coating and its effect on osteoblasts	Display coating for orthopedics	[90]
4	Allofenac with specific coatings as a drug delivery system	Treatment of orthopedic pain and inflammation	[91]
5	Researching 4D Printing to Develop Coated Expandable Drug Delivery Systems	For hollow muscle organs	[92]
6	Development of an intrabladder drug delivery indwelling device	Shape recovery implementation using specific printing technologies	[95]
7	Proposed excretory gastric retention system	Shape memory polymer based	[96]
8	Developing shape memory devices for gastric retention drug delivery	Involving 4D printing for personalized treatment	[93]
9	Film coating for 4D printing organ retention sustained release system	Evaluate the feasibility of multi-function devices	[97]
10	Prototype expandable organ retention using specific materials	For 4D printing and improved performance	[98]
11	Focusing on the progress of 4D printing intrabladder drug delivery systems	Combining the advantages of local treatment	[99]
12	Manufacturing microneedles using specific technologies	It has 4D characteristics and can deliver drugs	[100]
13	Exploring Stereolithography to Make Scalable Drug Elution 4D Devices	It has super-fast printing speed	[101]

capabilities of adaptable materials, is able to fabricate carriers that can autonomously release drugs. It is foreseeable that intelligent DDS constructed by 4D printing will bring a more comfortable and safe treatment experience for patients (Table 4).

The application scope of 4D printing in drug delivery systems (DDS) far exceeds that of orthopedics, and it shows great potential and far-reaching significance in cancer treatment and chronic disease management. In cancer treatment scenarios, such as metastatic bone disease in patients with advanced cancer, local chemotherapy drug carriers made of specific materials can be used to achieve high-concentration drug delivery to the lesion site with the help of 4D printing technology, effectively reducing the spread of drugs throughout the body, minimizing damage to healthy tissues, significantly improving treatment effects and reducing the risk of systemic side effects. In the field of chronic disease management, such as intra-bladder indwelling devices, with their unique shape memory characteristics, they can stay in the bladder for a long time and continuously release drugs, avoiding the inconvenience of traditional frequent dosing, greatly reducing the frequency of dosing, and improving patient adherence to treatment. These applications fully demonstrate that 4D printing DDS can be flexibly created according to different diseases and patient needs. Compared with traditional dosing methods, it has obvious advantages in reducing systemic side effects, stabilizing drug concentration, and improving treatment accuracy. It brings patients a safer and more comfortable treatment experience and promotes medical technology to a new height.

Conclusions and future trend

4D printing has shown transformative potential in the field of orthopedic treatment. Its main benefits are significant. In terms of personalized treatment, various orthopedic models and surgical guides can be customized according to the patient's unique bone structure and condition, providing accurate reference for surgical simulation and actual operation, which greatly meets the needs of personalized medical care. From a precision point of view, whether it is model construction or the production of surgical guides, it helps doctors to perform precise cutting and implantation operations, effectively improving the accuracy and success rate of surgery, thereby improving patient treatment outcomes.

However, we must also acknowledge that the current application of 4D printing technology faces many challenges. In terms of material selection, the development of smart materials is still in its infancy, and more diverse material types and better performance optimization are required to meet the special requirements of orthopedic treatment. In terms of biocompatibility, the good compatibility of smart materials with human tissue is the key, which requires in-depth investigation of its interaction mechanism with human physiology to ensure that there are no adverse side effects such as rejection. The accuracy and stability of printing also need to be improved urgently, and the printing technology needs to be continuously optimized to ensure the quality and effect of implants while speeding up the printing speed. In addition, the high cost limits its wide popularity. Reducing costs and enhancing the operability of the technology are necessary measures to promote its wide application in orthopedic treatment.

Although there are challenges, the field of scientific research and engineering innovation is constantly exploring and innovating around these issues. With the in-depth research of smart materials, the gradual conquest of biocompatibility issues, the improvement of printing accuracy and stability, and the effective control of costs, we have reason to be optimistic about the future of 4D printing in orthopedic treatment. It is foreseeable that 4D printing technology will continue to evolve in orthopedic treatment, bring better treatment results to patients, set off a new wave in the medical community, open up more possibilities and hopes for orthopedic treatment, and lead orthopedic medicine to a new era of more accurate and efficient personalized treatment.

Abbreviations

SME	Shape memory effect
PLA	Polylactic acid
PGA	Poly(glycolic acid)
HA	Hydroxyapatite
TCP	Tricalcium phosphate
RGSM	Radial gradient shape memory
FDM	Fused deposition modeling
HUVECs	Human umbilical vein endothelial cells
Col–Dex	Collagen–dexamethasone
DLP	Digital light processing
PLMC	Polylactide–co-trimethylene carbonate
DDS	Drug delivery systems
SSE	Semi-solid extrusion
FDM	Fused deposition modeling
PVA	Poly (vinyl alcohol)

Acknowledgements
We would like to acknowledge the participants who donated their time and effort for the study.

Author contributions

CS and AS wrote the main manuscript text and prepared Figs. 1–4. All authors reviewed the manuscript.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors consent to the publication.

Competing interests

The authors declare no competing interests.

Received: 25 October 2024 Accepted: 7 January 2025
Published online: 21 January 2025

References

1. Wei S, Ma J-X, Xu L, Gu X-S, Ma X-L. Biodegradable materials for bone defect repair. Mil Med Res. 2020. https://doi.org/10.1186/s40779-020-00280-6.
2. Qasim M, Chae DS, Lee NY. Advancements and frontiers in nano-based 3D and 4D scaffolds for bone and cartilage tissue engineering. Int J Nanomed. 2019;14:4333–51.
3. Zhao W, Yue C, Liu L, Liu Y, Leng J. research progress of shape memory polymer and 4D printing in biomedical application. Adv Healthcare Mater. 2023. https://doi.org/10.1002/adhm.202201975.
4. Sahafnejad-Mohammadi I, Karamimoghadam M, Zolfagharian A, Akrami M, Bodaghi M. 4D printing technology in medical engineering: a narrative review. J Brazil Soc Mech Sci Eng. 2022. https://doi.org/10.1007/s40430-022-03514-x.
5. Lai J, Liu Y, Lu G, Yung P, Wang X, Tuan RS, Li ZA. 4D bioprinting of programmed dynamic tissues. Bioactive Mater. 2024;37:348–77.
6. Wychowaniec JK, Brougham DF. Emerging magnetic fabrication technologies provide controllable hierarchically-structured biomaterials and stimulus response for biomedical applications. Adv Sci. 2022. https://doi.org/10.1002/advs.202202278.
7. Kang X, Zhang XB, Gao XD, Hao DJ, Li T, Xu ZW. Bioprinting for bone tissue engineering. Front Bioeng Biotechnol. 2022;10:92.
8. Kanu NJ, Gupta E, Vates UK, Singh GK. An insight into biomimetic 4D printing. RSC Adv. 2019;9(65):38209–26.
9. Mohammadi M, Zolfagharian A, Bodaghi M, Xiang Y, Kouzani AZ. 4D printing of soft orthoses for tremor suppression. Bio-Design Manuf. 2022;5(4):786–807.
10. Ge Q, Dunn CK, Qi HJ, Dunn ML. Active origami by 4D printing. Smart Mater Struct. 2014;23(9):094007.
11. Han X, Saiding Q, Cai X, Xiao Y, Wang P, Cai Z, Gong X, Gong W, Zhang X, Cui W. Intelligent vascularized 3D/4D/5D/6D-printed tissue scaffolds. Nano-Micro Lett. 2023. https://doi.org/10.1007/s40820-023-01187-2.
12. Bonetti L, Scalet G. 4D fabrication of shape-changing systems for tissue engineering: state of the art and perspectives. Prog Addit Manuf. 2024. https://doi.org/10.1007/s40964-024-00743-5.
13. Loukelis K, Helal ZA, Mikos AG, Chatzinikolaidou M. Nanocomposite bioprinting for tissue engineering applications. Gels. 2023;9(2):103.
14. Tamay DG, Usal TD, Alagoz AS, Yucel D, Hasirci N, Hasirci V. 3D and 4D printing of polymers for tissue engineering applications. Front Bioeng Biotechnol. 2019. https://doi.org/10.3389/fbioe.2019.00164.
15. Wang H, Guo J. Recent advances in 4D printing hydrogel for biological interfaces. Int J Mater For. 2023. https://doi.org/10.1007/s12289-023-01778-9.
16. Reddy RDP, Sharma V. Additive manufacturing in drug delivery applications: a review. Int J Pharm. 2020;589:119820.
17. Soleymani S, Naghib SM. 3D and 4D printing hydroxyapatite-based scaffolds for bone tissue engineering and regeneration. Heliyon. 2023;9(9):e19363.
18. Roughley MA, Wilkinson CM: The Affordances of 3D and 4D Digital Technologies for Computerized Facial Depiction. In Biomedical Visualisation, Vol 2. Volume 1138. Edited by Rea PM; 2019: 87–101.[Advances in Experimental Medicine and Biology].
19. Pingale P, Dawre S, Dhapte-Pawar V, Dhas N, Rajput A. Advances in 4D printing: from stimulation to simulation. Drug Deliv Transl Res. 2023;13(1):164–88.
20. Noroozi R, Arif ZU, Taghvaei H, Khalid MY, Sahbafar H, Hadi A, Sadeghianmaryan A, Chen X. 3D and 4D bioprinting technologies: a game changer for the biomedical sector? Ann Biomed Eng. 2023;51(8):1683–712.
21. Osouli-Bostanabad K, Masalehdan T, Kapsa RMI, Quigley A, Lalatsa A, Bruggeman KF, Franks SJ, Williams RJ, Nisbet DR. Traction of 3D and 4D printing in the healthcare industry: from drug delivery and analysis to regenerative medicine. ACS Biomater Sci Eng. 2022;8(7):2764–97.
22. Lui YS, Sow WT, Tan LP, Wu Y, Lai Y, Li H. 4D printing and stimuli-responsive materials in biomedical applications. Acta Biomater. 2019;92:19–36.

23. Li Y, Zhang F, Liu Y, Leng J. 4D printed shape memory polymers and their structures for biomedical applications. Sci China-Technol Sci. 2020;63(4):545–60.
24. Lee J, Kim H-C, Choi J-W, Lee IH. A Review on 3D Printed Smart Devices for 4D Printing. Int J Precis Eng Manuf-Green Technol. 2017;4(3):373–83.
25. Lai J, Wang C, Wang M. 3D printing in biomedical engineering: Processes, materials, and applications. Appl Phys Rev. 2021. https://doi.org/10.1063/5.0024177.
26. Kalogeropoulou M, Diaz-Payno PJ, Mirzaali MJ, van Osch GJVM, Fratila-Apachitei LE, Zadpoor AA. 4D printed shape-shifting biomaterials for tissue engineering and regenerative medicine applications. Biofabrication. 2024;16(2):022002.
27. Chopra V, Fuentes-Velasco V, Nacif-Lopez SR, Melendez-Malpicca J, Mendez-Hernandez AS, Ramos-Mendez-Iris LF, Arroyo-Jimenez DA, Reyes-Segura DG, Gonzalez-Y-Mendoza P, Sanchez-Hernandez KA, et al. Advancements in 3D–4D printing of hydroxyapatite composites for bone tissue engineering. Ceram Int. 2024;50(20):38819–40.
28. Chen X, Han S, Wu W, Wu Z, Yuan Y, Wu J, Liu C. Harnessing 4D printing bioscaffolds for advanced orthopedics. Small. 2022. https://doi.org/10.1002/smll.202106824.
29. Chen A, Su J, Li Y, Zhang H, Shi Y, Yan C, Lu J. 3D/4D printed bio-piezoelectric smart scaffolds for next-generation bone tissue engineering. Int J Extreme Manuf. 2023;5(3):032007.
30. Borse K, Shende P. 3D-to-4D structures: an exploration in biomedical applications. Aaps Pharm. 2023. https://doi.org/10.1208/s12249-023-02626-4.
31. Arif ZU, Khalid MY, Zolfagharian A, Bodaghi M. 4D bioprinting of smart polymers for biomedical applications: recent progress, challenges, and future perspectives. React Funct Polym. 2022;179:105374.
32. Joshi S, Rawat K, Karunakaran C, Rajamohan V, Mathew AT, Koziol K, Thakur VK, Balan ASS. 4D printing of materials for the future: opportunities and challenges. Appl Mater Today. 2020;18:100490.
33. Patdiya J, Kandasubramanian B. Progress in 4D printing of stimuli responsive materials. Polym-Plastics Technol Mater. 2021;60(17):1845–83.
34. Ahmed A, Arya S, Gupta V, Furukawa H, Khosla A. 4D printing: fundamentals, materials, applications and challenges. Polymer. 2021;228:123926.
35. Leist SK, Gao DJ, Chiou R, Zhou J. Investigating the shape memory properties of 4D printed polylactic acid (PLA) and the concept of 4D printing onto nylon fabrics for the creation of smart textiles. Vir Phys Prototyping. 2017;12(4):290–300.
36. Yang CC, Wang BJ, Li DC, Tian XY. Modelling and characterisation for the responsive performance of CF/PLA and CF/PEEK smart materials fabricated by 4D printing. Vir Phys Prototyping. 2017;12(1):69–76.
37. Flieger M, Kantorová M, Prell A, Rezanka T, Votruba J. Biodegradable plastics from renewable sources. Folia Microbiol. 2003;48(1):27–44.
38. Lee YH, Nakamura T, Shimizu Y, Yamamoto Y, Kiyotani T, Tsuda T, Teramachi M, Takimoto Y. Regeneration of serous membrane on gelatin-processed polyglycolic acid (PGA)-human collagen membrane and its efficacy on the prevention of adhesion. J Biomed Mater Res Part A. 2003;64A(1):88–92.
39. Obradovic B, Martin I, Freed LE, Vunjak-Novakovic G: Towards functional cartilage equivalents: Bioreactor cultivation of cell-polymer constructs. In Contemporary Studies in Advanced Materials and Processes: Yucomat Iv. Volume 413. Edited by Uskokovic DP, Battiston GA, Milonjic SK, Rakovic DI; 2003: 251–256.[Materials Science Forum].
40. Constante G, Apsite I, Alkhamis H, Dulle M, Schwarzer M, Caspari A, Synytska A, Salehi S, Ionov L. 4D biofabrication using a combination of 3D printing and melt-electrowriting of shape-morphing polymers. ACS Appl Mater Interfaces. 2021;13(11):12767–76.
41. Invernizzi M, Turri S, Levi M, Suriano R. 4D printed thermally activated self-healing and shape memory polycaprolactone-based polymers. Eur Polymer J. 2018;101:169–76.
42. Agarwal T, Chiesa I, Costantini M, Lopamarda A, Tirelli MC, Borra OP, Varshapally SVS, Kumar YAV, Reddy GK, De Maria C, et al. Chitosan and its derivatives in 3D/4D (bio) printing for tissue engineering and drug delivery applications. Int J Biol Macromol. 2023;246:125669.
43. Edo GI, Yousif E, Al-Mashhadani MH. Chitosan: modification and biodegradability of by-products. Polym Bull. 2024. https://doi.org/10.1007/s00289-024-05510-8.
44. Taghizadeh M, Taghizadeh A, Yazdi MK, Zarrintaj P, Stadler FJ, Ramsey JD, Habibzadeh S, Rad SH, Naderi G, Saeb MR, et al. Chitosan-based inks for 3D printing and bioprinting. Green Chem. 2022;24(1):62–101.
45. George SM, Nayak C, Singh I, Balani K. Multifunctional hydroxyapatite composites for orthopedic applications: a review. ACS Biomater Sci Eng. 2022;8(8):3162–86.
46. Kumar A, Kargozar S, Baino F, Han SS. Additive manufacturing methods for producing hydroxyapatite and hydroxyapatite-based composite scaffolds: a review. Front Mater. 2019. https://doi.org/10.3389/fmats.2019.00313.
47. Zhang SM, Luo QM, Cao RR, Li SP: Molecular modification of hydroxyapatite to introduce interfacial bonding with poly (lactic acid) in biodegradable composites. In Asbm6: Advanced Biomaterials Vi. Volume 288–289. Edited by Zhang X, Tanaka J, Yu Y, Tabata Y; 2005: 227–230.[Key Engineering Materials].
48. Zhang SM, Liu J, Zhou W, Cheng L, Guo XD. Interfacial fabrication and property of hydroxyapatite/polylactide resorbable bone fixation composites. Curr Appl Phys. 2005;5(5):516–8.
49. Hwangbo H, Lee H, Roh EJ, Kim W, Joshi HP, Kwon SY, Choi UY, Han IB, Kim GH. Bone tissue engineering via application of a collagen/hydroxyapatite 4D-printed biomimetic scaffold for spinal fusion. Appl Phys Rev. 2021. https://doi.org/10.1063/5.0035601.
50. Nommeots-Nomm A, Ligorio C, Bodey AJ, Cai B, Jones JR, Lee PD, Poologasundarampillai G. Four-dimensional imaging and quantification of viscous flow sintering within a 3D printed bioactive glass scaffold using synchrotron X-ray tomography. Mater Today Adv. 2019;2:100011.
51. Jiang QS, Zhou LM, Yang Y, Long H, Ge LM, Li DF, Mu CD, Lai WL, Xu ZL, Wang Y. Injectable NGF-loaded double crosslinked collagen/hyaluronic acid hydrogels for irregular bone defect repair via neuro-guided osteogenic process. Chem Eng J. 2024;497:11.
52. Keerthana J, Hewavitharana K, Wijesekara K. Biomaterial composites synthesis and characterization of biocomposite of bovine bone-based hydroxyapatite-poly(lactic acid)-maleic anhydride. J Natl Sci Found. 2024;52(2):271–9.

53. You DQ, Chen GC, Liu C, Ye X, Wang SL, Dong MY, Sun MY, He JX, Yu XW, Ye GC, et al. 4D printing of multi-responsive membrane for accelerated in vivo bone healing via remote regulation of stem cell fate. Adv Funct Mater. 2021. https://doi.org/10.1002/adfm.202103920.
54. Zhou WM, Dong XM, He Y, Zheng W, Leng JS. In-vitro and in-vivo studies of 4D printed shape memory scaffolds with bioactive fillers and coating for enhanced bone tissue regeneration. Smart Mater Struct. 2022;31(10):105002.
55. Du R, Zhao B, Luo K, Wang MX, Yuan Q, Yu LX, Yang KK, Wang YZ. Shape memory polyester scaffold promotes bone defect repair through enhanced osteogenic ability and mechanical stability. ACS Appl Mater Interfaces. 2023;15(36):42930–41.
56. Liu C, Lou YT, Sun ZY, Ma HY, Sun MY, Li SJ, You DQ, Wu JJ, Ying BB, Ding WH, et al. 4D printing of personalized-tunable biomimetic periosteum with anisotropic microstructure for accelerated vascularization and bone healing. Adv Healthcare Mater. 2023. https://doi.org/10.1002/adhm.202202868.
57. Luo K, Wang L, Wang MX, Du R, Tang L, Yang KK, Wang YZ. 4D Printing of Biocompatible Scaffolds via <i>In Situ</i> photo-crosslinking from shape memory copolyesters. ACS Appl Mater Interfaces. 2023;15(37):44373–83.
58. Eryildiz M: Biomimetic design and fabrication of thermally induced radial gradient shape memory scaffolds using fused deposition modeling (FDM) for bone tissue engineering. Proceedings of the Institution of Mechanical Engineers Part L-Journal of Materials-Design and Applications 2024.
59. Kumar M, Sharma V. Shape memory effect of four-dimensional printed polylactic acid-based scaffold with nature-inspired structure. 3D Printing Additive Manuf. 2024;11(1):10–23.
60. Shakibania S, Ghazanfari L, Raeeszadeh-Sarmazdeh M, Khakbiz M. Medical application of biomimetic 4D printing. Drug Dev Ind Pharm. 2021;47(4):521–34.
61. Wan ZQ, Zhang P, Liu YS, Lv LW, Zhou YS. Four-dimensional bioprinting: current developments and applications in bone tissue engineering. Acta Biomater. 2020;101:26–42.
62. Zhao ZY, Fan CJ, Chen F, Sun YT, Xia YJ, Ji AY, Wang DA. Progress in articular cartilage tissue engineering: a review on therapeutic cells and macromolecular scaffolds. Macromol Biosci. 2020. https://doi.org/10.1002/mabi.201900278.
63. Ngadimin KD, Stokes A, Gentile P, Ferreira AM. Biomimetic hydrogels designed for cartilage tissue engineering. Biomaterials Science. 2021;9(12):4246–59.
64. Filipowska J, Tomaszewski KA, Niedzwiedzki L, Walocha J, Niedzwiedzki T. The role of vasculature in bone development, regeneration and proper systemic functioning. Angiogenesis. 2017;20(3):291–302.
65. Zhao W, Zhang FH, Leng JS, Liu YJ. Personalized 4D printing of bioinspired tracheal scaffold concept based on magnetic stimulated shape memory composites. Comp Sci Technol. 2019;184:107866.
66. Wei SA, Ma JX, Xu L, Gu XS, Ma XL. Biodegradable materials for bone defect repair. Mil Med Res. 2020. https://doi.org/10.1186/s40779-020-00280-6.
67. Cui CX, Kim DO, Pack MY, Han B, Han L, Sun Y, Han LH. 4D printing of self-folding and cell-encapsulating 3D microstructures as scaffolds for tissue-engineering applications. Biofabrication. 2020;12(4):045018.
68. Agarwal T, Hann SY, Chiesa I, Cui HT, Celikkin N, Micalizzi S, Barbetta A, Costantini M, Esworthy T, Zhang LG, et al. 4D printing in biomedical applications: emerging trends and technologies. J Mater Chem B. 2021;9(37):7608–32.
69. Shin DG, Kim TH, Kim DE. Review of 4D printing materials and their properties. Int J Precis Eng Manufacturing-Green Technol. 2017;4(3):349–57.
70. Grinberg D, Siddique S, Le MQ, Liang R, Capsal JF, Cottinet PJ. 4D printing based piezoelectric composite for medical applications. J Polym Sci Part B-Polym Phys. 2019;57(2):109–15.
71. Schwartz JJ, Boydston AJ. Multimaterial actinic spatial control 3D and 4D printing. Nat Commun. 2019. https://doi.org/10.1038/s41467-019-08639-7.
72. Wong KC, Kumta SM, Geel NV, Demol J. One-step reconstruction with a 3D-printed, biomechanically evaluated custom implant after complex pelvic tumor resection. Comput Aided Surg. 2015;20(1):14–23.
73. Cheng C-Y, Xie H, Xu Z-y, Li L, Jiang M-N, Tang L, Yang K-K, Wang Y-Z. 4D printing of shape memory aliphatic copolyester via UV-assisted FDM strategy for medical protective devices. Chem Eng J. 2020;396:125242.
74. Langford T, Mohammed A, Essa K, Elshaer A, Hassanin H. 4D printing of origami structures for minimally invasive surgeries using functional scaffold. Appl Sci-Basel. 2021;11(1):332.
75. You D, Chen G, Liu C, Ye X, Wang S, Dong M, Sun M, He J, Yu X, Ye G, et al. 4D printing of multi-responsive membrane for accelerated in vivo bone healing via remote regulation of stem cell fate. Adv Funct Mater. 2021. https://doi.org/10.1002/adfm.202103920.
76. Elshazly TM, Keilig L, Alkabani Y, Ghoneima A, Abuzayda M, Talaat W, Talaat S, Bourauel CP. Potential application of 4D technology in fabrication of orthodontic aligners. Front Mater. 2022. https://doi.org/10.3389/fmats.2021.794536.
77. Vasiliadis AV, Koukoulias N, Katakalos K. From three-dimensional (3D)- to 6D-printing technology in orthopedics: science fiction or scientific reality? J Funct Biomater. 2022;13(3):101.
78. Zhou W, Dong X, He Y, Zheng W, Leng J. In-vitro and in-vivo studies of 4D printed shape memory scaffolds with bioactive fillers and coating for enhanced bone tissue regeneration. Smart Mater Struct. 2022;31(10):105002.
79. Deng Y, Zhang F, Liu Y, Zhang S, Yuan H, Leng J. 4D printed shape memory polyurethane-based composite for bionic cartilage scaffolds. Acs Appl Polym Mater. 2023;5(2):1283–92.
80. Choudhury S, Joshi A, Agrawal A, Nain A, Bagde A, Patel A, Syed ZQ, Asthana S, Chatterjee K. NIR-responsive deployable and self-fitting 4D-printed bone tissue scaffold. ACS Appl Mater Interfaces. 2024;16(37):49135–47.
81. Li Y, You J, Lv H, Wang C, Zhai S, Ren S, Liu X, Zhang Y, Zhou Y. 4D-printed dual-responsive bioscaffolds for treating critical-sized irregular bone defects. Chem Eng J. 2024;489:151205.
82. Liu C, Lou Y, Sun Z, Ma H, Sun M, Li S, You D, Wu J, Ying B, Ding W, et al. 4D printing of personalized-tunable biomimetic periosteum with anisotropic microstructure for accelerated vascularization and bone healing. Adv Healthcare Mater. 2023. https://doi.org/10.1002/adhm.202202868.
83. Barmouz M, Uribe LV, Ai Q, Azarhoushang B. Design and fabrication of a novel 4D-printed customized hand orthosis to treat cerebral palsy. Med Eng Phys. 2024;123:104087.

84. Guo W, Zhou B, Zou Y, Lu X. 4D printed poly(l-lactide)/(FeCl3-TA/MgO) composite scaffolds with near-infrared light-induced shape-memory effect and antibacterial properties. Adv Eng Mater. 2024. https://doi.org/10.1002/adem.202301381.
85. Hao Y, Wu C, Su Y, Curran J, Henstock JR, Tseng F. A 4D printed self-assembling PEGDA microscaffold fabricated by digital light processing for arthroscopic articular cartilage tissue engineering. Prog Additive Manuf. 2024;9(1):3–14.
86. Liang W, Zhou C, Jin S, Fu L, Zhang H, Huang X, Long H, Ming W, Zhao J. An update on the advances in the field of nanostructured drug delivery systems for a variety of orthopedic applications. Drug Deliv. 2023. https://doi.org/10.1080/10717544.2023.2241667.
87. Ma X, Gao Y, Zhao D, Zhang W, Zhao W, Wu M, Cui Y, Li Q, Zhang Z, Ma C. Titanium implants and local drug delivery systems become mutual promoters in orthopedic clinics. Nanomaterials. 2022;12(1):47.
88. Cui M, Hu N, Fang D, Sun H, Pan H, Pan W. Fabrication and evaluation of customized implantable drug delivery system for orthopedic therapy based on 3D printing technologies. Int J Pharm. 2022;618:121679.
89. Phull SS, Yazdi AR, Ghert M, Towler MR. Bone cement as a local chemotherapeutic drug delivery carrier in orthopedic oncology: a review. J Bone Oncol. 2021;26:100345.
90. Finsgar M, Kovac J, Maver U. The development and characterization of bioactive coatings for local drug delivery in orthopedic applications. Prog Org Coatings. 2021. https://doi.org/10.1016/j.porgcoat.2021.106350.
91. Shi L-B, Tang P-F, Zhang W, Zhao Y-P, Zhang L-C, Zhang H. Aceclofenac-hydroxypropyl-β-cyclodextrin complex for prolonged and improved drug delivery for orthopedic applications. J Biomater Tissue Eng. 2017;7(4):327–32.
92. Uboldi M, Gelain A, Buratti G, Gazzaniga A, Melocchi A, Zema L. Development of 4D printed intravesical drug delivery systems: scale-up of film coating. J Drug Deliv Sci Technol. 2023;87:104875.
93. Inverardi N, Scalet G, Melocchi A, Uboldi M, Maroni A, Zema L, Gazzaniga A, Auricchio F, Briatico-Vangosa F, Baldi F, Pandini S. Experimental and computational analysis of a pharmaceutical-grade shape memory polymer applied to the development of gastroretentive drug delivery systems. J Mech Behav Biomed Mater. 2021;124:104814.
94. Baniasadi M, Yarali E, Foyouzat A, Baghani M. Crack self-healing of thermo-responsive shape memory polymers with application to control valves, filtration, and drug delivery capsule. Eur J Mech Solids. 2021;85:104093.
95. Melocchi A, Inverardi N, Uboldi M, Baldi F, Maroni A, Pandini S, Briatico-Vangosa F, Zema L, Gazzaniga A. Retentive device for intravesical drug delivery based on water-induced shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility. Int J Pharm. 2019;559:299–311.
96. Melocchi A, Uboldi M, Inverardi N, Briatico-Vangosa F, Baldi F, Pandini S, Scalet G, Auricchio F, Cerea M, Foppoli A, et al. Expandable drug delivery system for gastric retention based on shape memory polymers: development via 4D printing and extrusion. Int J Pharm. 2019;571:1.
97. Uboldi M, Melocchi A, Moutaharrik S, Cerea M, Gazzaniga A, Zema L. Dataset on a small-scale film-coating process developed for self-expanding 4D printed drug delivery devices. Coatings. 2021;11(10):2.
98. Uboldi M, Pasini C, Pandini S, Baldi F, Briatico-Vangosa F, Inverardi N, Maroni A, Moutaharrik S, Melocchi A, Gazzaniga A, Zema L. Expandable drug delivery systems based on shape memory polymers: impact of film coating on mechanical properties and release and recovery performance. Pharmaceutics. 2022;14(12):3.
99. Uboldi M, Perrotta C, Moscheni C, Zecchini S, Napoli A, Castiglioni C, Gazzaniga A, Melocchi A, Zema L. Insights into the safety and versatility of 4D printed intravesical drug delivery systems. Pharmaceutics. 2023;15(3):93.
100. Che QT, Seo JW, Charoensri K, Nguyen MH, Park HJ, Bae H. 4D-printed microneedles from dual-sensitive chitosan for non-transdermal drug delivery. Int J Biol Macromol. 2024;261:21.
101. Oh YC, Ong JJ, Alfassam H, Diaz-Torres E, Goyanes A, Williams GR, Basit AW. Fabrication of 3D printed mutable drug delivery devices: a comparative study of volumetric and digital light processing printing. Drug Deliv Transl Res. 2024. https://doi.org/10.1007/s13346-024-01697-5.

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