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# 4D Printing in Drug Delivery: Application of Shape-Morphing Materials in Controlled Drug Release

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***Abstract***

*Four-dimensional printing technology has transformed the pharmaceutical landscape, offering unprecedented opportunities for innovation in drug development and delivery. This emerging technology enables the creation of complex geometries and customized structures, facilitating the design of personalized medications tailored to individual patient needs. Personalized dosing and drug release profiles, customized pill shapes and sizes for improved swallowability. Enhanced drug solubility and bioavailability, rapid prototyping and testing of pharmaceutical products. Development of complex drug delivery systems such as implants and microneedles. Improved patient compliance through customized medication regimens, reduced production costs, and increased efficiency. Enhanced drug stability and self-life, potential for localized and targeted drug delivery. This study explores the current state of four-dimensional printing in pharmaceuticals, highlighting its benefits, challenges, and future directions. The integration of four-dimensional printing technology has the potential to revolutionize the pharmaceutical industry, transforming the way drugs are designed, manufactured, and delivered. Development of four-dimensional printing polymeric materials and technology.*

**Keywords:** 4D printing, pharmaceuticals, personalized medicine, drug development, drug delivery, smart materials, shape memory polymer

## INTRODUCTION

Additive manufacturing (AM) technology, often known as four-dimensional (4D) printing, has been available for decades. It allows users to create personalized 4D things using computer software and CAD [1]. This technology has significantly impacted on intelligent manufacturing, as well as several businesses, the public sector, and the government, in recent years. 4D printing, a new and creative technology, has made it possible for us to use AM technology. Materials that can be programed to change digital data in the virtual world into tangible items in the real world to offer creativity and previously unheard-of capabilities [2].

MIT's Tibbits group coined the phrase "4D printing" in 2013, and since then, the associated materials, 3D printers, stimulus mechanisms, and guidelines for creativity. Numerous studies have been conducted on design and applications [3]. According to this theory, materials with different thermal expansion coefficients or swelling ratios could be created using 4D printing technology and then altered based on how they change shape [4]. The ability of a 4D printed static item to change shape is the primary feature of 4D printing.

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Different external stimuli can cause 4D printed things to change shape, causing the printed objects to fold, expand, or shrink as intended [5, 6].

Even after the stimulus has been eliminated, this transient form can persist. Subsequent external stimuli could cause SCM to return to its initial configuration. The shape-based polymeric material system to examine the possibilities of 4D printing, this article will discuss memory material applicable in medical fields [7]. Two types of mechanisms in 4D printing are Thermos and Hydro-mechanics [8].

When a composite polymer is made of hydrophilic, expandable, and non-active rigid components, it is said to be hydro-active. This kind of polymer uses moisture or water as an external trigger to actively alter its form. This kind of morphological modification is typical. Polymers have dried or after the moisture component has been eliminated. Additionally, by using specialized design, the polymers could be designed to maintain their irreversible forms even after the moisture was eliminated [9, 10].

**Research in 4D Printing**

Published research article on 4D printing, they used smart materials to create objects [11]. 4D printing, following the preliminary investigation by Tibbits and his group. Examples of these uses include the development of movable soft robots and developing self-repairing materials, altering their shape, and building structures that can adjust to changing environmental circumstances [12].

**3D Printing vs 4D Printing**

Using a digital CAD file to create a 3D structure is called 3D printing. It is used in the preparation of personalized medicine [13]. The process entails adding materials in layers until the desired shape is achieved. On the other hand, 4D printing is a step forward from 3D printing, and it covers the use of materials that can change their characteristics over time [14].

***4D Printer***

A 4D printer is essentially a 3D printer with the added capability of producing objects that change over time or in response to environmental stimuli – hence the fourth "dimension" being time or transformation.

***Mathematical Modeling 4D Printing***

Mathematical modeling in 4D printing plays a crucial role in predicting, designing, and optimizing the behavior of printed structures that change shape or function over time in response to external stimuli (like heat, moisture, light, etc.).

***Smart Material Used in 4D Printing***

- Shape memory polymers (SMPs) change shape with temperature changes.
- Hydrogels expand or contract in response to water or pH.
- Liquid crystal elastomers (LCEs) respond to heat and light with controlled deformation.
- Magneto-responsive materials move or reshape in response to magnetic fields.
- Electroactive polymers (EAPs) react to electric stimuli to bend or move.

***Stimulus***

Stimulus-responsive 4D printing (or just 4D printing) refers to the use of 3D printing techniques to create objects that change shape or function over time when exposed to an external stimulus. The fourth dimension here is time, and the transformation is triggered by stimuli such as:

***Common Stimuli in 4D Printing***

- *Temperature (thermal stimulus):* Materials expand, contract, or bend with heat (e.g., shape-memory polymers).
- *Moisture or water (hydration stimulus):* Hydrogels swell or shrink in response to water.

 

- *Light (photo-responsive stimulus):* Certain polymers change shape when exposed to specific light wavelengths.
- *pH or chemical exposure:* Materials that react to acidity/basicity and alter structure.
- *Electric or magnetic fields:* Electroactive or magnetoactive materials that deform under electrical/magnetic influence.

## 4D CREATION

Different kinds of SMP might be explored and developed by scientists thanks to the development of AM techniques in the 1980s. Since then, scientists have given SMP a lot of attention and have been working on it constantly [15]. Numerous AM fabrication techniques, including stereolithography, digital light processing, binder jetting, material jetting, selective laser sintering/melting, and fused deposition, enabling composites to be created in three-dimensional structures and intricate designs. Numerous investigations employing 3D printing technology on food, ceramics, thermosets, and thermoplastic composites [15–20]. Over time, the combination of smart materials and 3D printing technologies allowed us to create 4D active things in response to external inputs [21]. Before testing, the printed object's residual stresses and strains might then be examined. The primary distinction between 4D and 3D printing [22]. It is possible to activate functional groups with either a permanent or temporary shape. One fascinating example is origami, which is the craft of creating a gigantic three-dimensional item out of a little piece of flat, two-dimensional paper made of various photocurable substances [23, 24]. Figure 1 presents 4D printing manufacturing.

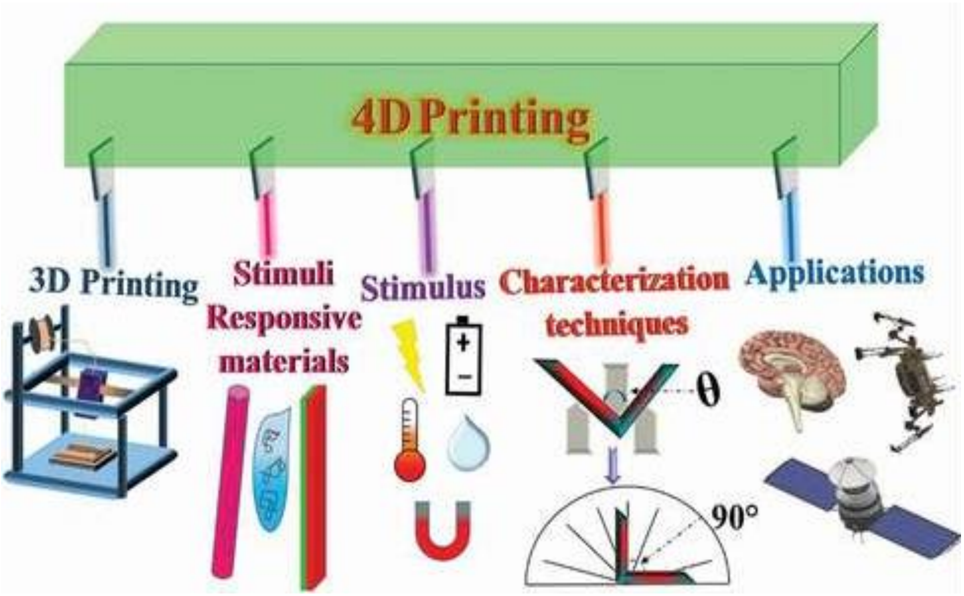


**Figure 1.** 4D printing manufacturing/4D creation.

## THE TECHNOLOGY OF 4D PRINTING

Powder bed fusion, binder jetting, material extrusion, and material extraction are the seven categories into which the American Society for Testing and Materials (ASTM) has divided more than fifty AM technologies. Vat photo-polymerization, sheet lamination, direct energy deposition, and jetting. These categories include the various 3D technologies that use intelligent materials for 4D printing (Figure 1) [25].

### Vat Photo Polymerization

Due to their shared use of photopolymers, DLP and SLA have comparable processes. Since the DLP uses traditional light sources, the primary distinction between the two is the light source that is used. For instance, an arc lamp with a liquid-crystal display panel. Because it is applied to the entire surface in a single pass, it is faster than SLA [26].

 

**Digital Light Processing**

This printing technique has emerged as a very promising way to quickly manufacture intricate 3D and 4D objects by using light as a cross to incorporate micro to nano-scale details, providing a source link. Achieving a high printing resolution, preserving design integrity, and offering a variety of printing materials are just a few of its many benefits [27].

**Projection Micro-Stereo Lithography**

At micro-scale DLP, optical lens systems, often referred to as projection micro-stereo lithography (PMSL), can achieve high resolution. One microfabrication method that adapts 3D printing is called PMSL. Technologically, it allows for the quick photopolymerization of an entire layer at micro-scale resolution with a UV light burst. Controlling the material qualities is made feasible by the mask's ability to adjust the intensity of individual light pixels [28]. Figure 2 illustrates the technology of 4D printing.

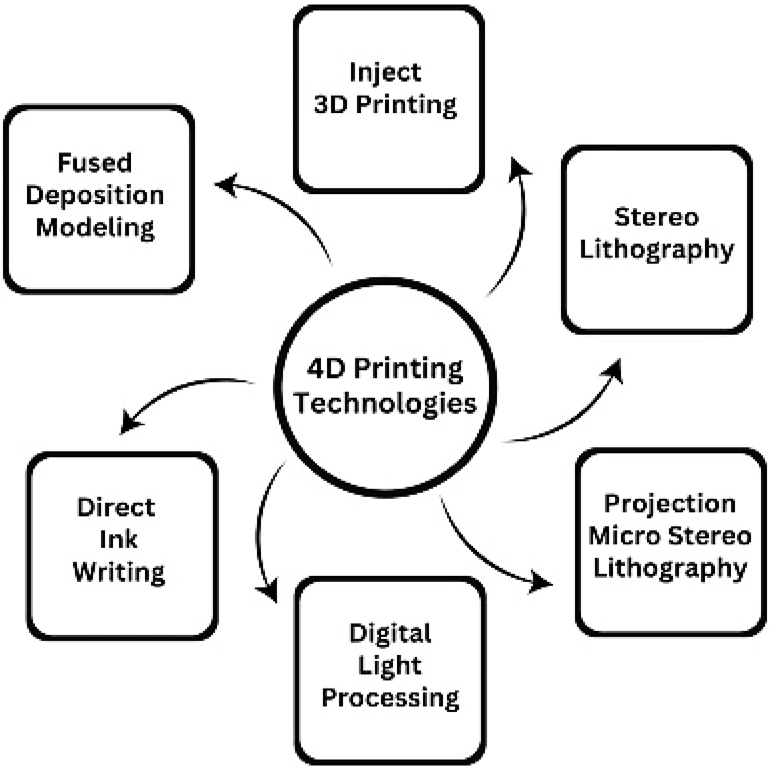


**Figure 2.** The technology of 4D printing.

**DESIGN OF 4D PRINTING MATERIALS**

Description of the first hydrophilic crosslinked polymer over 50 years [29]. Static and bioinert hydrophilic polymer networks have given way to dynamic and bioactive hydrogel systems that may guide certain biological responses thanks to systematic hydrogel design [30]. The biological systems in the human body are always responding and adapting to the changing biological inputs and surroundings. This advanced flexibility is achieved by recognizing and reacting to cues such as changes in light levels, regularly, either biological traces or temperature. Understanding the production and processing of the constituent hydrogel materials – which can expand or contract in response to a range of stimuli – is therefore a vital first step in developing smart hydrogel systems for healthcare. Different stimuli-responsive hydrogels can be divided into six main groups, including heat (temperature), magnetic fields, electrical voltage/current, light, PH of the media, and water [31].

The creation of a range of 4D printed hydrogels is made possible by the hydrogel design's responsiveness and manipulation under various stimuli-specific therapeutic uses. To construct dynamically responsive smart hydrogels that are practical for 4D, this section examines the mechanisms that change hydrogel structures, highlighting features of the development of stimuli-sensitive biomaterials. Hydrogels that respond to temperature and alluring stimuli for controlling transformers a temperature variations, especially in the 36°C–38°C range which represents the human body or environmental conditions. At a crucial temperature, thermo-responsive hydrogels can experience a dramatic sol-gel transition and display temperature-dependent phase behavior [32, 33].

Additionally, the magnetic field has been investigated as a possible external trigger for regulating smart hydrogel characteristics. Because electromagnetic fields may engage distant actuation with quick response time and remain biocompatible even at high field strengths, they are advantageous for stimulation, particularly for in vivo uses. To give hydrogels magnetic responsiveness, exogenous additives, such as ferromagnetic or paramagnetic, are added to the polymeric matrix. This enables quick and significant actuation behaviors in response to magnetic fields [34].

Electrical responsive hydrogels, which draw inspiration from artificial muscle biomimicry, can expand or contract in response to an externally provided electrical field or a solvent-induced one [35, 36]. Electrical responsive hydrogels are essentially based on the mobility of ions in response to an electrical field and the reorganization of the ion concentration profile at the hydrogel-swelling media interface for the controlled release of medication. The state of equilibrium is accomplished by balancing counterions drawn by the surrounding swelling medium with fixed charges on the polymer backbone. Since, there is osmotic pressure since the ion concentration is not evenly distributed inside and outside the gel [37].

## 4D PRINTING PROCESS

Temporal changes between many states (often a transition from a temporary to a permanent state) are what give 4D printed structures their inherent dynamism conformation when exposed to outside stimuli [38]. The design process becomes much more difficult as a result, requiring careful evaluation of three fundamental parameters: The choosing of materials that respond to stimuli, (i) what kinds of external inputs will be used, and (ii) the rational design of the 4D printed object's geometry and/or topology [39].

Moreover, the mechanics of design cannot be underestimated, as it plays a pivotal role in the predictability and controllability of self-morphing behaviors. Devising a suitable geometry is essential for conveying the intrinsic material properties and stimulus responsiveness into the desired mechanical performance. As such, there is a growing emphasis on the necessity to develop complex algorithms and computational tools for the geometrical and topological optimization of 4D printed constructs. The stimulus itself, acting as a trigger for dynamic change, requires careful selection and calibration. Stimuli can range from light, heat, and humidity to more specialized triggers, such as electric or magnetic fields, and even biological molecules such as enzymes. The type of stimulus chosen has direct implications for the application at hand. For instance, in the biomedical context, the use of bio-responsive stimuli is a key to the development of smart drug delivery systems or tissue scaffolds that adapt to the physiological environment. To elucidate, consider the application of 4D printing in drug delivery systems. In such a scenario, the geometric design should facilitate controlled substance release, while material selection should ensure biocompatibility and responsiveness to physiological stimuli (e.g., pH changes in the digestive tract). Furthermore, the external stimulus (e.g., a bio-responsive element) should be carefully aligned with the specific medical requirements, whether they relate to time-release mechanisms or targeted drug delivery. This section, therefore, aims to provide a comprehensive review of the critical elements underpinning the 4D printing process, including an analysis of the most promising stimulus-responsive materials, a classification and evaluation of applicable external stimuli, and a discussion on the advancements in design methodologies for 4D constructs.

## BIOMEDICAL APPLICATION

The development of 3D printing has unquestionably led to advancements in the creation of intricate structures, especially for use in biomedical applications like tissue engineering. The incapacity to replicate the dynamic and changing properties of natural biological tissues is the main cause of diseases. The transport of vital nutrients and oxygen to engineered tissues is significantly hampered by the elusive objective of vascularization. One revolutionary approach to overcoming these constraints is 4D (bio)printing. 4D bioprinting, in contrast to its 3D equivalent, makes it easier to create synthetic tissues with dynamic properties. These structures can enclose stem or vascular cells, which promotes their quick maturation and long-term functional behavior [40].

**Biomedical Devices**

4D printing is indeed emerging as a transformative technology in the field of biomedical engineering, significantly contributing to the evolution of minimally invasive medical devices and procedures. One of the most important applications lies in the domain of cardiovascular engineering. For example, sez expanding stents fabricated through 4D printing technologies show considerable promise for the treatment of vascular diseases, as corroborated by multiple studies [41, 42].

**Drug Delivery System**

The pharmaceutical and biomedical industries place a great deal of importance on controlled drug delivery systems, an area in which 4D printing technology provides unmatched prospects. 4D printing facilitates the temporal and spatial control of drug release in a programmable manner, triggered by specific biological signals or environmental stimuli (e.g., pathological anomalies in vivo) [43].

**Implants and Scaffolds**

The use of 4D printing technology in regenerative medicine and tissue engineering has great potential to overcome the drawbacks of conventional 3D-printed scaffolds and implants. Plants. The capacity of 4D printed structures to dynamically adjust to physiological conditions is one of their main advantages; this allows them to provide a more reliable solution for tissue growth and function [44]. 4D printed structure development of scaffolds and implants tailored for the regeneration of various tissue types, including bone, cartilage, and muscle. Thus, this section discusses different potentials and innovative applications of 4D printed scaffolds and implants, specifically focusing on their roles in regenerating bone, cartilage, muscle, and other tissues.

**Muscle Tissues**

The intricate nature of skeletal muscle tissues, characterized by their unique anisotropic structures known as myofibers, necessitates advanced techniques for successful tissue engineering [45, 46]. In this approach, iron nanoparticles are incorporated into the printable hydrogel. When exposed to a magnetic field, these nanoparticles move unidirectionally, forcing the collagen fibers to orient themselves in parallel arrangements. This magnetic field-assisted alignment is a crucial step toward achieving anisotropic scaffolds that closely mimic native skeletal muscles and tissues.

**Wound Closure**

Rapid and efficient intervention is required for trauma-induced organ damage, with difficulties also extending to fractures, nerve damage, and other bone and soft tissue injuries [47]. The use of 3D/4D printing in the preparation of wound dressings marks a significant stride in medical technology. Customized dressings can be produced to fit wounds of diverse shapes, which contribute to accelerated wound healing [48].

## CONCLUSIONS

4D printing presents a transformative approach to drug development and delivery, enabling personalized medicine, accelerating formulation development, and enhancing drug delivery systems. While regulatory and technical challenges persist, ongoing research and innovation are likely to overcome these barriers. The integration of 4D printing into pharmaceuticals promises to reshape the industry, making treatments more accessible and personalized. Beyond healthcare, there are new areas emerging for 4D printed smart hydrogels, which include the fashion industry, the food industry, and building/architecture. For instance, in the fashion industry, responsive clothes and accessories can be developed for healthcare settings, such as aged care and disability sectors, where multi-stimuli responsive hydrogels can be embedded into clothes and supporting aids to not only monitor health conditions but also to respond in real time to the needs of the user. In the food industry, 4D printed foods are being developed to introduce innovation into food packaging, cooking, and consumption. For the building/architecture industry, 4D printed smart hydrogels can be embedded into buildings and infrastructures to keep the structures warm or cold depending on the external conditions, or to monitor bridges and roads for defects that can be corrected before fatal failures.

4D printing materials, SMPs are regarded as one of the most promising 4D materials, increasing rigidity and a quicker reaction rate. The application of 4D printing in dentistry enables dental parts, medicines, and equipment to be personalized for the benefit of healthcare professionals and patients. Custom 4D implants, devices, and operating equipment decrease surgery and recuperation times and enhance operational and implant success. In the future, this technology will provide great opportunities. 4D printing is used in several biomedical disciplines. The study comprehended the utilization of this cutting-edge technology in vital medical domains, e.g., drug delivery, medical devices, orthopedics, tissue engineering, and dentistry. The article synthesized a thorough review of the recent progressions of 4D printing in the field of medicine, its noteworthy contributions, and its impact across diverse healthcare areas. The study also addressed the limitations associated with 4D printing and provided some future recommendations related to the exploration of new materials and optimization of printing specifications to enhance the versatility and performance of this printing technique.

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