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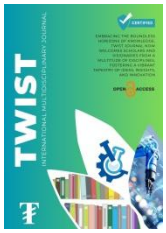

A Review on 4D Printing Technology for Fabrication of Intelligent, Programmable and Functional Structure

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Abstract
One of the most significant developments of the twentieth one was 3D printing, which has made it possible for us to create three-dimensional objects based on digital models. The development of 3D printed objects' structural and functional aspects is the focus of 4D printing. Structures made with 4D printing are dynamic and malleable; they can change over time in terms of form, characteristics, and functionality. Intelligent sensitivity and programmable activity enable 4D materials to react to a variety of stimuli, including light, heat, pH, magnetic fields, and so forth. These stimuli are broadly classified as physical, chemical and biological stimuli. When developing or 4D printing goods a variety of stimuli-responsive materials are used, including shape-memory materials, shape-memory alloys, and shape-memory polymers. Hydrogels are three-dimensional networks of cross-linked polymers that have the ability to absorb and retain large amounts of water while maintaining their unique shape. Compared to traditional hydrogels, smart hydrogels have a number of benefits, including high specificity, excellent controllability, multifunctionality, etc. Hydrogels are the material of choice for four-dimensional bio printing because they can be used to create living structures like tissues, organs, or cells. Various 4D printing applications include 4D hydrogel drug delivery systems, oral formulations, micro needles etc. Oral formulations include shape memory expandable GRDDS. Microneedles are generally used for enhancing tissue adhesion. High responsiveness, high precision, and regulated drug release are essential features of 4D-printed drug constructs. Although 4D bioprinting has opened up a novel direction for the drug delivery industry, regular commercialization and clinical implementation of both still remain a long way off.

Keywords
Shape memory polymers, Bio printing, 4D printing, Hydrogels

INTRODUCTION

The current period is growing increasingly modern due to ongoing developments in several branches of science and technology. The most notable improvement over the currently used 3-Dimensional printing (3DP) and conventional manufacturability is found in the new additive manufacturing process known as 4-Dimensional printing (4DP). Traditional 3DP was unable to produce items with intelligent features, but it could create complicated product architectures in a single phase.(Awad et al., 2018) 3D printing, one of the most innovative technologies of the early 2000s, has empowered the construction of three-dimensional items from a digital model. The extension and time-lapse technique known as 4D printing demonstrates the ability of 3D printing to convert 3D structures into functional structures when exposed to various environmental stimuli, including light, pH, temperature, and microwaves. This technology was invented by scientists from self-Assembly Lab in Massachusetts Institute of Technology (Trenfield et al., 2018).

When four-dimensional (4D) printing first surfaced in 2013, it sparked interest in several scientific domains, such as biological research and smart materials. The use of 4D printing is already widespread. Time serves as the fourth dimension in 4D printing, allowing for the production of objects that independently change their morphology in reaction to various environmental factors. The 4D printing method is based on the principles of 3D printing and integrates an extra dimension in along with the x, y, and z axes, namely time. Products can evolve over time and frequently do so in reaction to environmental factors.(Momeni et al., 2017) Tamay and colleagues recently reviewed a number of factors related to 4D printing, including the variety of raw material, the catalyst applied to three-dimensional objects for modification, the process for 3D to 4D conversion, the ability to transform materials, and hypothetical and numerical software—which can result in shape shifting. The capacity of 4D printing to create customized, scalable, and intelligent materials may be advantageous to the medical sector. The technique may be useful in managing the cell viability of the construct after it has been transplanted into the human body and subjected to changes in body temperature. In the biomedical domain, it is sometimes denoted as 4D bioprinting.

Advantages of 4D printing

- Positive market trends and effective materials and processes are advantages.
- It gives 3D printing materials intelligent functionality, such as sense and actuation capabilities.
- Disruptive platforms can be used to create new goods and technologies with broad applications across various industry sectors.
- It is viable to use 4D printing to create objects with self-triggering and recognizing capabilities.
- Assembly duration is short after manufacturing.
- The flaws in the products produced are reduced.
- High sensitivity and productivity.
- It is made of smart material and can be printed in multiple colors and different materials (Sydney Gladman et al., 2016).

Disadvantages of 4D printing

- Its novelty and need for expensive and scarce materials and equipment are two of its main drawbacks.
- A highly skilled and experienced workforce is needed to operate 4D printers. Cross scale imaging is necessary; hence a high-resolution imaging platform is needed.
- Compared to 5D printing, it has a comparatively low modulus.
- With regard to environmental temperature, they are less stable.
- When compared to 5D printing, 4D printing components are weaker. across several cycles, a decline in change capacity. The stimulation uses energy, which results in a weak actuation.
- Smart material loading in the printer head of 4D printing equipment is challenging (Ge et al., 2016).

4D – PRINTING

The cutting-edge notion of 4D printing technology will have a remarkable impact on the contemporary manufacturing sectors. The structural and functional development of 3D printed things is the aim of 4D printing. With the use of certain 4D printing technologies, structures that may alter in form, function, and qualities over time can be created instead of ones that are set in stone. Self-assembling, self-repairing, and multitasking are just a few of the incredible qualities of things made with 4D printing (Momeni et al., 2017). Because of printer independence and time constraints, the method became more sensible. 4D printed materials are programmable and have an intellectual sensitivity that allows them to respond to various stimuli, including temperature, pH, light, magnetic radiation, etc. Three elements form the basis of this new technology: intelligent machines, intelligent materials, and the geometric "software" (Norman et al., 2017).

HISTORY OF 4-D PRINTING

A research team at MIT came up with the original notion for printing objects in four dimensions. Professor of Architecture and Research at Massachusetts Institute of Technology, SKYLAR TIBBITS (MIT). MIT's self- assembling lab was established in February 2013 with a focus on the development of programmable materials and 4D printing (Tibbits, 2014).

In 1980 development of 3D printing processes and 1990 Main 3D printers and CAD tool was popular. In the year 2000 a functioning kidney was produced via 3D printing. Spectrum Z510, the first high-definition colour 3D printing device on the market, was introduced by Z Corp in 2005. First 3D-printed prosthetic limb produced in 2008.In 2010 applications and innovation was done (Firth et al. 2018). The first 3D printed prototype vehicle wasurbee, which debuted in 2010. The first artificial jaw was produced and placed in 2012. In2013, 4D printing concepts, and MIT 4D printing was pass (Kopeček & Yang, 2012).

Materials for illustrating the Design Factors for Four-Dimensional Printing

Materials: The constitution of the substances to be used in the production of the hydrogel ink is the first significant issue that needs to be acknowledged for 3D printing. The bio-ink contains the hydrogel-forming agents (polymers, crosslinkers, monomers, and rheology modifiers) as well as other biomolecules that promote the proliferation of cells in the 3D printed bio-construct. The hydrogel composition may contain one or more monomers that are synthetic, biobased, or bio imitated. Cell-containing biomaterial inks are known as bio-inksa variety of factors including the intricate biology of the living object created by 3D printing, numerous cells may be employed in the ink (Boley et al., 2019).

Actuators must be added to the inks in 4D printing in order for the 3D printed living objects to react intelligently. Actuators can be used to introduce properties like magnetic, electrical, and oxidative ones during printing by adding materials that accomplish this, or they can be used to introduce properties like light, pH, temperature, humidity, etc. on gels that are sufficiently sensitive after printing. This additional material needs to be considered during 4D printing because its presence may have a substantial impact on the hydrogel ink's rheological and processing properties, which in turn may have an impact on printability.

Shape: Shape is the second consideration in 3D printed entities. Accurately replicating the microscopic structure of the organ or biological construct being printed is a crucial need for 3D printing living constructs. When using 4D printing, great care must be given to ensure that the 3D printed structure's shape is taken into account prior to as well as after the actuator application. The 3D printed construct is dramatically altered once the actuator (stimuli) is applied. The structure should have enough area in the printed pattern to either expand or shrink without impairing the hydrogel's strength or other physical qualities. In order to verify the structural integrity of the shape and the impact of stimuli on it, the necessary simulations must be run before the print. The kind of alteration the stimuli cause—permanent or temporary—is another crucial factor to take into account (Bom et al., 2022).

Printing Technology: The printing process selection is a crucial consideration as it impacts the printer's resolution and the substances that can be utilised. Extrusion-based printing, digital light processing, laser-guided direct writing, two-photon photopolymerization, and stereolithography are examples of common solutions. The printing technology employed can determine the printing resolution, which can vary from hundreds of nanometers to hundreds of microns. The resolution of the printing process should match the smallest detail that needs to be tenaciously reproduced in the living tissues.

As was already indicated, choosing a printing method is important, especially when using 4D printing. It is frequently essential to create material gradients in order to create stimulus response hydrogels. The gradients in the material's characteristics or structural elements would aid in regulating the printed construct's shape-changing behavior. The option of having numerous print heads that can produce gradients in material properties must therefore be taken into consideration when choosing an acceptable print process.

Interlaying pattern: It depends on the situation whether the spatial structure's gradients are 2D or 3D. It is important to carefully evaluate the design and size of the interlaying pattern since the printed structure's spacing can vary based on the nature of external stimuli. The distance between the interlaying patterns must be modified when creating the digital file for 3D printing in order to account change in the overall dimensions of the printed structures in response to outside stimuli.

Post-processing: The strengthening and physical qualities of printed constructs must be improved through post-processing. Additional curing, heating, and drying steps may be used in the post-processingAdditional nanostructures can be added to the current print structure through plasma refining and other nano-smoothening techniques (Groll et al., 2018).

In this section, we address the design concerns for 3D printing and the idea of incorporating time-dependent smart, 4D printing is essentially an extension of 3D printing in numerous ways (J. M. Lee & Yeong, 2016).

4D PRINTING – SHAPE MEMORY POLYMERS (SMPS)

Due to dynamic processes that are stimulated and exhibit properties akin to shape changes with respect to time in 4D printed materials, shape memory polymers are gaining more interest. One of such examples in shown in Fig. 1, where 4D printing is used in modification of trachea.

Heat-activated SMPs, which exhibit a wide variety of adjustable mechanical, thermal, and optical properties, are the shape memory polymers with the greatest number of applications. A transition temperature (T_{trans}), usually the melting point (T_m) is utilized to regulate the shifting of molecular segments that stabilize the short time shape in thermally initiated shape memory polymers. Chemical or physical crosslinks are typically used to establish the permanent shape. Upon heating the SMPs above their T_{trans}, the moving molecular segments become "soft," which permits the application of a deformation to establish the temporary shape; conversely, upon cooling below the Ttrans, the molecular switching segments "freeze," rendering the previously created temporary shape immobile (Campbell et al., 2014).

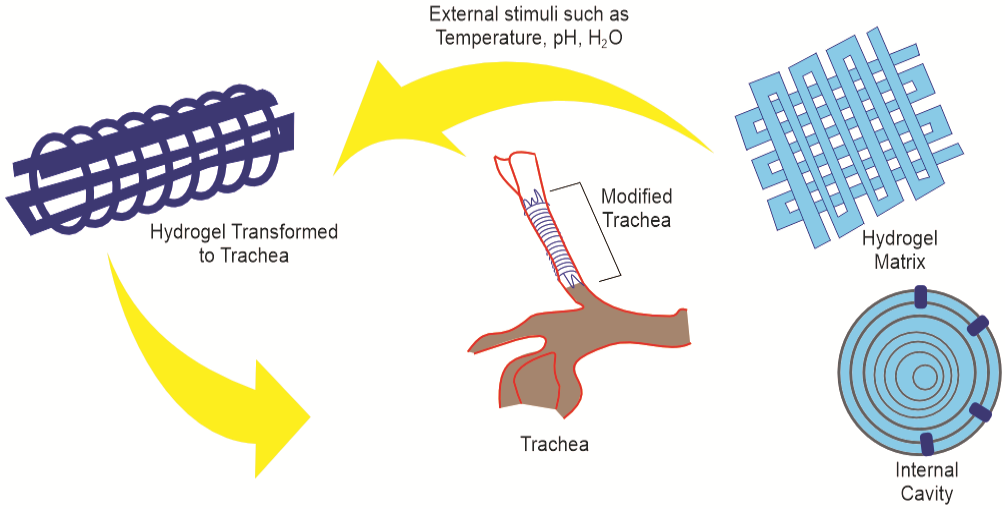

Fig. 1 4D printing used in modification of Trachea

A wide range of other materials with a variety of shape fixation and shape recovery methods have been documented along with heat-initiated SMPs. Indirect heating is one of the actuation methods. For instance, temperature changes brought on by near-infrared light or electronic triggers help the form recovery process.

In contrast to form memory alloys, shape memory polymers are advantageous as they have a large degree of compositional plasticity in stimulus response that can be readily adjusted by production and crosslinking degree. In 1984, research into polynorbornene-based polymers' shape memory property was initially conducted. In the future, research into the synthesis of shape memory polymers with caprolactones, acrylates, and acrylamide was conducted. Furthermore, extremely flexible formulations of polyurethane polymers with shape memory have been created, leading to a large range of transition temperatures and improved refining capabilities (Manchun et al., 2012).

In essence, shape memory polymers are matrix of polymeric molecules that contain both net points and chain segments. The chain segments are interconnected by the net points, which also give the material stability and control over its permanent shape. The production of net points in shape memory polymers can be accomplished by crosslinking covalent bonds and intermolecular interactions. These are capable of deforming when exposed to an external stress during the shape programming process. More reversible net points, or reconfigurable elements, are added to stabilise the temporary shape. These prevent recoiling and limit the mobility of the polymeric chain divisions. (2014) Yasin and associates. As a result, when the pressure that was exerted is released, a transient shape may be retained. The material maintains its temporary shape until it is exposed to the right external stimulus that breaks down its internal structural barriers and starts the process of recovering its original shape. They have a number of benefits over form memory alloys, including better biocompatibility and shape recovery, higher elongation, and reduced density. In order to create composites with advantageous qualities, these polymers can also be added to a variety of additives, including carbon fibers, nanotubes, and magnetic particles (Senatov et al., 2016).

Types of shape memory effects

The ability of materials to remember pre-determined shape even after it has undergone several deformations is known as shape memory effect. This phase transformation is mainly affected by temperature (Otsuka, K., & Wayman, 1999).

1. One –way SME

The shape memory effect is limited to heating in this SME. The SMP doesn't change shape after it cools down from its heated state. A SMP is capable of being stretched into new shapes when it is cold (below A), and it will remain in that shape till the temperature is increased over the transition temperature. The configuration returns to its initial form when heated. The metal will hold its heated form until it deforms once more when it cools. Keep in mind that shape recovery occurs only when heating.

2. Two – way SME

While Two way SME is not a fundamental quality of SMP, it can be demonstrated through training techniques, which are particular thermo-mechanical treatments.

TWSME stands for thermocycling-sensitive spontaneous metamorphism. Put another way, this characteristic allowed SMP to undergo spontaneous form changes during both heating and chilling. As the material masters the behaviour, it may be used to reversibly change its shape between two distinct ones without the application of strain or stress by simply adjusting the temperature across

STIMULI

Based on one or more stimuli, a 4D-printed structure can change its attributes, functionality, or shape. However, a mechanism for interaction must be found so that the printed smart structure can react appropriately to stimuli. It is possible to categorize the mechanisms (Campbell et al., 2014).

Stimulus responsive materials for 4D printing

Materials employed in production of 3D printing can be broken down into different categories, including metal, glass, plastic, and food However, most of materials used for 3D printing cannot be employed in 4D printing as they do not react to stimuli. Given this, choosing the appropriate materials for 4D printing is essential. Better usability than that of 3D printed materials is required for 4D printing technology. In reaction to particular stimuli, smart materials—also referred to as stimulus-responsive materials—can change in nature, properties, or other aspects. Thus, medication delivery, tissue regeneration, medical devices, diagnostics, etc. can all be linked to the properties of smart materials utilized in medicine. A thorough understanding of external stimuli of biological or physical origin, can influence the properties of these smart materials is crucial for the successful 4D printing of materials. Various types of stimuli used in 4D printing are depicted in Fig. 2. The necessary stimulus types have a lot of promise for use in bioengineering applications. All of these stimuli are taken into account in the actual world and frequently occur in situations where they can cause diverse changes in smart materials.(Wang et al., 2016) Because each stimulus is suitable for a certain application and substance, it is important to match the stimulus type chosen to the intended usage. Additionally, the smart materials are chosen in accordance with the applied stimuli. A 3D printer's beginning point for items with shifting shapes receives the same stimulus by applying the stimulus for the start transformation (Khoo et al., 2015).

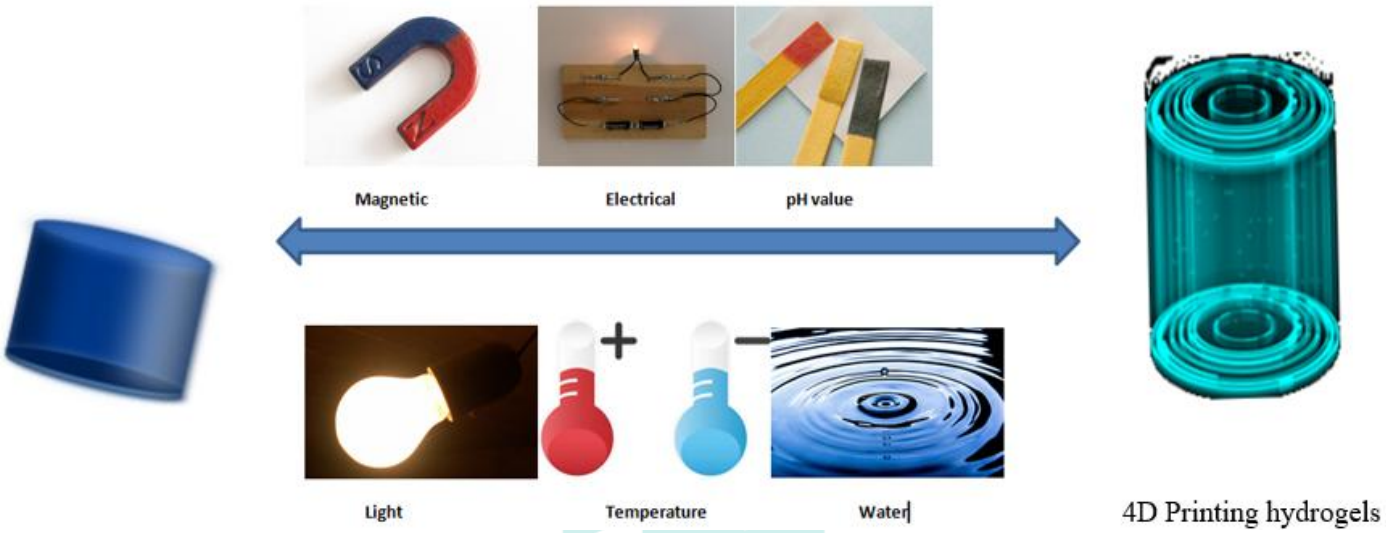

Fig. 2 Types of Stimuli

HYDROGELS

Hydrogels are cross-linked polymer network structures that are three-dimensional (3D) and can store a lot of water while maintaining their distinctive shape to from a 4D printing hydrogels. They have recently received a lot of interest due to their ability to change their, characteristics, and functions in response to outside stimuli. In comparison to traditional hydrogels, smart hydrogels have a number of benefits, including high specificity, good controllability, multifunctionality, tune ability, great spatial and temporal resolution, and remote modulation. Smart hydrogels have been thoroughly investigated over the past 20 years for use in medication delivery, tissue engineering, bio sensing, agriculture, and the healthcare industry (Ullah et al., 2015).

The majority of materials that are utilized in 3D printing cannot be used in 4D printing since they are not stimuli-responsive. In light of this, selecting the right resources for 4D printing is crucial. 4D printing technology needs to be more user-friendly than 3D printed materials. Smart materials, also called stimulus-responsive materials, can alter in composition, characteristics, or other ways in response to certain stimuli. Consequently, drug administration, tissue repair, equipment for medicine, diagnostics, etc. (CAD).

The ability to create patient-specific scaffolds and constructs with unique characteristics has been made possible by advancements in 3D printing technology over the past few decades. For usage in regenerative medicine and drug delivery applications, it is a very efficient method for creating 3D hydrogels with exact govern their size, shape, and morphology. Modification of skull as represented in the Fig. 3 is one such example. The majority of hydrogels and 3D printed biomaterials used in healthcare today are static; they cannot respond to biological stimuli or changes in the internal environment of the body. Future healthcare product design now has new avenues to explore because to developments in dynamic materials, which may respond over time to environmental stimuli.

Despite a recent surge in research on traditional 3D printed hydrogels, the advancement of 4D printed hydrogels continues to remain in its early stages. With the use of 4D printing, the most cutting-edge hydrogel systems are presented in this review along with their potential for on-demand medical delivery (Boley et al., 2019).

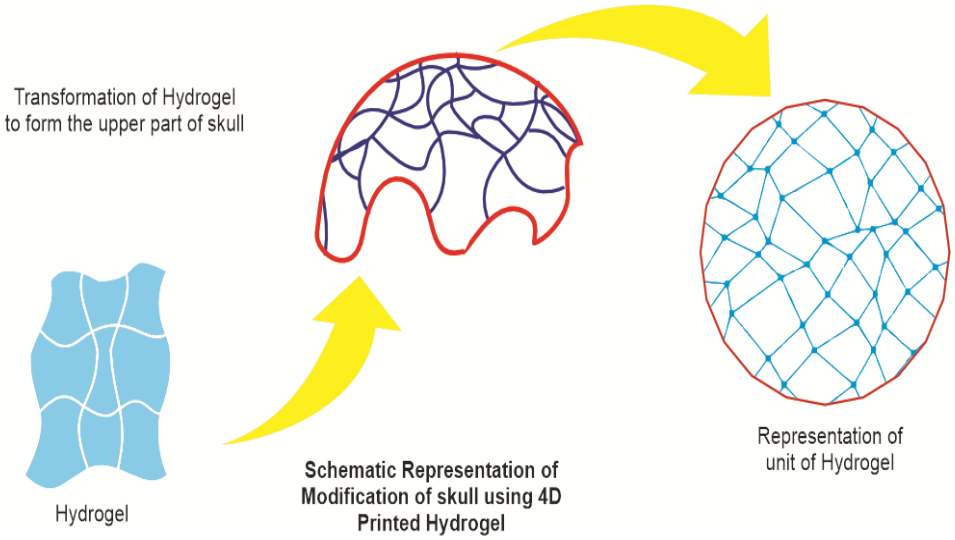

Fig. 3 Schematic representation of modification of skull using 4D printed hydrogel

Types of hydrogels

1. Thermo-Responsive Hydrogels

Thermoresponsive hydrogels have the ability to display temperature-dependent phase behaviour and undergo a sharp sol-gel transition at a crucial temperature. Lesser critical solution temperature (LCST) hydrogels and upper critical solution temperature (UCST) hydrogels, which determine the upper bound of a temperature range where partial mixing takes place, are two distinct types of thermos-responsive hydrogels. Above UCST, the hydrogel systems are bloated. Because of its Materials with large volume changes at relatively low critical temperatures—roughly 32—or by mixing with additional polymers include poly [di (ethylene glycol) ethyl ether acrylate], poly (N-isopropyl acrylamide) (pNIPAM), as well as its derivatives, predominate in the literature on LCST hydrogels (PDEGA). UCST hydrogels, on the other hand, expand in reaction to temperature increases. More design options for the next generation of smart hydrogels are made possible by this beneficial heat reactivity. Interpenetrating networks of polyacrylamide (pAAm) and polyacrylic acid (pAAc) are the most often used UCST hydrogels (Schild, 1992).

Furthermore, current studies have shown that customizable LCST and UCST transformations can be included into physiological fluid-based smart biomaterials, including resilin, elastin-mimetic proteins, highly elastic proteins, and resilin-mimetic proteins. (Kim and others, 2015) Considerable research emphasis has also been devoted to improving thermo-responsive hydrogels' biocompatibility and biodegradability. Increased biodegradability can be attained by adding biodegradable monomers to their polymeric backbone, such as benzo methylene dioxepane or methacrylate polylactide, or by using hydrolytically and enzymatically labile linkages. A smart hydrogel that is both heat-responsive and biodegradable can be created by functionalizing natural polymers including chitosan, cellulose, and gelatin containing poly(L-alanine-co-L-phenylalanine), poly (ethylene glycol), and glycerol phosphate. This material may be utilised in 4D printed drug delivery devices (Andersson, 1998).

2. Magnetic Responsive Hydrogels

Research has been done on magnetic fields as a potential external trigger for regulating smart hydrogel characteristics. Electromagnetic stimulation is an effective stimulus, especially for in vivo applications, because it can immediately engaged remote movement and is biocompatible even at high field strengths. Hydrogels are rendered magnetically sensitive by the addition of exogenous materials, such as ferromagnetic or paramagnetic, to their polymeric matrix. As a result, actuating behaviours in responses to magnetic fields can be swift and powerful. Magnetically-sensitive smart hydrogels can be created by combining gelatin, pNIPAM, pAAm, and magnetic additives such as metal oxides (such as ferrous ferric oxide), metal alloys (such as iron and neodymium alloy), and functionalized magnetic nanoparticles (Shankar et al., 2017).

Moreover, covalent and coordination bonds were used to construct more intricate magnetically sensitive hydrogels with greater interaction between the magnetic particles and the polymer network. When these hydrogel systems are coupled, gelation frequently occurs naturally without the requirement for extra cross linkers during synthesis. The two main ways that magnetic responsive in hydrogels can be used to induce controlled drug release are by alternating between turning on and off the magnetic field and reorienting the magnetic field to align either parallel or perpendicular to the direction of drug diffusion. Presently being studied *in-vivo* in animal models are a number of magnetic responsive smart hydrogels that could be used in clinical medication administration (Ding et al., 2020).

3. Electrical Responsive Hydrogels

Electrically sensitive hydrogels, modelled after artificial muscle biomimicry, have the ability to expand or compress in reaction to an externally applied or solvent-generated electrical fieldBecause it is rapid, accurate, and responsive, an electrical field from the outside can be employed as a stimulus with special benefits for administering medications. The

reorganisation of the ion concentration gradient across the hydrogel-swelling media interaction and the movement of ions when exposed to an electrical field are the main ideas behind electrically sensitive hydrogels for the release of drugs control. Equilibrium is reached when the counter ions attracted to the fixed charges on the polymer's backbone by the surrounding swelling media are balanced (Kawata et al., 2001).

Ionisable groups are usually found along the side chains or polymeric backbone of electrically sensitive hydrogels, which are polyelectrolytes. Osmotic pressure, which results in swelling or DE swelling, is created when the ion concentration isn't evenly distributed both within and without the gel. Numerous artificial polyelectrolytes and related copolymers, Electrically sensitive hydrogels have been created using a variety of materials, such as poly (vinyl alcohol), poly (sodium maleate-co-sodium acrylate), PVA/pAAc, pAAc/poly(N-vinylpyrrolidone), and sulfonated polystyrene (s-PS). Electrophysiological response of proteins, polysaccharides, and polypeptides is a characteristic of natural polyelectrolytes.

Hydrogels that are hybrid and electrically sensitive can be made by combining them with synthetic polymers. For example, fibrin protein can be combined with poly(acrylic acid), chitosan with poly(N, N-dimethyl acrylamide), as well as alginate with poly(methacrylic acid) to develop 4D printed drug delivery systems (Sun & Mak, 2001).

4. Photo-Responsive Hydrogels

For the regulated distribution of therapeutic drugs, it is especially useful to remotely induce the swelling and shrinking of 4D printed hydrogels. Reversible crosslinking and photo thermal excitation are the two main processes of photo-responsive hydrogels. Both approaches can be accomplished through incorporating photoactive compounds into the hydrogel matrix. Provided it concerns reversible crosslinking, hydrogel matrices can photo-cleave or photo-isomerize under light, resulting in reversible contraction, when photoactive moieties such as azobenzene or o-nitro benzyl groups are present -the lengthening of polymer chains (Kaehr & Shear, 2008).

Using photo thermal nanomaterials, which swiftly transform light exposure into heat dissipation, to control the varying dehydration-hydration processes present in photographic-responsive hydrogels is a second way to achieve light-induced deformation. Many nanomaterials, including inorganic nanoparticles like gold and neodymium oxide, black phosphorus, and carbon-based polymers, have been incorporated into photo-responsive hydrogels. The photoresponsiveness of pNIPAM-AAc hydrogels has been demonstrated by researchers through the addition of gold Nano rods. Additionally, smart hydrogels consisting of agarose and pNIPAM, which contain single-walled Nano carbons (SWNTs) and single-walled Nano horns (SWNHs), have been reported by others to display distinct phase transitions in response to near-infrared radiation. Such advanced photo-responsive technologies hold great potential for drug delivery systems manufactured via 4D printing.

5. pH Responsive Hydrogels

Together with physical stressors, physiological circumstances (such as the blood's slightly alkaline state or the stomach's naturally low pH) have also been used to start the swelling-controlled release of medications from hydrogel carriers. Systems that can adjust to varying pH conditions are useful for healthcare applications since disease-related pH alterations occur in diverse areas of the human body.

One can adjust a hydrogel network's pH sensitivity by changing its internal pendant functional groups' ionic character and hydrophilicity. Categorised into two primary groups, pH-responsive hydrogels are anionic and cationic. Anionic hydrogels' pendant groups ionise at pH values greater than their acid disintegrating constant (pKa) and swell at pH levels that are higher, which are usually basic. Even at pH levels below their pKa, the physical interactions between the polymer chains cause the polymer networks to stay folded in low-pH settings (Qian et al., 2019).

Conversely, because the pH is higher, cationic hydrogels constrict and expand below pKa. Copolymers with cross-linked carboxyl group-containing polymer networks, such as those made of polyacrylic acid, polymethacrylic acid, and polycarboxymethyl agarose, are frequently used to create anionic hydrogels. Catalytic hydrogels frequently contain monomers with amine and amide groups, such as AAM, 2-(diethylamino)ethyl methacrylate (DEAEMA), and dimethylaminoethyl methacrylate (DMAEMA), along with their copolymers. Because emerging hydrogels are composed of proteins that resemble resilin, silk, and soy protein along with biopolymers like alginate, gelatine, chitosan, and albumin, they may be more biodegradable and pH sensitive than synthetic alternatives (SCHMALJOHANN, 2006).

6. Water Responsive Hydrogels

Cross-linked, to be three-dimensional interconnected macromolecular networks with a very high liquid swelling capacity are known as super absorbent polymers.They are also referred to as water sensitive hydrogels. These hydrogels can effectively contain and release therapeutic compounds in biological contexts. Ionic monomers are frequently used to make water-responsive hydrogels, and they are only weakly cross-linked. They thus display a remarkable ability for water absorption.

Nowadays, most synthetic or petrochemical water-responsive hydrogels are composed of acrylic monomers, which include acrylamide (AAm), acrylic acid (AAc), and its copolymers. In recent years, there has been a clear shift away from synthetic options that have weak biocompatibility and degradability towards "greener" options when it comes to water responsive hydrogels. Thus, novel bio-based water-responsive hydrogels are being created using renewable raw materials like cellulose, soy protein, starch, natural gums, and chitin, as well as their hybrids and composites. This offers a flexible and efficient path towards 4D printed hydrogels for medication delivery applications (Bashari et al., 2018).

Smart Hydrogel Drug Delivery Development

Since the first cross-linked hydrophilic polymer developed more than 50 years ago, systemic hydrogel design has progressed to fixed, bio-inert hydrophilic polymer chains to changing, bioactive hydrogel systems using the ability to control a particular biological processes like cellular growth while wound healing and streaming drug delivery. The biological systems of the human body constantly adjust to changing external surroundings and biological signals. By recognizing and responding to cues like as variations in light, daily temperatures, or metabolic indicators, this sophisticated adaptability is attained. In order to design smarter hydrogel systems for healthcare, it is important to first understand the manufacture and processing of their constituent hydrogel substances, that can swell or contract in accordance with a range of stimuli. The responsiveness and manipulation of hydrogel design to these stimuli enables the fabrication of diverse 4D printed hydrogels for particular therapeutic objectives. This section highlights aspects of the creation of stimuli-responsive biomaterials and looks at techniques for changing hydrogel structures to provide dynamic responses.

4D BIO PRINTING

4D printing is a significant new technology in the biomedical industry because it enables the creation of devices with self-assembly and self-treatment qualities. Hydrogels are used to produce a bio-printed framework without scaffold and are the preferred material for 4D bio printing. With the use of 4D printing technology, cell-based structures can be printed that resemble nature without the need for a scaffold, mould, or liquid delivery medium. Bioprinting is the process of using 3D/4D printing to create living structures, such as tissues, organs, or cells (Ashammakhi et al., 2018).

According to the definition provided by Chua et al., bio-printing is defined as "The process of constructing biologically relevant elements, such as molecules, cells, tissues, and biodegradable biomaterials, according to a predetermined pattern in order to carry out one or more biological tasks" (A. Y. Lee et al., 2017).

Ion responsive smart hydrogels have already been used by researchers to create tissues that move like muscles. Future success in treating vascular disease appears to be attained through the use of 4D printing in tissue engineering. With this technology, artificial vascularization may be accomplished. For instance, scientists have printed a cylinder-shaped structure layer by layer by embedding various types of cells in a hydrogel matrix. This structure is cylindrical and has a blood vessel-like appearance. These cells can mature and form an essential vascular structure when the maturation factors are activated.(Devillard et al., 2018) A bone graft, for example, can be made using 4D printing to create artificial hard tissues. Investigators created a bone graft using with a grid pattern and covered it with MSCs made from human nasal inferior turbinate tissue to help with graft mineralization. (Pati and associates, 2015) Following a brief period of culture, the printed bone graft displayed maturation following printing (Pati et al., 2015). Studies conducted in vivo and in vitro demonstrated improvements in the conductive and inductive properties of the graft. But compared to natural bones, the synthetic graft's mechanical strength was lower. As seen in Fig. 4, this creation thus needs more improvements for a real-life application. Mini tissues can be created via 4D bioprinting, and over time, they will integrate and grow into larger tissues. This technology might advance soon to the point where printing intricate structures like physiological organs and mature tissue would be feasible (Norotte et al., 2009).

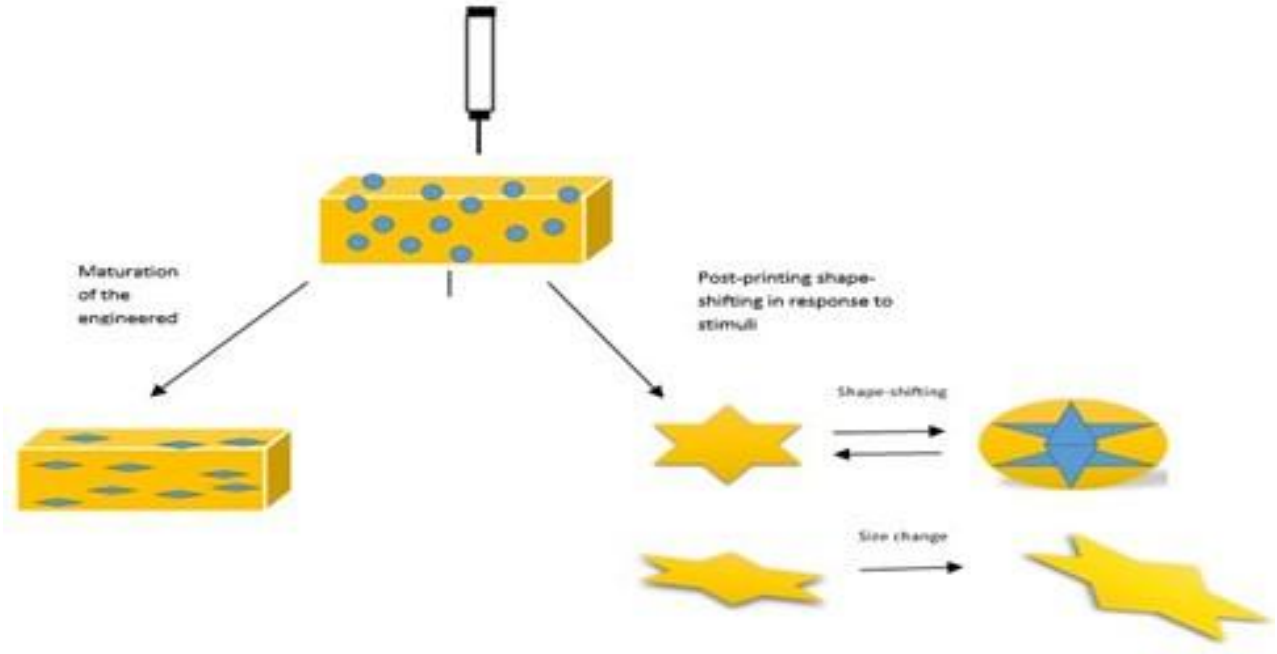

Fig. 4 Schematic representation of 4D- bioprinting

4D bio-printing technology has three steps as shown in Fig. 5**.** For bio-printing to work, a bio-ink is required. The structural characteristics of printed organs or tissues are determined by these bio-inks. Biomaterials including fibrin, collagen, gelatine, silk, alginate, etc. have been used to create bio-inks. It can also be combined with various materials to

create a single, multiple, or mixed use. The physicochemical properties of the printer's bio-ink must include physicochemical properties. Furthermore, stem cells such as embryonic and human bone marrow stem cells could be employed as bio-ink. Because these cells have the ability to repair themselves, they can be used in regenerative medicine. Additionally, biomaterials and nanomaterials are combined to create eorgans and tissues (Hong et al., 2013).

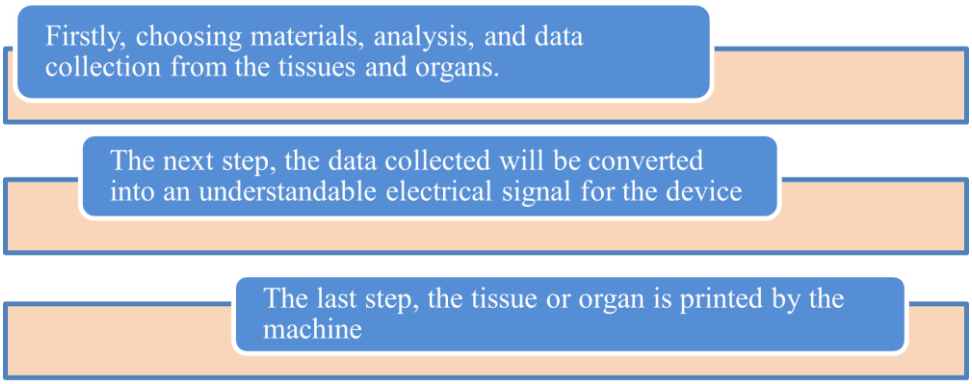

Fig. 5 Steps involved in 4D printing

Various methods can be used in bio printing

1. Extrusion printing
2. Stereo-lithography
3. Inkjet printing
4. Laser assisted
5. DLP-based printing dynamic optical projection Stereo lithography (DOPsL)

Extrusion is one of the most commonly used method of bioprinting. The complex and multicellular tissues are typically rebuilt using DLP and injection techniques. Extrusion printing is the most popular of these techniques due to its ink compatibility, high throughput, and economical nature. Notwithstanding its benefits, extrusion printing has certain drawbacks, including the need for constant and careful nozzle adjustment and the possibility of ink disruption during the printing process.

While there are benefits and uses for 3D bioprinting, a major drawback of this method is that it only takes into account the printed structure's initial state and presumes it to be lifeless. For instance, dynamic structures allow living tissues to regenerate or repair themselves after damage, but dynamic structures cannot be created by 3D bioprinting. In contrast to 3D bioprinting, Smart biomaterials and cell pulling forces are used in 4D bioprinting to produce vibrant, dynamic structures. The printed bio-architects may alter their functionalities when influenced by stimuli (Zhu et al., 2019).

Additionally, the structures created using this method have a higher resolution when contrasting 4D bio-printing with alternative cell deposition techniques. We are able to produce organs that resemble natural tissues by utilising the capabilities and methods of 3D printers in conjunction with intelligent materials. The primary distinction between 4D bioprinting and 3D bioprinting, despite their similarities, is that the structures printed through 4D bioprinting are capable of exhibiting physical or chemical morphological changes in response to specific stimuli. Consequently, 4D printing has a good chance of being applied in the fields of tissue engineering, transplantation of organs, bio-robotics, and biosensors thanks to this feature. The main benefits of 4D bioprinting are its ability to produce tissue-engineering outputs in large quantities, high-resolution printing of different cell types, and the creation of excellent cell density tissues (Azam et al., 2011).

CONCLUSION

4D printing is advancing to its peak due to its shape forming abilities. It is feasible to develop drug delivery technologies that can adapt and change in response to the various conditions by using smart materials as a feedstock. As a result, these "smart drugs" can deliver a more focused drug Because of its capacity to make shapes, 4D printing is reaching its pinnacle. Utilising smart substances as a feedstock, it is possible to construct medication delivery devices that can adjust and vary in reaction to the different situations. Consequently, these "smart drugs" are able to provide a more targeted release of drugs that is adaptable to the physiological situation. A few materials that are multi-responsive and self-assembling have been investigated for 4D printing. To identify raw materials that can be used as the feedstock for 4D printing technology, additional in-depth research is necessary.

There are a few materials that can assemble on its own and can exhibit multiple responses. These materials have been researched for 4D printing. It is important to do more thorough study to recognise raw materials that can serve as the feedstock for 4D printing technology. It is simple and quick to print, which has enormous benefits for humanity. Current advancements in stimuli-responsive smart hydrogels and their properties for use in medicine. The latest developments in additive manufacturing technologies' core concepts, workable solutions, and challenges are also thoroughly examined and examined in light of the novel 4D printed smart hydrogel the carrier systems for the effective administration of medicinal medications.

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