

## 3D 4D printing of chitosan-based scaffolds for wound dressing applications

Seyed Morteza Naghib<sup>1,\*</sup>, Seyedeh Neda Hosseini<sup>1</sup>, Anahita Beigi

*Nanotechnology Department, School of Advanced Technologies, Iran University of Science and Technology (IUST), Tehran 1684613114, Iran*



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### ABSTRACT

This essay offers a glimpse into the exciting field of chitosan-based material 3D/4D printing for wound-related uses healing. The development of personalized wound dressings and scaffolds has shown great promise when chitosan—a natural polymer with inherent wound-healing properties—is combined with cutting-edge printing techniques. An introduction to chitosan-based materials frequently used in wound dressings follows a succinct evaluation of 3D/4D reproducing technology and its importance in the medico string. Following that, the essay explores the benefits of using chitosan-based materials for wound healing, highlighting their biocompatibility, antibacterial qualities, and capacity to quicken the healing process. Also, it discusses how 3D/4D printing techniques enhance the customization and effectiveness of wound medical bandages made from chitosan by enabling precise tailoring to patient-specific needs. This essay examines the possible future effects of combining chitosan-based materials with 3D/4D printing to create more sophisticated wound healing solutions. It draws attention to chances for creating cutting-edge wound dressing designs that can enhance tissue regeneration and improve patient outcomes in general. Before widespread adoption in clinical settings can be accomplished, there are still issues and constraints that must be resolved. Regulatory concerns, scalability challenges, and guaranteeing the long-term safety and effectiveness of printed chitosan-based products are a few of these. In conclusion, while utilizing chitosan-based materials in conjunction with 3D/4D printing technologies holds great promise for improved wound healing applications, further research is needed to complete realize the capacity of this novel approach in clinical practice and overcome current obstacles.

### 1. Introduction

Split or full-thickness skin substitutes that imitate natural functional skin have been developed as a result of advancements in skin tissue engineering and wound healing. These alternatives have been thoroughly investigated and are currently being utilized in clinical settings to hasten recovery and enhance quality of life. Skin wounds are becoming a major healthcare concern because of the rise in trauma and pathological conditions. The four stages of normal wound healing are extracellular matrix (ECM) remodeling, proliferation, inflammation, and hemostasis. The natural extracellular matrix (ECM), bioactive substances, and cells interact during these stages. Pathophysiological conditions, on the other hand, have the capacity to seriously impede this process, resulting in large trauma wounds that fail to heal and lose skin tissue. The majority of non-healing wounds are related to illnesses like diabetes or accidents, which have been a substantial financial and social burden for many years. Homeostasis and swelling are the first steps of

the wound remedial cascade, during which immune cells and blood platelets are enlisted to reduce blood loss and eliminate pathogens. Growth factors and chemokines secreted by these cells draw in other cells and initiate the proliferation phase. This stage is determined by the establishment of Granular texture, angiogenesis, and re-Epithelialization, which cause the sore to contract. Remodeling is the last stage, during which the matrix gradually transforms into either semi-functional scar tissue or functional skin [Archana et al. \(2013\)](#); [Madni et al. \(2021\)](#).

An important threat to public health, chronic wounds affect millions of people each year and are defined as wounds that do not solder well after three months or are not repaired promptly and place a heavy financial strain on them. In developed nations, their prevalence is estimated to be between 1% and 2% of the population. They are commonly referred to as non-healing or ulcers. The four types of chronic wounds that the wound care community classifies are venous sore, power sores, diabetic sores, and arterial inadequacy sores. Patients' health and quality of life are greatly impacted by chronic wounds, which can lead to

\* Corresponding author.

E-mail address: [naghish@iust.ac.ir](mailto:naghish@iust.ac.ir) (S.M. Naghib).

<sup>1</sup> These authors contributed equally to this work and are the first author.

ache, to lose of function and stimulus, turmoil, chagrin, pine, scandal, public isolation, pecuniary hardship, extended hospital bedridden persistent issues, or even demise. 6.5 million men in the US drain from chronic wounds, which result in annual costs of over \$25 billion for complications. Chronic wounds can be difficult to treat with traditional medical techniques, so this is required. investigating fresh approaches to enable quick and efficient treatment. Tissue engineering and medicine have come back into favor recently as viable strategies for promoting tissue regeneration (Järbrink et al., 2016; La Monica et al., 2024; Heras et al., 2020).

One important development in tissue engineering is the growing appendix in creating tissues that closely resemble the physiological structure and syntax of their indigenous counterparts. Scaffolds are matrices that facilitate cell connector, multiplication, and extracellular matrix deposition. They are used in the majority of tissue engineering techniques. These methods fall short in terms of controlling the scaffold's internal geometry also the customized repartition and inter-connectivity of its pores. These issues have been minor. It was solved with the advent of 3D signet, which makes it May to fabricate complex, Patient visa structures and biomimetic with repeatability, layer-by-layer control over the material-forming organization. For tissue engineering and regenerative medicine (TERM) Application programs, common 3D reproduceing techniques include powder bed fusion (PBF), material extrusion (ME), material jetting (MJ), and vat photopolymerization (VP). Muscle, cartilage, bone, skin, vasculature, and neural tissue are among the tissue types that 3D printing has partially succeeded in creating in vitro. Nevertheless, the ability to engineer intricate out-of-plane shapes and to obtain temporal changes in features of multi-material constructs is severely limited by 3D printing. These constraints are especially noticeable when fabricating curved or tubular living structures, which typically call for the use of sacrificial materials and emphasis, adding to the Processing steps after printing and length enhancement the construction period overall. The next race of fabrication technologies is called four-dimensional (4D = 3D + time) cachet, which combination of the same construction principles three-dimensional (3D) Printing using stimuli-responsive biological materials and adds a post-printing stage. This stage involves the use of one or Additional stimuli to cause the printed structure to change, changing the construct's structure or functionality. Different definitions have emerged as 4D printing gains popularity, including the following: the steady deterioration of 3D-printing frameworks, the maturation of 3D-printed tissues, the scaffold's functional changes, procedures by enzymes under control, or supramolecular regulation of cell-hydrogel metabolism (Kalogeropoulou et al., 2024; Haleem et al., 2020; Mir-onov et al., 2006).

Polymers are essential for biomedical applications; new polymeric Substances such as blends and compounds have provided technological advances due to their unique properties. Biopolymers comprise polysaccharides as cellulose and starch, as well as carbohydrate polymers generated by fungi and bacteria. Additionally, Biopolymers based on animal protein like collagen, chitosan, wool, silk, and gelatin are also considered biopolymers. In many forms, the origin of carbohydrates has demonstrated promising industrial applications. The primary building block of crustaceans' exoskeleton, chitin, is alkaline deacetylated to produce chitosan, a basic polysaccharide with a high charge density. It is a somewhat reactive substance that can be made into a powder, paste, film, or fiber, among other forms. Chitosan can interact with a variety of substances and is soluble in diluted aqueous acetic, lactic, malic, formic, and succinic acid molecules that are negatively charged including phospholipids, bile acids, fatty acids, anionic polysaccharides, and proteins. Biomedical materials based on chitosan have drawn interest because of their special qualities, which include biodegradability, non-toxicity, antibacterial activity, and biocompatibility. Because of its ability to promote hemostasis and hasten tissue regeneration, it is advantageous for the healing of wounds. Because natural products are more biocompatible than synthetic ones, they are the preferred choice

for biomedical research. Because it is broken down by specific human enzymes, chitosan is biodegradable. Chitosan's structural resemblance to glycosaminoglycans and its hydrophilic properties that a desirable Materials for the frameworkused in tissue engineering. N-acetylglucosamine, its monomeric unit, is found in hyaluronic acid, an extracellular macromolecule that plays a crucial figure in wound recovery. In general, biomedical materials based on chitosan have many advantages, such as biodegradability, non-toxicity, antibacterial action, and biocompatibility (Ahmed & Ikram, 2016; Bahavarnia et al., 2024; Wang et al., 2023).

By combining 3D printing technology with intelligent materials to create shape-changing mechanisms over time, 4D printing has greatly increased its influence across several industrial sectors. With this technology, you can have more flexibility and versatility because a single structure can perform multiple tasks.4D printing, a groundbreaking technology that integrates 3D printing with intelligent materials to create shape-changing mechanisms over time, has revolutionized various industrial sectors by offering enhanced flexibility and versatility. Through 4D printing, a single structure can now perform multiple functions, allowing for the design of systems that break free from traditional mechanical constraints and overcome limitations in mechanical systems by employing intelligent materials. This technological advancement holds immense potential, particularly in the medical field, where the development of biocompatible smart material systems is poised to revolutionize healing processes. In the realm of tissue engineering, bioprinting technologies have witnessed remarkable advancements, paving the way for the creation of biomimetic constructs with strong bioactivity and biocompatibility. Furthermore, the integration of chitosan with other innovative materials in bioprinting processes is amplifying the capabilities of tissue engineering, offering new possibilities for creating intricate and biologically relevant structures that mimic natural tissues with precision. As bioprinting continues to advance, the synergy between intelligent materials, such as chitosan, and cutting-edge printing technologies is unlocking unprecedented potential in the field of regenerative medicine, promising transformative solutions for complex medical challenges. 4D printed materials have a promising future because they can be used to design new systems that are not constrained by certain degrees of freedom and to overcome the shortcomings of mechanical systems. This can be accomplished by substituting intelligent materials for conventional mechanical components. The development of biocompatible smart material systems has the capacity to transform the medical field and increase the effectiveness of healing. Relying on appropriate bio-inks with optimal printability, bioprinting technologies have made significant strides toward creating functional and biomimetic constructs for tissue engineering applications with strong bioactivity and biocompatibility. In this field, chitosan, along with other natural and synthetic materials, is becoming more and more popular (Badhe et al., 2023). Bioprinting technologies have made great strides in technology over the past few decades, enabling the creation of biomimetic and functional structures for tissue engineering applications. The use of an appropriate bio-ink or bio-inks with optimal printability which should also have high biocompatibility and bioactivity is crucial to achieving the intended outcome of the bioprinting process. Chitosan is one of many artificial and natural materials that are gaining popularity (Badhe et al., 2023).

## 2. Evolution of hydrogel wound dressings

George D. Winter carried out research in the 1960s that demonstrated the best conditions for wound healing, particularly for chronic wounds, are moist surroundings. Subsequent research has corroborated this finding, which has affected the wound dressing market as well as medical approaches to wound care. Increased moisture in the wound allows for more even reepithelialization, whereas dry wounds may result in uneven and inefficient healing. Wound exudate, which contains important agents for healing, is generally less present in dry wounds,

leading to delayed healing. However, excessive moisture can also disrupt healing by causing skin maceration and providing an optimal environment for bacterial colonization (Sheokand et al., 2023). Until mid-1962, research on wound dressings and wound healing was largely neglected. Previously, it was believed that if the wound was kept dry and not covered, it would heal faster. These speculations were considered before establishing appropriate requirements for wound healing materials. The first generation of wound dressings, or wound films, was created by Winter. He demonstrated how, when these materials are applied to wounds on pigs, the healing process occurs at least twice as quickly as when the wounds are exposed to air (Winter, 1962; Winter, 1963).

By this time, there had been a surge in studies and research on the creation of wound dressings, which demonstrated that the use of suitable wound dressings could speed up tissue regeneration by holding the environment humid and highly compatible while Barrierting bacterial putrefaction. The level of wetting in the dressing's wet and dry sections determined how wound dressings were categorized in the 1980s. In terms of physical healing, dressing dried wounds was thought to be a good idea. By the middle of the 1970s, the most widely available dressing materials were woven cotton gauze or nonwoven rayon blended with cotton or polyester fibers (Edwards et al., 2001).

Conventional or dry dressings keep the surface of the wound dry, minimize its size, and permit the absorption of all secretions and fluids from the wound that could leak and cause additional contamination. As a result, this behavior is categorized as an antagonistic force against bacterial growth and is essential for mammalian cell survival and tissue regeneration. Previous studies have demonstrated that Winter drift dry wound dressings can cover the entire wound area, thereby decreasing the amount or rate of epithelialization and the quantity of dressing needed. Consequently, gauze dressings, also known as dry dressings, which were once frequently used as wound dressings, are no longer very helpful due to the following issues: 1. The incapacity to shield the injury from microbial invasion, 2. It is extremely painful for the patient while it is being removed because of their increased skin adhesions, 3. Microbial attack is facilitated by accumulated wound secretions on the wound surface, which lower their absorption power. 4. Low permeability of gas, 5. Not appropriate for long-term wounds 6. Keeping the wound dry to slow down the rate of cell proliferation and epithelialization (Noori et al., 2015; Buote & Dressings, 2024).

According to research results, wound healing occurs much faster with wet dressings than with dry dressings. Wound healing and newly formed skin on the wound skin can only be achieved in a moist environment. Therefore, wet dressings are considered a suitable dressing option for skin repair and wound dressing. On the other hand, these types of dressings have inherent permeability and high-water content. The following should be accomplished by ideal wound dressing materials (Nguyen et al., 2023): keeping the area surrounding the wound moist, transmission of suitable gases, removing excessive secretions, but not to the extent of saturating the outer surface of the wound, protecting the wound from microorganisms, infection, or contamination, stop wound dryness, etc. (CHI et al., 2024).

In this regard, wound healing occurs more effectively and faster in a moist environment, which creates a moist environment instead of a dry environment by the hydrogel. It is important that can control wound using hydrogels to create and allow cell division and epithelialization operation. This emphasizes why hydrogels are the ideal material for dressing wounds. Research reveals that the amount of water and bodily fluids lost by skin that is scarred is nearly 20 times higher than that of skin that is healthy and normal. Therefore, without interfering with the process of epithelialization or cell proliferation by hydrogels, the water permeability of the used medical bandages should also control dehydration the production of wound secretions and calluses (Hackert et al., 2024).

An essential component of wound care is dressing. Wound dressings have three main purposes: a) creating a temporary protective physical

barrier, b) absorbing wound drainage, and c) providing the necessary moisture for optimal re-epithelialization. Dressing selection selects advanced features and can provide better dressing. Optimal moisture levels are required to achieve ideal wound healing. While absorbing extra fluid, the dressing's surface that comes into contact with the wound should stay moist (Fansler et al., 1995; Parimi, 2024). According to the researchers, at 35 °C, the average daily water loss from normal skin is about 250 gm-2/day; however, depending on the type of ulcer, this can reach 5000 gm-2/day. This indicates that membrane or thin-film dressings should be used, as they have high vapor-water permeability, high liquid capacity, and the ability to promote bacterial growth, repair, and improvement. Additionally, wound dressings should be easily removed or removed after treatment while also balancing the wound wall's adhesion (Fansler et al., 1995; Obagi et al., 2019).

Wound dressing has various purposes including promoting healing, preventing tissue damage, acting as a barrier against bacterial invasion, creating thermal insulation, facilitating debridement, supplementing with enzymes and growth factors, facilitating gas exchange, and reducing pain by protecting organs. The approach to choosing a wound dressing includes a detailed history and physical examination. Factors such as wound characteristics, patient needs, and available dressing options are considered to determine the most appropriate dressing. In summary, maintaining the appropriate level of moisture in the wound is critical for optimal healing, as overly dry and overly moist environments can inhibit wound healing. The improvement process of dressing selection depends on the anatomical and pathophysiological features of the wound. Advanced dressings can more closely resemble antimicrobial and pain-relieving properties (Obagi et al., 2019; Calavul, 2024).

These purposes have been growing the market for products used in wound care, and it is anticipated to reach >22 billion by 2024. Issues affecting this growth include the increasing prevalence of aging populations, a propensity for brief hospital stays, and chronic diseases like diabetes. In the sections that follow, the benefits of synthetic dressings over traditional, biological ones, and the main reasons for increased popularity of hydrogel dressings are explained (Srivastava et al., 2024) (Fig. 1). Chemical structure of hydrogel components: a) structure of cellulose; b) structure of chondroitin sulfate (Oprea et al., 2010).

### 1) Traditional or common dressings

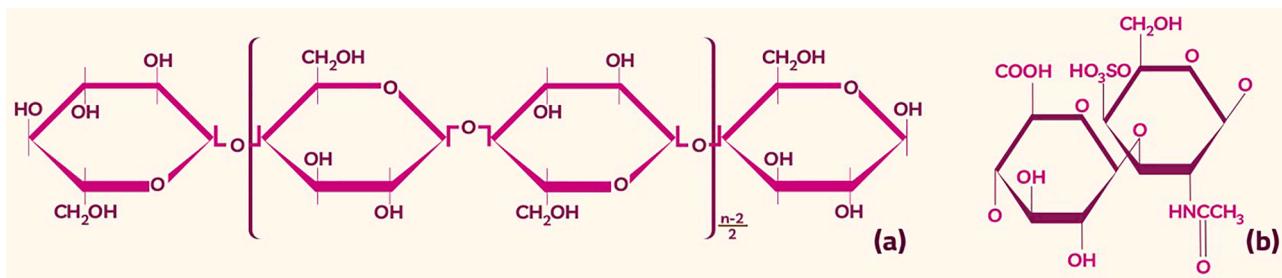
A large amount of wound secretions can be absorbed by gauze dressings or cotton-gauze compounds, which hastens the growth and contamination of bacteria and causes rapid dehydration. Furthermore, it can be challenging to remove the cover after the treatment because it may result in bleeding or harm to the newly formed epithelial flora (Edwards et al., 2001; Abbasipour et al., 2014; Sikka et al., 2024).

### 2) Biological dressings

"Skin grafts," or biological dressings, are the best materials thought to be able to finish the deep healing process for burns and chronic wounds. Fresh, natural skin from foreign bodies—such as humans, animals, or cadavers—is used in this procedure. The components of collagen, including elastin and lipids, are used in this procedure. The primary disadvantage of these materials is that, in cases of deep and large wounds, they may not be sufficient to donate a portion of the skin, necessitating the search for a new tissue donor (Kearney, 2001; Nagano et al., 2024).

### 3) Synthetic dressings

These dressings are composed of synthetic materials that are not present in the components of skin, such as polymers and inorganic materials. Synthetic dressings should be safe, mechanically stable, biodegradable, and provide an environment that is suitable for tissue improvement (Stashak et al., 2004; Divyashri et al., 2022). The majority of synthetic wound dressings have the same properties, including the sufficiency to keep the wound moist for better healing and the ability to encourage necrotic tissue autolysis by holding moisture at the wound surface. They vary greatly in terms of



**Fig. 1.** Chemical structure of hydrogel components: a) structure of cellulose; b) structure of chondroitin sulfate.

composition, absorbent capacity, hydrating ability, vapor permeability, flexibility, conformability, adhesive properties, indication, and handling, in addition to having unique advantages, restrictions, and disadvantages. The following categories apply to synthetic dressings: (1) films; (2) hydrocolloids; (3) foams; (4) hydrogels; (5) alginates; (6) hydrofibres, and (7) fibrous products and beads (Catanzano et al., 2021).

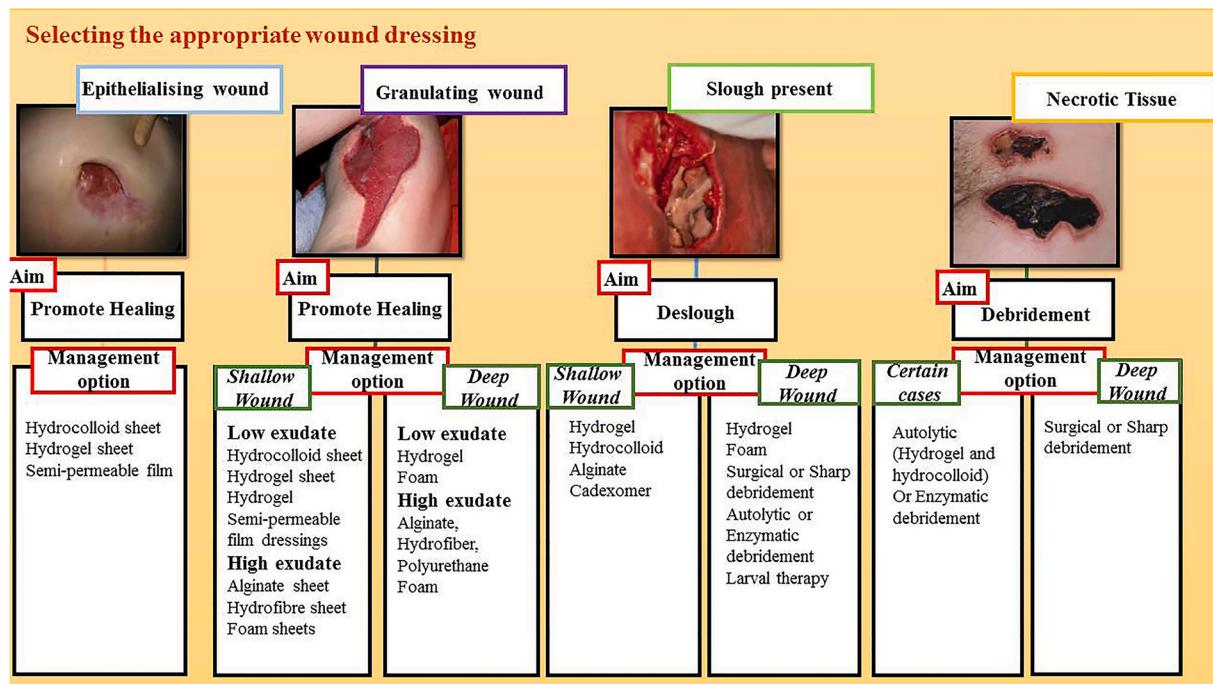
Because hydrogel dressings have so many benefits over very few drawbacks, they play a significant role in the application of sore care. At the moment, artificial organs, contact lenses, medication delivery systems, and wound dressings are all made of synthetic polymers. Unfortunately, the hydrogel's use is restricted to the polymeric membrane of wound dressings due to its lack of elasticity, stiff membrane, and incomplete hydrophilic properties (Kamoun et al., 2017). Polymeric membrane materials for wound dressings have been in high demand recently (Stashak et al., 2004).

It is widely acknowledged that wound healing occurs more quickly in a moist environment. Contemporary synthetic dressings allow for varying degrees of gas exchange and water vapor transmission while maintaining moisture at the wound's surface through either occlusive or absorptive qualities. Unlike other materials and methods of sore expurgatory, autolytic debridement is highly selective and does not harm the healing tissue because these medical bandages maintain a textured environment. The sore care professional can choose from a

variety of wound dressing categories. There are few Controlled research on effectiveness of dressing, and choice is frequently based on anecdotal evidence and personal preference. Knowing the features of dressing materials is essential to making wise decisions. All types of wounds and stages of healing cannot be covered by a single dressing category or brand. Frequent reevaluation is crucial when choosing a product. The frequency of dressing changes varies and is influenced by the properties of the wound and the dressing used. Concepts and goals for appropriate wound care should be established. By lowering discomfort, minimizing odor, minimizing dressing changes, stopping exudate leakage, simplifying personal hygiene, and promoting increased mobility, optimal wound care can enhance the quality of life (Auböck, 1999). (Fig. 2) illustrates how the available dressings are chosen based on the wound's depth, amount of exudate, and wound bed characteristics (Rezvani Ghomi et al., 2019; Catanzano & Boateng, 2020).

### 3. Sources for synthesizing hydrogel dressings

Over time, the string of biomaterials has affected by many changes. It includes materials from both natural and synthetic sources that are employed in a manifold of disciplines, including biology, medicine, mechanics, material science, and bioengineering. Biomaterials have been used for thousands of years; animal sinew, tendons, and fibers were used as sutures by the ancient Egyptians. The development of biologically inspired biomaterials is fueled by our growing perception of the



**Fig. 2.** Effective parameters in choosing the appropriate wound dressing (Bell & Dot, 2007; Dealey, 2008; Rezvani Ghomi et al., 2019).

biology of sore healing in the field of biomaterials today. These biomaterials have improved qualities to carry out intended functions while simulating *in vivo* processes. The creation of these innovative biomaterials is aided by techniques like level correction by additive manufacturing, 3D printing, small component modeling and nanotechnology.

According to IUPAC defines a "polymer" as a material made up of a top relative molecular weight of macromolecules. This definition covers a wide range of polymer compounds, blends, and molecules. Polymers comprise a diverse range of materials that can be classified into various groups (Colmenares & Kuna, 2017). The majority of biomaterials are classified as polymers, which are made up of lengthy chains of covalently bonded natural or artificial molecules. These chains are made up of units known as monomers, which might be different types of molecules or the same molecule. Depending on the kind of monomers they contain, polymers go by different names, including plastic, rubber, proteins, peptides, and oligonucleotides among others. Thousands to hundreds of thousands of monomers are often linked together to form long polymer chains in biomedical applications. The polymers' stability and other qualities are improved by this crosslinking, which qualifies them for a variety of medical uses (Biswal et al., 2023; Balavigneswaran & Muthuvijayan, 2021). There are two primary types of hydrogels: those that are produced synthetically and those that are found naturally. The extracellular matrix (ECM) and non-mammalian sources, such as brown seaweed alginate, are the sources of naturally occurring hydrogels. They have built-in ligands that offer strong cell adhesion. Hydrogels that are found naturally have benefits like biocompatibility and the capacity to replicate the natural extracellular matrix. On the other hand, hydrogels that are synthetically prepared are made through chemical synthesis and can be tailored to suit particular needs. They can be made more effective by functionalizing them with ECM proteins or other bioactive molecules, even though they lack intrinsic cell adhesion characteristics. The advantage of synthetically prepared hydrogels is that their properties can be adjusted to suit particular needs. Each kind of hydrogel has benefits and applications of its own. Existed naturally while synthetically prepared hydrogels offer customization and versatility for a range of applications, natural hydrogels adhere to cells naturally (Balavigneswaran & Muthuvijayan, 2021).

### 3.1. Natural sources

Natural hydrogels are hydrogel polymers derived from natural biomaterials. Examples include hydrogels made from natural proteins like cellulose, starch, collagen, gelatin, chitosan, peptides/proteins, and their derivatives (Fig. 4). These natural hydrogels offer biodegradability, biocompatibility, and supportive characteristics for cellular attachment. However, they may have drawbacks such as variations in properties between batches, difficulties in synthesis and processing, and inconsistent material properties. Despite these limitations, natural hydrogels find numerous applications in tissue engineering (Chimisso et al., 2020; Kaliaraj et al., 2023; Saroia et al., 2018).

#### 3.1.1. Chitosan

A polysaccharide called chitosan is taken from the exoskeletons of fungi, insects, and crustaceans. Its structure is different from cellulose's, with an amino group occupying the place of the hydroxy group at carbon-2. Deacetylating chitin in alkaline solutions yields chitosan. It is made up of repeating units of D-glucosamine (GlcN) and N-acetyl-D-glucosamine (GlcNAc) copolymers, that by  $\beta$ -(1-4)-glycosidic bonds and dispersed throughout the polymer with a minimum acetylation level of 60 %. The molecular weight and level of acetylation of chitosan affect its solubility at neutral pH. Higher molecular weight chitosan needs a degree of acetylation above 40 % to be soluble, whereas lower molecular-weight chitosan is soluble. Chitosan's limited solubility in aqueous solutions has an impact on how effective it is against microorganisms and its interaction with the membranes and cell walls of bacteria. By

adjusting its molecular weight, grade of deacetylation, and Mutual effects with hydroxyl and amine groups, chitosan's physical properties can be changed. These changes fall into one of three categories: molecular, chemical, or physical imprinting methods. Chitosan shares structural similarities with glycosaminoglycans, which are crucial for cell-to-cell adhesion and are present in the extracellular matrix. Because of its diverse biological characteristics, chitosan can be used in biomedical applications. It destroys microbial cells selectively and is safe for use with mammalian cells. It is also biocompatible. Enzymes such as lysozyme, which hydrolyze the  $\beta$  (1-4) linkages between N-acetylglucosamine and glucosamine, are responsible for its biodegradability. In addition to its hemostatic, fungistatic, and bactericidal qualities, it promotes tissue regeneration and quickens the formation of osteoblasts. Compared to other natural polysaccharides, chitosan is more plentiful and can be found in a variety of sources. Chitosan is used as an edible coating in the food production craft to prolong the durability of fruits and vegetables. It forms shielding layers that lessen dehydration and water evaporation. Additionally, chitosan has found use in the cosmetics sector where it is mixed with other materials to increase the mechanical qualities and thickness of hair. In addition, chitosan functions as a chelating agent to extract organic pollutants and trap heavy metals. All things considered, chitosan's varied qualities and easy accessibility render it beneficial for an extensive array of uses in the food, cosmetic, and biomedical industries (Pan et al., 2023).

Because of that's superior qualities from the point of view of biodegradability, biocompatibility, antibacterial activity, and cell affinity, chitosan is a great option for creating a hydrogel that can heal itself for use in biomedical applications. The construction of a dynamic physical or chemically crosslinked three-dimensional network is the key to incorporating an automatic self-healing properties on hydrogels based on chitosan. Owing to the chitosan chain's abundance of hydroxyl and amine groups, dynamic covalent bonds such as borate ester, acyl hydrazone, imine, and disulfide bonds as well as non-covalent interactions such as hydrogen bonding, electrostatic interactions, hydrophobic interactions, etc. have been introduced to construct dynamic three-dimensional structures in self-healing chitosan-based hydrogels properties. Meanwhile, imine bonds can form and can be reversed in a physiological setting, making preparation simple and allowing for widespread use in the biomedical fields (Nie et al., 2023; Rajabi et al., 2021).

Chitosan hydrogels have been utilized in 3D stamping technologies to address capacity uses in tissue engineering and drug delivery systems. Different reversible connections, such as hydrogen bonds, hydrophobic interactions, electrostatic/ionic interactions, and combinations, can form physical hydrogels. Their lack of auxiliary crosslinkers and low toxicity make them advantageous. However, because of loops, flaws, and micro-heterogeneity in the polymeric structure, they frequently have low mechanical strength. Chemical crosslinkers can be used to create irreversible covalent bonds to overcome these shortcomings. Chemically crosslinked hydrogels are resistant to dissolution even at very high pH levels and have good mechanical qualities. Chemically crosslinked hydrogels' characteristics are determined by their cross-linking density, which is based on the ratio of Transverse bonding agent moles to the polymer repeating unit moles. Unlike the majority physical hydrogels, covalent bonds can break and the hydrogel cannot be corrected by itself. At low shear rates, physical chitosan hydrogels show shear thinning treatment, which improves needle flow (Rajabi et al., 2021; Bento et al., 2023).

A non-protein matrix for the growth of three-dimensional tissues, chitosan also acts as a hemostasis, promoting natural blood clotting and mitigating pain. It also activates macrophages for tumoricidal activity, promotes cell proliferation, and organizes histoarchitectural tissue. Moreover, it releases N-acetyl- $\beta$ -D-glucosamine, which promotes Natural synthesis of hyaluronic acid at the site of pain, ordered collagen deposition, and fibroblast proliferation. Many biomedical applications, such as drug and gene delivery, wound healing and tissue engineering, can be

made using chitin and chitosan. For various biomedical uses, these materials can be transformed into hydrogels, scaffolds, micro/nano-particles, nanofibers, seeds, sponges, and membranes. All things considered, these materials may hasten the healing of wounds and minimize scarring (Jayakumar et al., 2011; Arjun et al., 2023). The chemical structure of chitosan can be seen in the picture (Fig. 3).

### 3.2. Synthetic polymers

Synthetic polymers, primarily made through electrospinning, are used for wound and burn dressings due to their high specific surface area and small pores. These materials have bactericidal properties, including electrospun polyurethane-dextran nanofiber mats containing ciprofloxacin hydrochloride, water-soluble polymer-carrageenan hydrogels, cellulose acetate, poly-L-lactide, and poly (lactide-glycolide) impregnated with shikonin. They also have antimicrobial, anti-inflammatory, antioxidant and anti-tumor properties. New chitosan-poly (N,N-diethylacrylamide) cross-linked polymer network films also have growing biomedical applications for medical wound dressings. Bactericidal films based on chitin derivatives and silver nanoparticles are also growing, poly (ethylene glycol)-protein conjugates are an occlusive wound dressing material that were evaluated. (Shingel et al., 2006), Low permeability nets based on polyethylene glycol-gelatin for use in wound treatment (Bader et al., 2009), Gelatin sponges made from cross-linking including glutaraldehyde (GA), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDAC), and D-fructose (Ulubayram et al., 2002), Esterified Polyvinyl Alcohol-Gelatin Hydrogel Membrane for Wound Medicine Compatible with L929 Fibroblast Cell Line and Mouse Spleen Cells (Pal et al., 2007), polyvinyl alcohol-sodium carboxymethylcellulose membranes loaded with fucidic acid (Lim et al., 2010), New porous cryofoam for use in the treatment of potential wounds, starting with polyvinyl alcohol and polyacrylic acid hydrogels (Smith et al., 2009), polyvinyl alcohol/polyethylene Q3 glycol-tannin based hydrogel (Mhessn et al., 2010), curcuminloaded polylactic acid nanofibers for sore healing (Nguyen et al., 2013), Collagen-poly-L-lactic acid composite materials for wound healing bandages (Lee et al., 2007a), polylactic acid-based polymers and copolymers are candidate biodegradable materials (Luckachan and Pillai, 2011). New absorbent and bactericidal polyurethane walls for medical wound dressings (Yari et al., 2012), polyurethane foam combined with pH-sensitive alginate/bentonite hydrogel for Sore medical bandages (Oh et al., 2011), polyvinylpyrrolidone-alginate hydrogel containing nano-silver as a wound dressing (Singh and Singh, 2012), resveratrol fixed on polyvinyl pyrrolidone hydrogel medical bandages for dermatological use (Momesso et al., 2010), nanofibrous wall combined with Emodin Polyvinyl Pyrrolidone electrospinning in drug delivery and speeding up wound healing (Dai et al., 2012), polyurethane films according to fatty acid for consumption of medical pain bandages (Gultekin et al., 2009), poly-3-hydroxybutyrate-poly-L-caprolactone biodegradable porous films/membranes (Kil'deева et al., 2006; Franco et al., 2011), non-

woven matrices from poly-L-caprolactone homopolymers and poly-L-lactide- $\epsilon$ -caprolactone (Vaseashta et al., 2006), silicone-coated non-woven polyester dressing enhances re-epithelialization in a sheep model of dermal wounds (Losi et al., 2012). The new research announced that carboxymethyl chitosan shows wound healing properties in vivo and in vitro by activating macrophages, fibroblast growth and releasing various cytokines. (Peng et al., 2011). Polyacrylate medical bandages, when soaked with Ringer's solution, absorb bacteria, proteins, and necrotic tissue (with about 38 % pain excision rate as well as collagenase), leaving a "washing effect" (Mogoşanu & Grumezescu, 2014; Hannen et al., 2023; Choudhary et al., 2020).

### 4. Synthesis of hydrogel dressings

After cellulose, chitin the second natural polymer is abundant. Partial deacetylation of chitin yields chitosan, a cationic polymer. It is made from randomly amplified N-acetyl-D-glucosamine (GlcNAc) and deacetylated D-glucosamine units (GlcN) joined by  $\beta$ -(1-4)-glycosidic bonds within the polymer. The number of GlcN units divided by the sum of the GlcN and GlcNAc units is known as the degree of deacetylation (DD). Fungi produce chitosan, which contains three different kinds of reactive functional groups: primary and secondary hydroxyl groups at positions C-2, C-3, and C-6, respectively, and amino groups (Piekarska et al., 2023). Chitosan is an excellent external object reactant with low to no fibrous encapsulation and excellent qualities like biocompatibility, biodegradability, antioxidant effect, and anti-inflammatory activityEnzymes including lysozyme, a glycoside hydrolase in the body, hydrolyze the  $\beta$  (1-4) linkages between N-acetylglucosamine and glucosamine. Give chitosan its ability to degrade biologically. On the other hand, chitosan degrades more slowly than natural polymers derived from animals, such as fibrin and collagen. In addition to having strong toxicity in any gram positive and negative bacteria, chitosan possesses inherent Germicidal measuresagainst a variety of filamentous fungi and yeasts. Its ionic interaction with negatively charged cell level confers antimicrobial properties by blocking intracellular substance transport, raising internal osmotic pressure, and causing cell lysis (Alemu et al., 2023).

Because chitosan contains positively charged amine groups, which react with the negatively charged surfaces of blood cells to cause thrombus formation, chitosan also functions as a hemostatic agent. The solubility and biological activities of chitosan in aqueous solution are dependent on various environmental factors, including pH and temperature, as well as the amount of protonated amino groups in the polymeric chain, molecular weight, DD, and distribution pattern of acetyl groups. Chitosan remains insoluble at neutral and alkaline pH. Chitosan is a valuable resource for a variety of applications in the food, pharmaceutical, biomedical, and cosmetics industries due to its abundance, low cost, and ecological interest (Hossain et al., 2020). 3D polymeric networks known as hydrogels can retain mechanical stability while swelling and absorbing aqueous liquids. They are hydrophilic, biocompatible, and flexible, which makes them useful for a variety of biomedical applications, including drug delivery, absorbable sutures, and injectable biomaterials. While polysaccharides such as chitosan have higher crosslinking rates that guarantee their printability, protein-based polymers, on the other hand, have cell adhesion sites that help cells function (Chamkouri & Chamkouri, 2021).

At the moment, chitosan and chitosan-based inks are used in several 3D printing technologies for capacity uses in tissue engineering, bone, cartilage, nerve, blood vessel, and drug delivery systems. These technologies can dispense inks as hydrogel or paste. To create chitosan hydrogels, crosslinking techniques that are both chemical and physical can be applied. Different reversible connections, including hydrogen bonds, hydrophobic interactions, electrostatic/ionic interactions, and combinations, can form physical hydrogels. In physical gels, stimuli like pH, temperature, magnetic field, or the addition of appropriate counterions typically cause the sol-gel transition (Sahoo & Biswal, 2021).

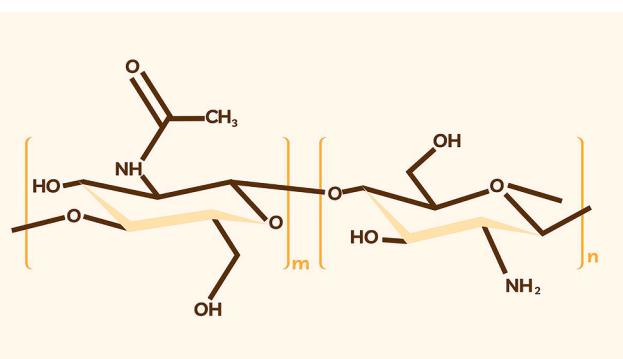


Fig. 3. Chitosan chemical structure (Suarato et al., 2016).

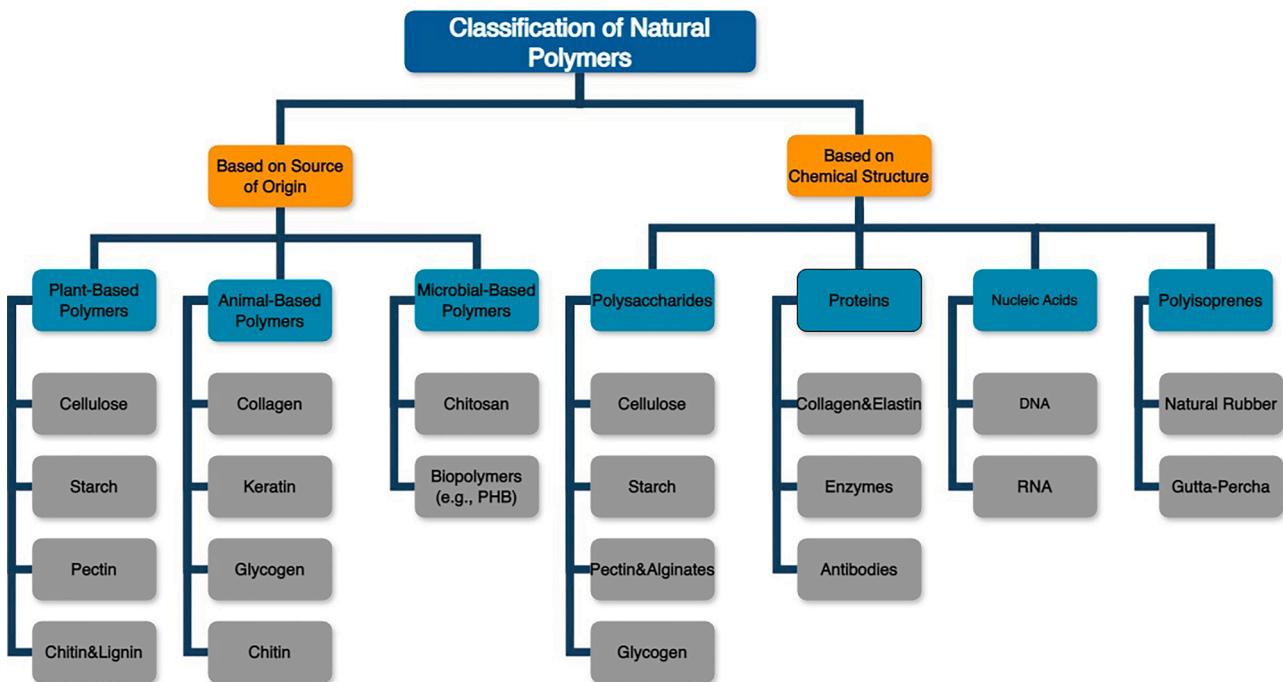


Fig. 4. Grouping natural polymers based on their source of origin and chemical structure.

Because they don't contain any additional crosslinkers and are low in toxicity, physical chitosan hydrogels are beneficial. However, because of loops, flaws, micro-inhomogeneity, and low property reproducibility, they frequently have low mechanical strength. Chemical crosslinkers can be used to create irreversible covalent bonds, which would improve these shortcomings. Covalently crosslinked hydrogels have strong mechanical characteristics and are resistant to dissolution at very high pH levels. The crosslinking density of hydrogels that have undergone chemical crosslinking is determined by the type of crosslinker used. The majority of crosslinkers used in covalent crosslinking are either cytotoxic or have an unclear physiological fate. Hydrogels can be made to have better mechanical, electrical, and drug-delivery qualities by adding various biomaterials. As a result, the hydrogel's intended use and method must be made evident (Rajabi et al., 2021; Yang et al., 2021). Chitosan and chitosan-based copolymers are therefore better for dressing wounds because of their tissue regeneration, biocompatibility, and biodegradability. The body can handle chitosan well, and it lessens side effects and speeds up the healing process. The natural breakdown that occurs with time reduces the need for frequent dressing adjustments. It also aids in healing and keeps wounds from becoming infected. Furthermore, it promotes tissue regeneration, which speeds up the healing process of wounds. These characteristics make chitosan and chitosan-based copolymers highly useful in applications involving wound healing (Paradowska-Stolarz et al., 2021).

## 5. Types of crosslinking

Hydrogel wound dressings have evolved, and various synthesis methods have been developed to create them. Here are some of the key types of crosslinking used from ancient times until now:

### 5.1. Natural sourcing

In ancient times, hydrogels were produced by using natural materials such as plant extracts, animal collagen, and polysaccharides like alginate or chitosan. These materials were often derived from natural sources and processed to form a hydrogel dressing.

### 5.2. Physical crosslinking

Physical methods like temperature changes, solvent evaporation, or pH adjustments have been used to create hydrogel dressings. For example, cooling a polymer solution can induce gelation, forming a hydrogel network. Physical crosslinking methods are relatively simple and don't need the application of chemical reagents.

### 5.3. Chemical crosslinking

Chemical reagents are used in chemical crosslinking to create covalent bonds between polymer chains, resulting in the formation of a hydrogel network. Common crosslinking agents include glutaraldehyde, genipin, or carbodiimides. Chemical crosslinking provides stability and control over the properties of the hydrogel.

### 5.4. Radiation crosslinking

Hydrogels can be crosslinked using ionizing radiation, such as gamma or electron beam irradiation. Free radicals produced by the radiation start crosslinking reactions, which result in the development of a hydrogel network. The hydrogel's properties can be adjusted and precise control over gelation is provided by radiation crosslinking.

### 5.5. Enzymatic crosslinking

Enzymes can be utilized to create hydrogel dressings, particularly for natural polymers like gelatin or fibrin. Specific enzymes, such as transglutaminase or thrombin, can catalyze crosslinking reactions between polymer chains, leading to the development of a hydrogel.

### 5.6. Hybrid approaches

Modern synthesis methods often combine multiple techniques to create hydrogel dressings with enhanced properties. For example, a combination of There are two types of crosslinking techniques: chemical and physical. Achieve better control over gelation kinetics and mechanical strength.

Hydrogel wound dressings have a long history, with crosslinking methods varying based on time and resources. New materials and technologies are continuously expanding the range of synthesis methods for hydrogel wound dressings (George et al., 2020). (Fig. 5) shows a schematic of how polymers are cross-linked by different methods (George et al., 2020).

## 6. Methods of making wound dressings

### 6.1. Sol-gel method

Converting a liquid sol, or colloidal suspension, into a gel network is the process known as sol-gel. When discussing wound dressings, the sol-gel process involves the conversion of a liquid sol (a colloidal suspension) into a gel network. In the context of wound dressings, this method typically uses bioactive materials such as inorganic oxides (silica, alumina, etc.) or biopolymers (gelatin, alginate, etc.) to form a gel matrix. The sol-gel method offers control over the composition, porosity, and bioactivity of the resulting wound dressing.

To create a sol-gel wound dressing, the process generally involves the following steps:

- Preparation of a sol by dispersing precursor molecules in a suitable solvent.
- Gelation of the sol through chemical reactions, such as hydrolysis and condensation.
- Shaping the gel into a desired form, such as a film or scaffold, through casting, dipping, or other techniques.
- Desiccating the gel to extract the solvent and produce a solid bandage.

Sol-gel wound dressings have antimicrobial qualities, can release bioactive agents under controlled conditions, and can create a moist environment for wound healing.

### 6.2. Electrospinning method

Using an electric field, electrospinning turns a melt or solution of polymers into ultrafine fibers. This method enables the creation of nanofibrous matrices for wound dressings that imitate the extracellular matrix's structure, encouraging cellular adhesion and tissue regeneration.

The following steps are usually involved in the electrospinning process:

- Preparation of a polymer solution or melt, which may include biodegradable polymers like polyurethane, polycaprolactone, or collagen.
- Transferring the polymer solution into a reservoir or syringe.
- Using a high voltage to produce an electric field between a grounded collector and the polymer solution.
- A charged jet of polymer solution is expelled from the syringe and elongated into fine fibers by electrostatic forces as the electric field is applied.
- The fibers are gathered onto the grounded collector to create a nanofiber nonwoven mat that can be used to treat wounds.
- The ability to encapsulate bioactive agents for controlled release, improved mechanical properties, and a high surface area-to-volume ratio are all provided by electrospun wound dressings.

### 6.3. Freeze-drying

This method involves freezing a hydrogel solution and then subjecting it to a vacuum to remove the frozen water via sublimation. The resulting porous structure provides high absorbency and a large surface area for enhanced wound healing.

### 6.4. Emulsion crosslinking

Emulsion-based methods involve the formation of an emulsion, typically with an oil phase and a water phase containing a polymer and agent for crosslinking. After that, the emulsion is crosslinked to create a hydrogel.

### 6.5. Spray-drying

In this technique, a hydrogel solution is atomized into fine droplets using a spray nozzle. The droplets are then dried through heated air, leading to the production of microspheres or dry powder that can be rehydrated upon application to the wound.

### 6.6. Electrohydrodynamic atomization (EHDA)

EHDA is a method that combines electrostatic forces and airflow to

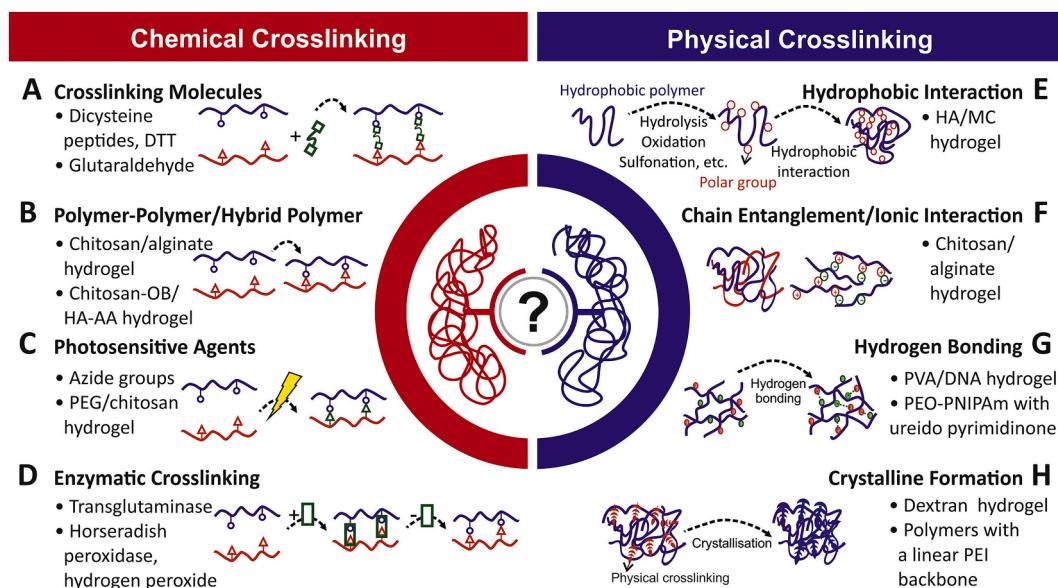


Fig. 5. Schematic of how polymers are crosslinked (George et al., 2020).

create small droplets or fibers from a polymer solution. This technique allows to creation of wound dressings using controlled morphology and porosity.

Hydrogels are soft 3D framework polymers with crosslinking density, which influences their performance. Chemical crosslinking is permanent and stable, while physical crosslinking is dynamic and dependent on external environments, affecting their structural stability (Li & Lin, 2021; Amiryaghoubi et al., 2024).

More sophisticated hydrogels are being developed to carry out specific tasks in specific environments, such as concerning pH, temperature, or particular molecules. Because of this, hydrogels can react to environmental cues, which improves their use in biosensing, tissue engineering, and targeted drug delivery. Smarter hydrogels can adapt to varying conditions, providing enhanced control and performance in biomedical, environmental, and technological fields. In the realm of wound dressings, smart hydrogels can offer controlled drug release, antimicrobial properties, and responsiveness to the wound environment, optimizing their effectiveness in promoting healing and minimizing infection (Idumah et al., 2024).

## 7. Smart hydrogels

Materials that react to changes in pH, temperature, light, electric field, and magnetic field are referred to as smart materials. These days, their capacity uses in biomedical, industrial, agricultural, electrical, healthcare, and hygienic products are drawing attention. Excellent responses are shown by these hydrogels to a variety of stimuli, including chemical and biological ones. The focus of recent advances in the synthesis of smart hydrogels is on their distinct characteristics and reactive behaviors. The development of smart hydrogels-water-absorbing polymeric networks that resemble soft tissue-has been made possible by the intelligent behavior of materials. These hydrogels can change in structure and volume phase in response to outside stimuli, opening up possibilities for sophisticated multidimensional technological applications and scientific observations. Hydrogels that respond to stimuli (SRHs) are superabsorbent materials that absorb and react to different variations in the pH, temperature, chemical species, ionic strength, electric field, and biological conditions are examples of environmental changes. These hydrogels can be produced chemically or physically. Physical hydrogels are created when polyelectrolytes that are oppositely charged or multivalent ions and surfactants interact with each other (Thang et al., 2023).

## 8. Stimulus-responsive hydrogels (SRHs)

### 8.1. Thermo-responsive hydrogels (TRHs)

Smart hydrogels known as thermoresponsive hydrogels (TRHs) can alter their formation and shape in response to temperature fluctuations. Hydrophobic groups like methyl, ethyl, and propyl groups are what distinguish them. Positively thermosensitive, negatively thermosensitive, and thermally reversible gels are the three categories into which TRHs fall. The type of monomer and crosslinker used in the synthesis of a hydrogel greatly influences its behavior, so choosing the right one is crucial. Because of its temperature-controlled phase transition behavior in aqueous solution at a lower critical solution temperature (LCST), the most common monomer, NIPAAm, is widely used to design drug release systems. PNIPAAm has been the subject of extensive research, particularly in the field of biomedical applications, due to its volume phase transition temperature (VPTT) at LCST being comparable to the temperature of the human body because of its quick on/off switch. Hydrogels derived from renewable resources can also be produced by combining NIPAAm with castor oil and bacterial cellulose (BC). The critical solution temperature regulates the solubility of thermoresponsive hydrogels, as the majority of them go through phase transitions in response to temperature changes. Due to their easy tunability from

the sol-gel state by changing temperature (rapid gelation), printability with good shape fidelity, high resolution, cell compatibility, natural shape, and vascularization, TRHs have emerged as the best material for advanced bioprinting applications. Gelatin and its derivatives, MC, agarose, collagen, pluronic and its derivatives, PEG/polyethylene oxide (PEO) based block polymers, and poly(N-PNIPAAm) and its derivatives can all be used to create TRHs for bioprinting (Nguyen et al., 2023).

A polymer solution must have low viscosity at 25 °C room temperature and the ability to form a gel above room temperature (LCST) to be used in biomedical applications. As carrier matrices, these materials can also be used in other biomedical and pharmaceutical applications. Initially, injectable thermosensitive hydrogels were created by combining chitosan and Pluronic-F127-loaded dexamethasone to treat osteoarthritis. When the temperature of these hydrogels varies, they display a sol-gel transition that prolongs the drug's presence in the joint and permits controlled release. Because of the positive charges in their structure, injectable thermosensitive hydrogels have exceptional bio-adhesive, non-toxic, biodegradable, and biocompatibility qualities. By mixing b-glycerophosphate-loaded paclitaxel with neutralized chitosan, they are also used to stop local tumor recurrence. At the locations of tumor resection, this gelling permits paclitaxel to be released continuously and managed the delivery over 30 days. This strategy appears as a treatment strategy to fight solid tumors, stop metastasis, and stop tumor regrowth. Following surgical excision of the tumor, a biodegradable device containing an anti-neoplastic agent is placed in the cavity created by the tumor, enabling the effective removal of any remaining malignant cells and a high local drug concentration. Ye Wang et al. also created thermosensitive hydrogels by mixing glycerol-loaded meloxicam (Mobic) with chitosan (Rezanejade Bardajee et al., 2020).

### 8.2. Light-responsive hydrogels (LRHs)

Hydrogels that exhibit reversible deformations in response to light sources such as UV, visible, and near-infrared light are known as light-responsive hydrogels (LRHs). They fall into two groups: one with near-infrared absorbing nanostructures embedded in thermoresponsive hydrogels, and the other with photolabile moieties. These hydrogels are made functionally light-sensitive by adding photochromic molecules into the hydrogel matrix, a process known as photochromism. They are capable of chemical changes, contraction-expansion of volume, and sol-gel phase transitions. By combining chromophore spirobifluorins, metallic nanoparticles, trans-cis photoisomerization, and the host-guest chemistry of substances like cyclodextrins and their derivatives, scientists have created light-responsive hydrogels. Because graphene oxide (GO) is sensitive to infrared light, PNIPAAm composite hydrogels made of glycidyl methacrylate (GO) functionalized graphene oxide nanofillers also display responsive to light. An embedded light-responsive polymeric nanoparticle recently, a double networked hydrogel that is both mechanically stable and thermoresponsive was created. Hydrogels derived from semi-conductive polymers and photo-responsive agents have also been created and investigated for production.

### 8.3. Electrically conductive hydrogels (ECHs)

Polymeric blends of highly hydrated hydrogels and electroactive polymers are known as electrically conductive hydrogels (ECHs), and they play a role in electrical conductivity as well as an on and off switch for electricity and light. A capacity gradient is created when a cross-linked polyelectrolyte gel that has swelled with water is placed between two electrodes and a DC voltage. The hydrogel then contracts anisotropically, releasing the water content. Ionic hydrogels have a contraction mechanism, whereas charge-neutral hydrogels have no contraction at all. Conductive materials like carbon-based materials, conductive polymers, and metallic nanoparticles are added as fillers to the hydrophilic hydrogel matrix to create ECHs. They are perfect for applications in soft electronics, micromachines, and human-machine

interfaces as well as flexible strain sensors due to their improved conductivity, stretchability, and flexibility. Conductive hydrogels based on bioelectronics and biosensors are being developed for several uses, such as drug delivery, glucose monitoring, pathogen detection, virus delivery, and environmental monitoring (Sikdar et al., 2021). Specialized polymers called electro-sensitive hydrogels cause the hydrogel to expand or stay instead to the external electric field. These hydrogels were created by Jin Qu et al. by combining oxide dextran and chitosan-graft polyaniline in a physiological setting. These hydrogels can release hydrophilic medications like amoxicillin and ibuprofen and are pH-sensitive and electro-responsive. Polyaniline is a useful tool for controlling hydrogel conductivity. The displacement of charged molecules under the electric field and the difference in Net charge difference in the polymer during oxidation or reduction or decrease can be used to explain the electric-driven release of drugs from conductive hydrogels. Hydrogels undergo an "on-off" pulse release when a voltage is applied, which lowers the conducting polymers and releases medications that are negatively charged. Essentially, voltage-releasing hydrogels release more medication than those lacking a voltage.

#### 8.4. Magnetically responsive hydrogels (MRHs)

By adding magnetic nanoparticles (MNPs) to a cross-linked polymeric matrix, one can achieve gadget, thermic, and audio behaviors that are responsive to magnetic fields. The addition of magnetic nanoparticles (NPs) broadens the hydrogel use; the best result is obtained by distributing the MNPs uniformly. It is important to regulate the MNP distribution inside the hydrogel network, that can be done by applying an external magnetic square. The characteristics of such a hydrogel are also influenced by variables such as the size and concentration of magnetic particles in addition to the hydrogel. Magnetic nanoparticle hybridized hydrogels are created by three main synthesis techniques: grafting, encapsulation or co-precipitation, and blending. The magnetothermal behavior of hydrogels is significantly influenced by the distribution arrangement, and the configuration of MNPs within the hydrogel can be controlled by the magnetic field. Chemotherapy can benefit from the phenomenon of magnetic hyperthermia, which is brought on by MNPs exposed to an alternating electromagnetic field. Mahdavinia et al. used carboxymethyl chitosan and carrageenan to create pH-sensitive, magnetic beads that were then used to administer the water-soluble, non-steroidal anti-inflammatory medication diclofenac sodium (Bryant & Nix, 2015).

#### 8.5. Sound responsive hydrogels (SORHs)

The ability of smart hydrogels to react to sound or ultrasonography makes them useful in a variety of industries, including biomedical ones like cancer treatment and drug release. Because of their interaction with ultrasound waves, these hydrogels can be activated and burst to release drug payloads specifically tissues. When SORHs interact with sound waves, they exhibit a debonding-reversible crosslinking behavior that enables controlled drug release. The way SORHs are synthesized varies according to their intended use. Kwok et al., for instance, created a SORH for on-demand medication release by utilizing the insulin polymer's methylene chain. By copolymerizing HEMA, HEA, PEGDMA, and insulin, the hydrogel slabs were crosslinked, and PEG was added to create large pores that could hold large protein molecules.

#### 8.6. Pressure responsive hydrogels (PRHs)

Hydrogels are unique in that they can sense pressure and react differently depending on the pressure. Super-elastic, Cell structure, and nanofibrous hydrogels, like such as derived from alginate and flexible SiO<sub>2</sub> nanofibers, exhibit these characteristics. High water-content hydrogels, such as those containing >97 % water, lack substantial recoverable deformation and strong mechanical strength. Cellular

fibrous network hydrogels, on the other hand, can exhibit notable pressure-related responses and improve mechanical properties. Hydrogels' ability to respond to pressure makes them useful for a variety of use, Contains bio-actuators, drug transfer systems, tissue-engineered scaffolds, flexible pressure sensors, and artificial skin. Mechanical shearing methods, such as UV- Arising from polymerization of a monodomain anisotropic gel, can also be used to create these hydrogels.

#### 8.7. pH-responsive hydrogels (PHRHs)

Polymers with ionisable pendant/ operational groups, such as -OH, -COOH, -NH<sub>2</sub>, -CONH<sub>2</sub>, -N\, and -SO<sub>3</sub>H, are used to create pH-responsive hydrogels. Depending on whether the solvent is basic or acidic, these hydrogels exhibit a reversible swelling-deswelling mechanism when exposed to it. The solvent must also have a specific pH and ionic strength. Polymers with anionic and cationic pendant groups have an impact on pH, which in turn affects how the hydrogels swell. The synthesis of pH-responsive hydrogels can be Dided using natural or synthetic polymers with ionizable functional groups. One benefit of these hydrogels is that medications can be taken orally and still be protected from the gastrointestinal system. pH-responsive hydrogels can be created using grafted polymerization, injection emulsion polymerization, radiation polymerization, crosslinking techniques, free radical polymerized chemical crosslinking, physical crosslinking, template Click reactions, covalent bonds, Polymerization etc. The main advantage of these hydrogels is their capacity to deliver drugs orally while protecting them from the gastrointestinal tract system. A novel drug-delivering pH-responsive hydro-porous hydrogel, for instance, was created by Hibbins et al. utilizing in situ free-radical copolymerization of the monomers AAm and methacrylic acid, with MBAAm serving as the chemical crosslinking Factor. N-vinylpyrrolidone (NVP), PEG diacrylate, and chitosan hydrogels that were pH-responsive were created using comparable techniques. To secrete a powerful non-steroidal anti-inflammatory medication like including piroxicam, which is used in the treatment and prevention of colon disease cancer, Chen et al. developed chitosan composite hydrogels. Additionally, these hydrogels exhibit superior swelling in weakly alkaline environments, which qualifies them for Use in drug delivery systems for the colon (Vuerstaek et al., 2006).

#### 8.8. Redox responsive hydrogels (RRHs)

Reactive oxygen species, or ROS, are chemicals that can detect and remove ROS from cellular metabolism, shielding cells from oxidative stress. In the human body, ROS are extremely reactive reagents that lead to the oxidative degradation of a variety of substances. Overproduction of ROS causes disruptions in bodily processes and may be the cause of systemic diseases. By decreasing their viscosity when combined with an oxidant and increasing it when combined with a reductant, redox-responsive hydrogels can lessen the effects of reactive oxygen species (ROS). Redox-sensitive entities can be incorporated during the fabrication process, enter a temperature-responsive environment to create redox-responsive hydrogels. This can be accomplished through ring-opening by polymerization with a thiol-one reaction, which exhibits redox sensitivity in response to chemical stimuli. RRHs can also be produced by redox-sensitive organometallic compounds, as shown by the hydrogel-based method of Nakahata et al. the chemistry of host-guest polymers. Another common method is crosslinking based on disulfide linkage.

#### 8.9. Glucose-responsive hydrogels (GRHs)

The field of stimulus-responsive hydrogels has advanced significantly in the modern era, especially in the synthesis of hydrogels that respond to glucose. These hydrogels are widely used in cutting-edge science, including as efficient insulin and medication carriers as well as self-monitoring of blood glucose (SMBG) for diabetic patients. They

can be used in vesicles, nanogels, microgels, nanogels, and mesoporous nanoparticles, among other forms. Dynamic covalent linkages are one common synthetic technique that uses a combination of PEO-b-PVP diblock polymer,  $\alpha$ -cyclodextrin ( $\alpha$ -CD), and phenylboronic acid (PBA)-terminated PEO the cross-linking of PEO was terminated to make a hydrogel solution. This process guarantees the stability and formation of the hydrogel, and since the hydrogel structure dissolves in glucose, it releases the loaded drug proteins efficiently. Moreover, GRHs that detect glucose stimulation have been produced through the use of free radical copolymerization using their porous structure.

#### 8.10. $CO_2$ Responsive hydrogels ( $CO_2$ RHS)

$CO_2$  stimulation can control  $CO_2$ -responsive hydrogels, frequently via a reversible switching mechanism. In supramolecular self-assembled hydrogels, these hydrogels can be made more versatile cross-linking them with organic metal cages or macrocycles. A novel class of star block copolymers (SBCP) featuring MOM as the core demonstrates  $CO_2$  responsiveness in the form of hydrogel formation, morphology transition, and thermoresponsiveness. These hydrogels are used in switchable vesicles, separation, encapsulation,  $CO_2$  capture, and monitoring. One of the interesting properties is the Inflation and reversible inflation in presence of  $CO_2$ . Lie et al. used a  $\beta$ -CD via ATRP to synthesize a  $CO_2$ -temperature-responsive hydrogel from PDMAEMA. The triblock copolymer self-assembles into cell vesicles to show good biocompatibility with both hydrophilic and hydrophobic segments. It also responds reversibly to temperature changes and  $CO_2$  gas presenting opportunities for controlled drug release and targeted drug transport.

#### 8.11. Enzyme responsive hydrogels (EZRHS)

The development of biomimetic responsive materials, like hydrogels that change structurally and interact with their surroundings when exposed to various enzymes, is greatly aided by the involvement of enzymes. The synthesis of novel responsive polymers, like EZRHS, has seen a rise in popularity thanks to enzyme-catalyzed reactions. Enzymes are biological materials that function as organic triggers, regulating physical characteristics and balancing material reactions to permit the release of biomolecules when required. Using An enzyme-catalyzed reaction where an enzyme functions as a vital a powerful vital biological catalyst causing chemical or morphological Developments within hydrogel cells is a common method for synthesizing EZRHS. Enzyme-mediated biological responses can be obtained in this case way, particularly in the biomedical field. When an enzyme is present, certain hydrogels can release biomaterials that have been trapped as a result of the hydrogel-forming polymer chains breaking down. These kinds of hydrogels can be created by covalently linking polymer chains together or by assembling several self-assembling molecules (hydrogelators) into supramolecular structures. Enzymes function specifically and are activated through the hydrogel's breakdown. As biocatalysts, they are attracted to control the liberate of medications and biomolecules at specific sites. Certain requirements, such as an enzyme-responsive substrate and changing the material's properties, must be satisfied for a polymer to be enzyme-responsive. Different chemical bonds are formed on the substrate as a result of enzymatic action, and these bonds can be used to release medication in a targeted way in response to particular enzymes.

#### 8.12. Antigen responsive hydrogels (ARHs)

Biosensors known as antigen- responder hydrogels show a change in voluminosity or mass when an antibody or its auxiliary is present. They can be chemical conjugation, corporal entrapment, or reversible reciprocal link of the antibody-antigen pair. By adjusting LMWG to promote self-assembly, supramolecular hydrogels can be created, which can then be improved to an enzyme-responsive and cell-responsive hydrogel.

These hydrogels can release fluorescent medications that are catalyzed by proteolysis specific to the prostate antigen, which may be helpful in the recognition of prostate cancer. By grafting a dextran column on a fluorescein isothiocyanate (FITC) antigen and a sheep anti-FITC IgG antimicrobial, a hydrogel-based smart wall can be provided. A similar mechanism for changing crosslink density in against goal molecules can be used to engineer a target-responsive hydrogel demonstrating the possibility of quantitative point-of-care examineing for diagnosis of lead ions, cocaine, and ochratoxin A with improved sensitivity and accuracy. Because additives are not used, It has been reported that  $\gamma$ -irradiation initiated copolymerization and cross-linking are more beneficial than chemically initiated cross-linking polymerization. This method yields non-carcinogenic sterilized hydrogels. The reducing the lifeactivity and heterogeneity of physically and chemically cross-linked hydrogels can be compensated for by template polymerization.

#### 8.13. Hydrogel production for targeted uses

Practical hydrogels can have some of their original physicochemical properties preserved after being surface functionalized. Surface structure construction, chemical grafting, and the physical incorporation of functional micro/nanomaterials are methods that can be used to accomplish this technique. This makes it possible to create hydrogels that are perfect for specific applications because they have remarkable mechanical properties, stretchability, self-healing, and extreme flexibility.

#### 8.14. Hydrogels with superior mechanical properties

In the fields of textures engineering, sewage treatment, sore repair, microbicide uses, and controlled liberation of the drug, hydrogels are widely used. Their applications have been limited, though, by their mechanical strength. Of soft textures, including ligaments and tendons, are prone to damage and do not self-repair, scientists have been investigating methods to mechanical upgrades characteristics of hydrogels. To setting the mechanical properties of hydrogels, methods like synergistic copolymerization effects, double networking, triple networking, interpenetrated networking, and used from additive nano algebraic networks. Double network hydrogels of PAAm and gelatin reinforced with GO nanosheets were created by Yan et al., and this improved the hydrogels' Resilience, tension stress/strain, and relenting qualities. A semi-interpenetrating networked hydrogel of BC and CHT was created by Wahid et al., and it outperformed neat hydrogels in terms of mechanical and thermal properties. Li et al. produced PVA, PVP, and PAAc-Zn<sup>2+</sup> triple-networked hydrogels with improved Stretching and friction characteristics. Combining segments of hydrophilic and hydrophobic polymers can give hydrogels a variety of characteristics, including strength and stiffness. By integrating lignin nanoparticles into PAAm hydrogel networks, Chen et al. were able to effectively distribute applied load and increase compressive stress. To increase the mechanical characteristics of hydrogels in load-bearing regions, researchers have devised a variety of techniques, including chemical Bidirectional binding, bidirectional and dual hydrogel network, and nano additives.

#### 8.15. Hydrogels with antibacterial properties

Hydrogels have been developed to improve their multifunctionality and high performance, especially natural polymer hydrogels. Various methods, including double-network, nanocomposite, macromolecular microsphere composite, and polyampholyte hydrogels, have been devised to confer desirable characteristics, like elevated water swelling, pliability, elastic qualities, self-healing capabilities, and accommodation with human physiological processes. Drug delivery, tissue engineering, food packaging, cosmetics and biomedical engineering fields have all benefited from the increased use of these qualities. Additionally, antibacterial hydrogels are being developed, some of which are naturally

antibacterial. These Hydrogels can be divided into three groups: hydrogels by built-in Bactericidal properties containing inorganic nanoparticles, and hydrogels containing bactericidal factors. Metals in particular, Ag, Au, Cu, and Zn are mostly incorporated into hydrogels as nanoparticles. Ag is most frequently utilized because of its strong antimicrobial qualities and low toxicity. Other metals with antibacterial qualities include zinc, copper, and gold. Antimicrobial and metal-binding qualities are shared by chitin and CHT, and certain hydrogels exhibit resistance against Escherichia coli.

#### 8.16. Hydrogels with cell adhesive properties

Hydrogels have the ability to act as framework for the growth and proliferation of cells, much like biological soft tissues. Magnetic PAAm hydrogels can serve as a multiple arrays cell culture matrix and as hydrogel interfaces for cell adhesives. Cell treatment, as imitating the extracellular matrix (ECM), is determined by the distribution, rating, and order of cell adhesives and also interactions between cells and the matrix. Tetraethyl ethylenediamine, Fe<sub>3</sub>O<sub>4</sub> MNPs, AAm monomers, and MBAAm combined with water can form a magnetic anisotropic hydrogel structure. This hydrogel shows great promise as a hypothermia therapy and anticancer drug. Human bloodline endothelial progenitor cells (EPC) can function as vessels in peptide-modified PEG scaffolds, offering them as a capacity cell source for uses such as vascular tissue engineering. EPC is encapsulated within a mild photocrosslinking process, a hydrogel made of PEG. A single network hydrogel consisted of poly-dopamine and polyacrylamide (PDA–PAAm) was created, exhibiting excellent elasticity, high toughness, cellular affinity and tissue adhesion. An important development in biomedical engineering is an alginate-based cell adhesive bio-hydrogel (AdHG) that can encapsulate and present mesenchymal stem cells (MSC) to the intended site. Alginate hydrogels modified with L-DOPA amino acid (DA) bind to cells very well. Such hydrogel-containing wound dressings offer infection resistance as well as a favorable physiological environment for the proliferation of cells. Another common method for creating hydrogel cell adhesives begins with preliminary polymer solutions and types of two-way grafting techniques. Additional techniques are needed for a prosperous tissue engineering process, such as cell culture, degradability, and biomechanical property customization, among others. Increasing polymer concentration and altering architecture can improve biomechanical properties.

#### 8.17. Hydrogels with self-healing properties

The capacity of materials to repair themselves after the damage has occurred makes them next generation material for high-efficiency structures (Table 1). Running covalent bonds and non-covalent interactions can be used to make self-healing hydrogels. Natural polymers like hyaluronic acid, chitosan and alginate are frequently employed in this regard. Self-healing hydrogels with greater strength and elasticity are made through unnatural polymers including PEG, PAAc, PVA, and PAAm. A series of Li-alginate/poly (acrylamide-co-stearyl methacrylate) hydrogels, which show maximum fracture energy and are fire-resistant, can be used for self-healing multifunctional composite hydrogel. Alignment of the level network with dangling hydrocarbon lateral chains containing polar groups can lead to the development of rapid self-repairing hydrogels. Synthesized by physical crosslinking of PVA, a fluorochromic hydrogel exhibits reasonable self-healing capability in response to light and ferric ions. Hydrogel-based self-treatment sodium alginate serves as a strong mutual bond in the one-pot polymerization process used to create CNC. The hydrogel's mechanical strength and capacity for self-healing are demonstrated by its ability to self-heal after a few hours of dissociation at room temperature (Sikdar et al., 2021).

#### 9. 3D printing of wound dressing

One special class of soft materials called hydrogels has a lot of capacity uses in skin care, personal care, and biomedicine, among other fields. Hydrogels are receiving more attention in research because of the quick integration of 3D structures and sophisticated synthesis methods (Table 2). To satisfy these demands, researchers are creating new synthesis and design techniques. There is still room for exploration in the growth of intelligent hydrogels with optimal physical and chemical properties, functional and untouched. Future studies should concentrate on creating hydrogels with the ability to modify plasticity, regulate immune cell activity, and reprogram cells to form, repair, and reconstruct tissues. The advantages of injectable hydrogels, such as their cytoadaptability, non-invasive prescription, top infiltrateability, controllable analysisability, and transfusionability, have drawn attention. But there are still obstacles to be solved, like striking a balance between strength and degradation and creating sophisticated, controllable hydrogels that are electrosensitive and respond more quickly for intelligent medication delivery. To sum up, tremendous advancements have been made in the last few decades to enhance the qualities of hydrogels and open up new application possibilities. There is an urgent need for full understanding of the synthesis procedures and the methods used to fine-tune the unique functional properties of smart hydrogels (Sikdar et al., 2021).

The largest organ of the body is the skin is essential for preserving homeostasis and serving as a barrier to infection and fluid loss. Skin wounds or injuries brought on by burns, trauma, long-term illnesses, and surgery can cause discomfort and disability, which presents a big problem for healthcare systems around the world. Acute (healing) and chronic (non-healing) skin wounds are distinguished by their causes and outcomes. Large wounds heal more slowly and are more prone to infections and fluid loss than small, acute wounds, which can be repaired and healed by the skin's natural healing process. Millions of people are impacted by chronic wounds, which compromise the structural and functional integration of the skin and present social and economic difficulties for healthcare systems. Chronic wounds have a mortality rate similar to that of cancer, and by 2023, it's anticipated that the cost of managing these wounds will reach USD 35 billion. Due to challenges there remain unmet therapeutic areas in the evaluation and management of wound care, skin wound repair and management despite a great deal of research. As a result, creating new and improved methods for skin wound healing is crucial for the advancement of medicine worldwide. Clinicians and researchers face many obstacles in the field of wound healing; by 2027, the worldwide market for wound care products is projected to grow to a value of USD 18.7 billion. There are two categories of skin wound therapies: conventional and regenerative. Changing dressings, controlling infections, and debriding injured tissues are all part of conventional wound therapy. Split-thickness skin autografts can save lives, but they come with a cost: a restricted number of donor sites, hypertrophic scarring, and changes to function.

The goal of regenerative wound healing is to repair damaged skin tissues and return the skin to its pre-damaged state through cutting-edge biomedical study technologies including stem cell therapy, gene therapy, bioactive biomaterial matrices, smart wound dressings, and bioengineered skin grafts. With this method, wounds can heal better and more effectively without leaving scars. Regenerative medicine has become more interested in stem cell-based therapies that employ various stem types of cells, incl as induced pluripotent stem cells (iPSCs) and mesenchymal fundamental cells. Its therapeutic capacity is however limited by poor survival of stem cells in the wound area because of a harsh inflammatory environment. Exciting new approaches for healing of patient-specific wounds for patients suffering from chronic wounds are presented by cell engineering techniques such as genome editing and genetically reprogramming stem cells. Different treatment approaches based on modern wound dressings, topical medication and increase in-vitro rendition, auto/allograft and xenograft, hyperbaric oxygen

**Table 1**

Examples of common methods of production of wound dressings.

Row	Name	Manufacturing Technique	Material	Increasing Properties	Application	Reference
1	Hydrocolloid Dressings	Mixtures of gelatin, pectin, and carboxymethylcellulose are combined and then formed into thin sheets	Gelatin, pectin, carboxymethylcellulose	Provides a moist environment, promotes autolytic debridement, and helps with granulation tissue formation	Hydrocolloid dressings are frequently applied to shallow wounds and pressure ulcers that exude low to moderate amounts of fluid	(Bryant & Nix, 2015)
2	Foam Dressings	Polyurethane or silicone foam is converted into thin sheets or shapes	Polyurethane or silicone foam	Absorbs exudate, cushions the wound, and provides thermal insulation	Foam dressings are frequently applied to wounds that leak a lot, like surgical wounds and leg ulcers	(Atiyeh et al., 2007)
3	Alginate Dressings	Brown seaweed is used to extract calcium or sodium alginate, which is then transformed into sheets or fibers	Calcium or sodium alginate	Absorbs exudate, forms a gel-like consistency, and helps with wound debridement	Alginate dressings are frequently applied to wounds that exude moderately to excessively, as venous leg ulcers and diabetic foot wounds	(Bryant & Nix, 2015)
4	Transparent Films	Polymers such as polyurethane or polyethylene are formed into thin, transparent sheets	Polyurethane or polyethylene	Provides a barrier against bacteria and external contaminants, allows visualization of the wound, and maintains a moist environment	For minor burns and other superficial wounds like abrasions, transparent films are frequently used	(Bryant & Nix, 2015)
5	Gauze Dressings	Cotton or synthetic fibers are woven or knitted into a mesh-like structure	Cotton or synthetic fibers	Absorbs exudate, provides a protective covering, and allows airflow	Gauze dressings are commonly used for various wound types, including surgical wounds and lacerations	(Bryant & Nix, 2015)
6	Silver Dressings	Silver nanoparticles or silver compounds are incorporated into dressings through various methods, such as impregnation or coating	Dressings infused with silver nanoparticles or silver compounds	Properties: Harnesses the antimicrobial properties of silver to help prevent or treat wound infections	Silver dressings are commonly used for infected wounds, chronic wounds, and burns	(Atiyeh et al., 2007)
7	Hydrofiber Dressings	Sodium carboxymethylcellulose fibers are processed into dressings using techniques such as spinning or weaving	Dressings composed of sodium carboxymethylcellulose fibers	Absorbs exudate, forms a gel-like consistency, and helps create a moist wound environment	For moderate wounds to severe discharge, including pressure sores and diabetic foot sores, hydrofiber dressings are frequently used	(Selimović et al., 2015)
8	Silicone Dressings	Soft silicone materials are processed into dressings with or without adhesive properties	Dressings made of soft silicone materials with or without adhesive properties	Providesatraumatic dressing removal, protects the wound, and helps maintain a moist environment	Silicone dressings are commonly used for superficial wounds, surgical incisions, and scar management	(Dykes et al., 2001)
9	Biologic Dressings	Dressings are isolated from man or animal texture through processes such as decellularization or processing techniques	Dressings taken from man or animal textures, as amniotic membranes or xenografts	Facilitates wound healing by providing growth factors, promoting cell migration, and reducing inflammation	Biologic dressings are commonly used for chronic wounds, ulcers, and burns	(Landén et al., 2016)
10	Compression Garments	Elastic materials are woven or knitted into garments or wraps with controlled pressure properties	Elastic garments or wraps that apply controlled pressure to limbs	Promotes lymphatic and venous circulation, reduces edema, and aids in the management of chronic wounds	Compression garments are frequently used to treat lymphedema, leg venous ulcers and post-operative swelling	(Mariani et al., 2008)
11	Composite Dressings	Multiple layers or materials, such as an catchy layer, a non-adherent layer, and an outer layer for protection, are combined to create composite dressings	Various combinations of materials, including non-adherent layers, absorbent layers, and outer layers (e.g., films or foams)	Composite dressings offer a combination of functionalities, such as exudate management, cushioning, and bacterial barrier	Because of their versatility, composite medical bandages can be applied to all types of wounds, such as surgery wounds, abrasions, and lacerations	(Gaspar-Pintilie et al., 2019)
12	Antibacterial Dressings	Antimicrobial agents, such as iodine, silver, or antimicrobial peptides, are added to dressing materials to create antibacterial dressings	Dressings infused or coated with antimicrobial agents	Antibacterial dressings help prevent or manage wound infections by inhibiting bacterial growth and colonization	Antibacterial dressings are frequently applied to wounds that are infected, chronic, or susceptible to infection	(Percival et al., 2008)
13	Collagen Dressings	Collagen dressings are made from either natural collagen extracted from animal sources or recombinant	Dressings derived from natural collagen or recombinant human collagen	Collagen dressings provide a scaffold for cell migration, stimulate	Collagen dressings are commonly used for	(Schultz & Wysocki, 2009)

(continued on next page)

**Table 1 (continued)**

Row	Name	Manufacturing Technique	Material	Increasing Properties	Application	Reference
14	Biological Dressings	human collagen produced through biotechnology processes	Dressings derived from living sources, either human or animal tissues	granulation tissue formation, and promote wound healing Biological dressings provide growth factors, cytokines, and extracellular matrix components to promote wound healing and tissue regeneration	chronic wounds, ulcers, and burns Burns, ulcers, complicated or non-healing wounds, and chronic wounds are all treated with biological dressings	(Marsili et al., 2021)
15	Negative Pressure Wound Therapy Dressings	A foam or gauze dressing, a Clear video and a vacuum source that creates a negative pressure inside the wound are the components of negative pressure wound therapy (NPWT) dressings	Gauze or Foam dressings, transparent film, and vacuum source	NPWT dressings promote wound healing by removing excess exudate, reducing edema, and stimulating granulation tissue formation	NPWT dressings are commonly used for complex wounds, large surgical wounds, and wounds with excessive exudate	(Apelqvist et al., 2008)
16	Alginate Dressings	Alginate dressings are made from natural polysaccharides derived from seaweed, such as sodium or calcium alginate	Dressings made from alginate fibers or powders	Alginate dressings absorb wound exudate, form a gel-like consistency, and promote autolytic debridement	Leg ulcers and cavity wounds, which exude fluid from their wounds moderately to heavily, are frequently treated with alginate dressings	(Froelich et al., 2023)
17	Foam Dressings	Foam dressings are created by compressing or laminating polyurethane or silicone foams into various thicknesses and configurations	Dressings made from polyurethane or silicone foams	Foam dressings provide absorption of exudate, cushioning, and protection while maintaining a moist wound environment	Pressure ulcers and surgical wounds that exude fluid moderately to heavily are frequently treated with foam dressings	(Cutting & White, 2002)
18	Hydrocolloid Dressings	Hydrocolloid dressings are created by combining hydrophilic colloidal particles, such as gelatin, pectin, or carboxymethylcellulose, with adhesives and backing materials	Dressings composed of hydrocolloid particles, adhesives, and backing materials	Hydrocolloid dressings provide a moist wound environment, absorb light to moderate exudate and support autolytic debridement	Hydrocolloid dressings are frequently applied to wounds that range from shallow to moderately deep, including minor burns and pressure ulcers	(Woo et al., 2012)
19	Film Dressings	Film dressings are created by coating thin, transparent polymeric films, such as polyurethane or polyethylene, with adhesive or non-adhesive layers	Dressings made from thin, transparent polymeric films	Film dressings permit moisture vapor exchange while acting as a barrier against germs and other environmental pollutants	Film dressings are frequently applied to non-exuding, superficial wounds like small cuts and incisions made after surgery	(Molan, 2006)
20	Honey Dressings	Honey dressings are created by combining medical-grade honey with various dressings, such as gauze or alginate, to facilitate application and minimize leakage	Dressings infused or impregnated with medical-grade honey	Honey dressings possess antimicrobial properties, promote autolytic debridement, and provide a moist wound environment	Honey dressings are commonly used for infected wounds, chronic wounds, and necrotic wounds	(Molan, 2006)

**Table 2**  
Different techniques of 3D printing.

Technique	Materials	Reinforcement	Properties	Applications	Reference
Fused Deposition	Thermoplastics	Fibers, continuous	Strength, toughness, flexibility, heat resistance	Prototyping, manufacturing	(Huang et al., 2015)
Stereolithography	Photopolymer resins	None	High resolution, smooth surface, brittle	Prototyping, dental applications	(Vijayaventkaraman et al., 2016)
Selective Laser	Metals, alloys	None	High strength, complex geometries, high resolution	Aerospace, automotive, medical	(Li et al., 2021)
Electron Beam	Metals, alloys	None	High strength, complex geometries, high resolution	Aerospace, automotive, medical	(Islam et al., 2024)
Inkjet-based	Polymers	None	Versatile, multi-material, high resolution	Tissue engineering, drug delivery	(Derby, 2010)
Shape Memory	Polymers with shape memory	None	Shape recovery, stimuli-responsive	Biomedical devices, drug delivery	(Lendlein & Kelch, 2002)

therapy, cell-based remedy and engineered skin linkage, Sealing with vacuum, electrotherapy, negative-pressure treatment, ultrasound, and The approach is based on exosome some of the techniques on types of wounds and intrinsic regeneration capacity. These therapeutic approaches do, however, still have drawbacks and restrictions. The development of non-invasive, cost-effective wound care therapies is

essential for high-quality wound healing. Damage or disorders that affect as a result, the integrity of the skin surgery, external factors, or pathological conditions such as vascular diseases or diabetes are referred to as sores in accordance with length of time and method of healing, they are split into acute and chronic wounds. Acute wounds from radiation, chemicals, and abrupt temperature changes usually heal

in 4–12 weeks. On the other hand, there are chronic wounds more challenging for treatment because of underlying pathologies, infections, inflammations, tumors, or other physical agents. Low mitogenic activity, increased cytokine and protease levels, low growth factor secretion, excessive manufacturing of reactive oxygen species and matrix metalloproteases, inhibited angiogenesis, fibrosis, and ECM degradation are all characteristics of chronic wounds. Chronic wounds take longer to heal, which makes infections more likely and hinders the best possible restoration of skin integrity. Therefore, to increase speed the healing process of wounds, more recent techniques and tactics are required. Healing a wound is a dynamic, intricate process divided into four phases: proliferation, tissue remodeling, inflammation, and homeostasis. These phases are interrelated. Following an injury, a well-coordinated series of events, including phagocytosis, growth factor release from cells, chemotaxis, collagen degradation, and remodeling, start the healing process. Since adult wound healing is slow that of infants and frequently leaves scars, creative approaches to high-quality, scarless healing are required. Because of their size or depth, chronic or non-healing wounds frequently leave behind unwanted scars because they are unable to properly heal skin tissue. Hemostasis, the first level of wound repairing, is the cease of bleeding caused by scab formation and vascular constriction. This procedure stops needless blood loss and restricts the growth of microorganisms after an injury. Salt and heat stage of wound treatment trend, which is one of its phases, is when immune cells migrating to the place of pain an attempt to stop microbial infection. Growth invoices and cytokines, including interleukin (IL)-1, IL-6, IL-17, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and transforming growth factor (TGF), also reactive oxygen species (ROS), are released during this phase. White blood cells travel to the wound locus via the bloodstream, where they absorb and break down microbiological pollutants. After starting the wound healing process, neutrophils, which have an anti-microbial function, reach the wound site first and stay there for 24 h. After an injury, the inflammatory phase usually lasts one to four days, preparing the wound for regeneration using necessary phagocytosis and debris elimination. Late-stage neutrophil apoptosis is caused by a change in macrophage phenotypes from pro- to anti-inflammatory. Initiating the proliferation phase, growth factors and cytokines generated during the inflammation phase draw in a variety of cells, such as fibroblasts, keratinocytes, endothelial cells, and stem/progenitor cells. Fibroblasts, endothelial cell proliferation, and wound re-epithelialization are the first steps in the reconstruction of skin tissue. To return the injured area's functional restoration to its pre-injury state, the remodeling phase entails producing different skin appendages and replacing granulation tissue with collagen type 1 synthesis. All these stages are frequently not completed by chronic wounds, which results in ongoing inflammation and sluggish wound healing. Assessing and treating chronic wounds requires a methodical approach. Surgical techniques, non-surgical therapies, and regimens based on pharmaceutical agents for the repair of skin wounds are examples of conventional wound management practices. Due to its effectiveness, surgical debridement is the gold standard in wound direction; however, it carries a higher risk of damaging surrounding tissues. Skin grafts are applied to wounds that have significantly lost tissue chronic wounds, and are divided into five categories: autografts, allografts, xenografts, gap-thickness skin links, and full-width skin links. The surgical gold standard for skin repair is autografts; however, there are certain drawbacks, including scarring, insufficient normal skin sites, and painful healing. In contrast to xenografts, which are obtained from other species and are connected to humans allografts offer donor peel that is immediately available for use as well as extended storage for future use. Medical pain bandages, local formulation, scaffold/hydrogel-Skin connections based on skin equivalents are examples of traditional non-surgical wound therapies. Gels, emulsions, doughs, creams, foams, lotions, and sprays are examples of positional formulations. Topical antibiotics are useful in preventing bacterial infections, but they should be stopped right away to

prevent allergic reactions and hypersensitivity. Collagenase and dexamphenol comprising ointments used to accelerate the healing process. Because of their beneficial effects are local formulations based on growth factors have been tested recently for wound redress. However, their limited bioavailability as a result of the wound site's quick clearance limits their use. New methods apply topically to the wound area growth factors that are enhanced in stability and bioavailability and are encapsulated in nanoparticles. To promote wound healing, wound dressings must be used to keep the surrounding air humid and have a high oxygen permeability. Wound dressings come in >3000 varieties, categorized into traditional, artificial, and biological products. Cotton bandage, human amniotic membrane, clear polymer film medical bandages, foam/sponge medical bandages, hydrocolloid medical bandages and polymer wound medical bandages are examples of popular and new step wound medical bandages, the following types of medical bandages are available: Alginic acid based medical bandages, hyaluronic acid based on chitosan and chitin, based on hydrogel, based on nanofibers, based on microbial cellulose, germicide, based on cells, etc. For >30 years, medical bandages based on polymer film have been used due to their high speed of vapor transfer, impermeability of bacteria and their capacity. Automatic scab removal. However, more development is required due to adhesiveness, the inability to absorb a large amount of ulcers and frequent discharges modifications.

3D printing possesses numerous advantages; yet, it also encounters obstacles and constraints. The advancement of optimal 3D printers necessitates cooperation among engineers, scientists, vendors, and pharmaceutical authorities. The obstacles encompass the standardization of printers and procedures, the use of safe materials and polymers, non-destructive analytical methods, regulatory considerations, and potential unintended outcomes. Regulatory challenges persist, as US FDA requirements for mass production and batch standardization are not readily applicable to 3D-printed individualized products. In 2017, the FDA released a technical guidance titled "Technical Considerations for Additive Manufactured Medical Devices," delineating parameters for quality control, including hardware, software, materials, patient-specific device design, operator training, quality control protocols, sterilization concerns, critical points for intermediate products, post-printing processes, and validation procedures (Di Prima et al., 2016).

Nonetheless, numerous inquiries persist, and further rules are anticipated imminently. It is imperative for regulatory authorities, pharmaceutical businesses, and academic researchers to proactively address these challenges and engage in discourse, facilitating the evolution of regulatory frameworks to encompass a broader range of 3D printing items in the market. Long-term stability assessments are essential for 3D-printed items(PDF10). Wound dressings such as 2nd Skin, Carrasyn, Clearsite, Elasto-Gel, FlexiGel, Transigel, Kendall Curafilm, Kendall Curagel, Normlgel, Hypergel, Nu-gel, Tegagel, and Vigilon possess FDA approval. These dressings create an optimal environment for wound healing and can be improved by integrating biomimetic components into printed products. Research indicates that biomimicry can enhance endogenous and foreign cells' adhesion, functionality, motility, and proliferation (Umur et al., 2023).

There are numerous FDA-approved film-based dressings on the market, with differing conformability, adhesiveness, and permeability. Due to their high absorption of wound secretions capacity, the ability to retain moisture and the ability to promote keratinocyte and fibroblast migration and increase, hydrogel-based moist wound dressings have drawn interest. These dressings work well on a variety of wound types and can now be purchased as injectable, self-healing, or hydrogels that release drugs, growth factors, or antibiotics for better wound healing. Bioengineered skin substitutes, which are composed of cells, growth factors, and biomaterials, imitate natural skin and promote skin regeneration by enclosing the wound area in a semi-permeable barrier. The capacity of skin substitutes to lower mortality and morbidity related to chronic wounds without requiring a follow-up surgical procedure is being investigated. There are three distinct classification of

skin substitutes, i.e. epidermis, dermal, and epidermal-dermal. AlloDerm, Transcyte, Integra, Dermagraft, and Matriderm are examples of epidermal replacements that are used to treat burns, chronic ulcers, and partial and full-thickness wounds. They fall short, though, in certain cases of skin injuries involving damage to both layers. More advanced cellular skin substitutes are required, which should resemble both the dermal and epidermal layers and supply growth factors, cytokines, and extracellular matrix elements to promote wound treatment of two commercial dermo-epidermal cellular equivalents for wound healing are called Aplikraft and OrCel. However, there are drawbacks to epidermal-dermal skin substitutes, including the possibility of tissue rejection and their high cost. Numerous cutting-edge techniques, including stem cell treatment, vacuum wound treatment, bioengineered skin equivalent, and the use of growth factor and cytokine therapy to promote sore healing are being investigated. Advancements in precision medicine and science have the capacity to improve the quality of sore healing (Kolimi et al., 2022).

For the clinical direction of infectious persistent sores, such as diabetic sores and foot wound, the development of multifunctional scaffolds for wound protection and healing is essential. Because of their physicochemical, drug release, and structurally tunable characteristics, hydrogels can significantly accelerate the recovery process. By combining mechanical, biological, and architectural engineering, hydrogels' healing properties can be further enhanced to create intricate biomimetic regenerative structures with a variety of biological functions. The characteristics of sore healing, as the preservation of an anti-fervor microsurroundings, the inhibition of oxidative stress, re-epithelialization, collagen establishing, and neovascularization, are enhanced by Bio-compatible bilayer scaffolds in which the skin structure is placed. Multifunctional strategies for effective healing acceleration are quickly emerging, combining structural engineering with multi-biological functionalizations using wound microenvironment regulators, regenerative biotherapeutics, and antimicrobial agent procedures. Multiple bioactives can be effectively integrated into a single biomaterial platform by 3D stamping technology, enabling the manufacture of three-dimensional multilayered structures by various structural and biological properties (Metwally et al., 2024).

Binder jetting, powder bed fusion, fused deposition modeling, and vat polymerization are some of the technologies used in 3D printing, which is one layer after another method of producing 3D objects. These technologies are the result of development across multiple industries, such as biomedical and pharmaceutical. These technologies were initially expensive and of poor quality, but they have since advanced with the introduction of precise, fast, and affordable 3D printers. The precise deposition of cell-laden biomaterials on a build platform is made possible by bioprinting, a combination of 3D additive manufacturing processing and cell biology. Bioprinting uses a variety of materials, including proteins, polymers, and extracellular matrix, to support cell viability and proliferation. Complex structures like vascular networks, bone or nerve transplant, cartilage, heart stains, and skin tissue have all been treated with it in regenerative medicine (Tabriz & Douroumis, 2022). Researchers from all over the world have been paying close attention to 3D printing technology, particularly in the health fields of health and medicine. 3D printing technology is becoming more popular every day, especially for biomedical uses including drug delivery, tissue engineering, implants, biosensing, immunotherapy, and medical devices (S et al., 2023). Innovative technologies like bioprinting and 3D printing are gaining interest from academia and industry due to their capacity uses in a diversity of sectors, as pharmaceutical delivery of drugs and regenerative medicine. Extrusion printing, laser printing, and droplet printing are examples of modern 3D printing methods that can be used to quickly and accurately fabricate pre-designed structures out of both natural and synthetic polymers (Intini et al., 2018).

The popularity of additive production, as well known as 3-D printing, has increased recently because of its high accuracy and speed of prototyping. The technology started in the late 1980s with the Rapid

Prototyping (RP) method, which made it possible to produce industrial goods quickly and precisely. In addition, it gives designers creative freedom and enables them to create tangible sculptures from sketches on paper. Compared to conventional production that only allows printing multiple parts individually without the need for tooling, printing a few parts into a single object can lower the cost of production. Manufacturing businesses profit from this since it reduces expenses and increases revenue. Complex geometries can also be printed by 3-D printing technologies, enabling producers to create a variety of industrial products like molds and other hard tooling items. Numerous industries, including the automotive, architectural, healthcare, entertainment, and goods sectors, frequently use this technology. For instance, stronger build-ins can be achieved through the printing spare parts with advanced mechanical features using nanomaterials or composites, boosting safety in space missions and auto racing. In the medical field, patients benefit from more comfortable and well-fitting teeth that are 3-D printed specifically for them. However, the fragility of the printed parts is the main disadvantage of manufacturing goods using 3D printing (Clarissa et al., 2022).

## 10. Types of 3-D printer

### 10.1. 3D printing based on extrusion

Extrusion-based 3D printing is a type of molten sediment where a heating chamber is used to melt hydrogel ink into a molten structure. A fine hydrogel structure for 3D printing is formed when hydrogel ink is extruded the lifting worktable and snout. Less resistance during printing, an unaltered shape after extrusion, strong structural integrity, and biocompatibility are among the prerequisites for the process. The mechanical qualities of this method are improved in terms of hardness, flexibility, and resistance to compression. Extrusion-based gradient, micro-extrusion, and the use of a static mixer are examples of innovative techniques. In contrast to traditional extrusion technology, which prints the ink on a frozen platform that has solidified, micro-extrusion uses a drive unit that has integrated computer software to print the hydrogel ink. Utilizing gradient technology based on extrusion, composite materials can be 3D printed, and scaffolds made of bionic materials.

### 10.2. Light and photopolymerization-based on three-dimensional printing

Extrusion-based 3D printing technology is not suitable for high-resolution hydrogel production due to its low resolution. Optical Projection Lithography (HLP), Single Laser Ablation (SLA), and Digital Light Processing (DLP) are three light and photopolymerization 3D printing techniques that have been developed to address this. HLP uses optical projection lithography to customize double-network hydrogels, while DLP uses digital light source irradiation to form 3D structures. While SLA cures hydrogel ink with a laser beam of 355 nm, HLP is capable of reading complex, multiscale, and multi-material 3D printing hydrogels. Excellent electrochemical performance and capacity neural field applications have been demonstrated by SLA. UV light does not penetrate photons very well, so researchers are currently looking into initiators and polymerization uses light to create an acceptable position for polymerization.

### 10.3. Inkjet-based 3D printing

By printing the hydrogel precursor onto the crosslinking agent or substrate, inkjet 3D printing technology enables precise control, customization, and miniaturization of patterned droplets. There are three types of inkjet printing currently available: Ink jet bath, ink jet gel and ink jet spray. However, multicomponent inks are usually used to a limited extent due to their printable viscosity. One example is micro-reaction inkjet printing (MRIJR), which uses a print head, construction platform, and cartridge of liquid binder. In order to formulate low-

viscosity hydrogels and print non-uniform 3D structures, MRIJR may print alginate salt hydrogel microstructures, preventing wetting of the substrate and deposition of hydrogels without reactive matrix.

#### 10.4. DIW technology

When creating 3D hydrogel, DIW technology is applied to hydrogel precursor solutions made of both synthetic and natural polymers. A translation platform with three axes, an optical microscope, a compressed air supply device and a cylindrical nozzle are used in the procedure. The fibers created by the ink are subsequently printed onto the movable XY-axis platform. Advantages of DIW technology include its suitability for intricate 3D structures, its ability to print non-linear patterns, its low frequency of nozzle changes, and its availability of multiple printing modes. A capacity material for intelligent machines and tissue engineering, Jiang et al. used DIW technology to prepare a 3D hydrogel printer with very high resistance with excellent mechanical characteristics and a variety of shapes (Liu et al., 2021).

### 11. The exceptional physical and chemical characteristics of 3D printed hydrogel

Superior chemical and physical properties are provided by 3D printing hydrogel in comparison to traditional and intelligent hydrogel. It is appropriate for creating controlled release systems in a variety of industries due to its swelling characteristics, self-healing capacity, superior electrical guidance, gel network structure with high strength, resistance, endurance and high flexibility. In phosphate buffer solution, the swelling capacity of 3D printed hydrogel can last for up to 28 days, which makes it appropriate for controlled release systems in a variety of applications. Furthermore, conductive hydrogel (CPH) has improved electrical conductivity, with a conductivity of  $1.2 \text{ S} (\text{cm}^2)$  and a tensile strength that is almost 8 MPa. CPHs are appropriate for sensor applications because they can heal well on their own and resist changes in external pressure. Apart from its capacity to swell and mend itself, 3D printing Hydrogel is extremely tough, which makes it difficult for it to break or deform. Hydrogel for 3D printing was created using PVA and chitosan; it had a toughness of up to  $9.92 \pm 1.05 \text{ kJ m}^{-2}$  and a tensile strength  $12.71 \pm 1.32 \text{ MPa}$  under strain  $302.27 \pm 15.70 \%$ . In addition, 3D hydrogel printing is unique. High frost resistance, excellent electrical conductivity, and the capacity to tolerate very low temperatures. It is reasonably safe to use due to its good extensibility, tensile stability, stretchability of up to 2500 %, and low working voltage. It is challenging to obtain these qualities in both intelligent and conventional hydrogel. Hydrogel 3D printing is therefore being studied and applied in a variety of fields (Liu et al., 2021).

#### 11.1. Base materials in 3D printing

##### 1) Polymer/plastics

Prototypes and consumer goods are frequently made using thermoplastics in 3-D printing. However, because of biocompatibility, the selection of polymers used in 3-D printing for tissue engineering is essential. Synthetic polymers like poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(glycolic acid) (PGA) are better for supporting tissues Compared to natural polymers including collagen and polysaccharides because they are stronger mechanically and break down more quickly. Because of their advantageous qualities, bioceramic materials such as hydroxyapatite (HA) and beta-tricalcium phosphate ( $\beta$ -TCP) are frequently utilized in 3-D printing, especially in bone tissue engineering. However, there is a reason of their low elasticity, fractures, and high stiffness, they can be challenging to use. Although metal-based polymers, like titanium alloy, can be non-biodegradable, they are beneficial for replacing lost bone possibly poisonous as a result of wear. For medical applications,

biocomposites which combine materials of various sizes - Can be used to make great scaffolding.

##### 2) Metals

Because of their strength and thermal characteristics, metals are frequently used in 3-D printing. This makes them perfect for creating objects that can withstand loads, like parts for cars and aircraft. Cobalt chrome metal is beneficial for high-stress tolerance engine parts because it increases tensile strength. With titanium, maraging steel, cobalt-chrome, tungsten, and nickel having high tensile strengths above 1000 MPa, most metals are used for functional purposes. Aluminum's low density and low cost make it a widely used material. Although titanium is more costly, it is low-density and twice as strong. Due to its ability to dampen vibrations, tungsten metal is perfect for use in the manufacturing of blades, ballast weight, and missile parts.

##### 3) Ceramics

Ceramics are ideal for a variety of applications because of their exceptional qualities, which include Low density, resistance, high electrical insulating ability, corrosion resistance, chemical stability and dimensional stability. Due to their high cost and lengthy processing times, traditional methods such as gel casting and molding have drawbacks. They also have trouble creating complex geometries and structures with linked holes. Moreover, the extreme hardness and brittleness of ceramic components make machining them challenging. Slurry-based and powder-based techniques can take the place of 3-D printing technology to solve these problems. Whereas powder-based feedstock makes use of powder beds containing loose ceramic particles, slurry-based feedstock employs inks. In ceramic 3D printers, green parts are produced through a series of processes that result in stronger ceramic end products. The ceramic prototype's bending strength greatly increases from 17 MPa for the initial prototype and 220 MPa for the final one (Okay, 2010).

### 12. Fabrication parameters

Hydrogen is a cross-linking material that can absorb a lot of water without dissolving. Their intelligence, softness, and capacity to hold water make them special. Hydrophilic functional groups attached to the polymer backbone give the material its capacity to absorb the water, while the cross-links between network chains give it resistance to dissolution. Due to the hydrogel's special characteristics, which prevent it from being entirely solid or liquid, intriguing relaxation behaviors result that aren't seen in either pure state. When exposed to Hydrogels have sudden changes in volume compared to external stimuli such as temperature, solvent quality, pH and electric field. At the critical stimulus level, these changes may be continuous or discontinuous. At a critical stimulus level, these changes can happen in a continuous or discontinuous manner. Over the past three decades, hydrogels' volume transition behaviors have drawn a lot of attention (Okay, 2010).

#### 12.1. Swelling properties

In solvent systems, the swelling mechanism of hydrogels keeps their three-dimensional structure intact. The presence of dissociated sodium carboxylate groups and hydrophilic groups, which raise osmotic pressure, affects the swelling behavior. Through the expansion of polymer coils, repulsion between negative charges favorably influences swelling. Infinite swelling is prevented by crosslinked polymers; swelling characteristics are influenced by network density, solvent type, and polymer-solvent interaction parameters. Using Gibbs free energy to describe the process, the equilibrium swelling theory and the Flory-Rehner theory aid in the explanation of swelling properties. The pH, temperature, electrical signal, enzyme content, and other ion types are examples of environmental variables that can alter and affect the physical texture of hydrogels. These alterations could manifest at the largest scale as the development of silt, alterations in size, and hydrogels' water content.

The hydrogel's volume changes as a result of variations in the solvent's pH and the concentration of mobile ions in the inner and outer regions of the gel relative to the external solution (osmotic pressure). The swelling profile and, consequently, the volume change are revealed by the functional groups' degree of ionization.

### 12.2. Mechanical properties

The physical properties of a material are essential for bioinks in 4D bioprinting, as they maintain their rigidity and avert collapse during and after the bioprinting process. A 4D bioprinted structure exhibiting robust mechanical strength and structural stability. At the moment, most of the shape-morphing hydrogels used are natural hydrogels that aren't very strong, which makes it harder to print stable structures that have the desired structural anisotropy. Although research indicates that basic self-bended and cell-laden hydrogel structures can maintain stability for several days in vitro, the structural integrity of 4D bioprinted constructs continues to encounter significant challenges, including loose or leaky tubular formations and fissures in the tubule walls, which are detrimental to vascular regeneration. Research indicates that the bending degree of self-folded scaffolds varies over time during in vitro incubation as a result of degradation and fluctuating swelling ratios. Cell-laden 4D constructs, especially micro-constructs, may undergo cell contraction forces during incubation, resulting in unintended deformation of shape-morphing constructs (Lai et al., 2024).

Smart biomaterials must possess adequate mechanical strength to resist deformation induced by cellular contraction forces. Implanted constructs must possess mechanical properties akin to those of native tissues to prevent mechanical discrepancies or transplant defeat. Bioprinted structures should possess adequate mechanical strength to facilitate cell growth and function until the cells can produce sufficient extracellular matrix to sustain themselves. This is especially important during the initial phase of tissue regeneration, when cells are not producing enough new extracellular matrix (Ding et al., 2023).

Biological applications constrain chitosan hydrogels due to their low mechanical strength and quick breakdown. Research indicates that their mechanical characteristics can be substantially improved via chemical modification methods, and their amalgamation with different polymers renders them optimal for wound healing (pdf14). Keihan et al. produced CTT-CS hydrogel and incorporated SF solution and Mg(OH)<sub>2</sub> nanoparticles to augment its mechanical strength. The CTT-CS hydrogel scaffold recorded a compressive strength of 65.42 kPa, while the SF scaffold demonstrated a superior compressive strength of 151.73 kPa. The compressive strength went up by >3.5 times (248.81 kPa) when SF was added and mixed with the CTT-CS hydrogel scaffold. When Mg(OH)<sub>2</sub> nanoparticles were added to the CTT-CS/SF hydrogel scaffold, the compressive strength went up by >2.5 times, to 649.56 kPa. This is because the nanoparticles and the hydrogel matrix formed hydrogen bonds. Adding SF and Mg(OH)<sub>2</sub> nanoparticles to the CTT-CS hydrogel makes it stronger against compression, which makes it suitable for medical uses like wound healing (Eivazzadeh-Keihan et al., 2021).

The most effective method for understanding Rubber application is one of the mechanical properties of hydrogels elastic theory, which links key bulk properties like crosslinking density, temperature, and rubbery modulus scales. However, the original rubber theory needs to be modified because it falls short of explaining hydrogels in aqueous media. The rubber elastic theory, which explains hydrogel structure in solvents, was developed by Peppas et al. (2000).  $\tau$ ,  $\rho$ , R, T, Mc, Mn,  $\alpha$ , extension ratio, and the average molecular weights with and without crosslinks,  $v^2$ , s and  $v^2$ , r, are all included in the theory.

### 12.3. Biomedical applications

Hydrogels are one of the most popular classes of polymers useful in the biomedical industry. With their biocompatible nature and resemblance to living tissue, hydrogels have a variety of properties that make

them suitable for a wide range of biomedical applications. These include tissue engineering, sore dressings, delivery of drugs and release systems, and more.

### 12.4. Drug delivery

Since hydrogels are biocompatible and mimic living tissue, they are a common class of polymers used in biomedical fields. They find application in Tissue engineering, wound medical bandages and drug delivery devices. For an accurate and intended demonstration, target drug release is essential. Whereas chitosan-based hydrogels work better in lower pH environments, CB hydrogels enable the intended drug delivery in neutral media. pH, temperature, and chemical species determine whether to use hydrogels based on chitosan or pure cellulose. Chitosan/pectin hydrogels' muco-stickiness properties and enzyme-affiliated analysis allow for Delivery of special colon. They provide target medicine carriers, encapsulate drugs, and prolong release time without requiring invasive surgeries. Hydrogels based on cellulose have enormous capacity for developing new technologies for the early diagnosis and treatment of illness. Liposomes, polymeric micelles, lipid-based micelles, and other nanoparticles, Applications for dendrimers, carbon nanomaterials, inorganic and metallic nanoparticles, and drug delivery to a specific place, biosensors, and contrast agents for medical imaging are numerous (Kabir et al., 2018).

### 12.5. Inhomogeneity of hydrogels

Hydrogels lose optical strength and clarity due to spatial gel inhomogeneity, or an uneven cross-link density distribution. This inhomogeneity can be observed using Scattering techniques such as light scattering, low-angle X-ray scattering, and low-angle neutron scattering. It is closely related to the spatial focus fluctuations. Due to network imperfections, the spatial heterogeneity is promoted by gel crosslink density whereas falling with ionization degree due to electrostatic repulsion, the Donnan capacity, and mobile counter ions. The scattering intensities are also influenced by the gels' degree of swelling. The intensity of the dispersion strongly depends on the concentration of the initial monomer used in the gel preparation process; The highest amount of scattering intensity occurs in the concentration of the thick polymer network. The inhomogeneity in PAAm gels is determined by the interaction of these opposing effects, Maximum output inhomogeneity of the gel at critical concentration of monomers.

### 12.6. Hydrogels with improved properties

Good mechanical performance hydrogels are essential for many applications involving soft materials. The Mechanical characteristics of hydrogels have been enhanced through the development of techniques like double network gels and topological gels. One method for producing nanocomposite hydrogels is the Spreading layered silicates or clays at the nanoscale in polymer networks. Synthetic hectorite clay, laponite, has a diameter of approximately 25 nm, a thickness of 1 nm, and the negative surface charge density stabilizes the distribution in water. In many applications, hydrogels' quick reaction to outside stimuli is also crucial. Nonetheless, the hydrogel volume change kinetics entail the diffusive process of the polymer network absorbing or desorbing the solvent. Increasing hydrogels' response rate has been a difficulty over the previous 25 years. Gels with dangling chains, macroporous gels, and submicrometer-sized gel particles are among the techniques to boost the response rate. Free-radical cross-linking copolymerization of the Monomer-crosslinked combination with an inert substance (diluents) yields macroporous hydrogels. Mapping the pore structure of cross-linked materials is of interest influenced by the inert diluent, which also serves as a pore-forming agent. Another method for creating hydrogels is to use inert templates, which can give the finished hydrogel matrix a macroporous structure.

### 12.7. Biocompatibility properties

The capacity of a material to elicit a suitable host response in a particular application is known as biocompatibility. A material is considered biocompatible if it is compatible with the body in terms of chemistry, biology, and mechanics. The interaction between materials and the host body's environment is known as biocompatibility. The value of biocompatible materials is widely acknowledged in the modern day, and a wide range of applications for these materials have been established. Patients now have longer life expectancies and better quality of life thanks to these drugs. Hydrogels are a class of materials that find extensive application because of their special qualities in the areas of drug release and biocompatibility.

## 13. Essential parameters for wound dressings

### 13.1. Categorization of hydrogel goods

The hydrogel products can be categorized according to several factors, as follows:

### 13.2. Arrangement according to the source

Hydrogels can be split into two categories according to whether they are synthetic or natural.

### 13.3. Classification based on the makeup of polymers

The preparation process leads to the formation of several significant hydrogel classes. Examples of these include the following:

- (a)

A polymer network derived from a single type of monomer - the main structural component of any polymer network—is referred to as a homopolymeric hydrogel. The cross-linked skeleton of homopolymers can be attributed to the type of monomer and the method used during polymerization.

- (b)

Copolymeric hydrogels consist of two or more distinct monomer species that have at least one water-soluble component. These monomer species are arranged randomly, in blocks, or an alternating pattern along the polymer network's chain.

- (c)

Several polymers an essential class of hydrogels known as interpenetrating polymeric hydrogel (IPN) is composed of two separate, network-formed, independently Synthetic and/or natural cross-linked polymer components. Cross-linked and non-cross-linked polymers constitute the two components of semi-IPN hydrogel.

### 13.4. Categorization according to configuration

Hydrogels can be categorized in the following ways based on their chemical makeup and physical structure:

- (a)

Amorphous, or lacking crystals.

- (b)

A complicated blend of crystalline and amorphous phases is known as semicrystalline.

- (c)

Crystalline.

### 13.5. Categorization according to cross-linking type

Depending on whether the cross-link junctions are chemical or physical, hydrogels can be classified into two groups. Permanent

junctions are found in cross-linked chemical networks, while the junctions are transient found in physical networks due to physical reactions such as hydrogen bonds, ionic compounds, hydrophobic compounds, or polymer chain entanglements.

### 13.6. Classification based on physical appearance

The way hydrogels appear as a matrix, film, or microsphere is dependent on the polymerization technique used during the preparation phase.

### 13.7. Arrangement based on network electrical charge

Based on whether the cross-linked chains of hydrogels have an electrical charge or not, these gels can be divided into four groups:

- (a)  
Neutral and nonionic.
- (b)  
Ionic, which can be either cationic or anionic.
- (c)  
Amphoteric electrolyte, also known as ampholytic, has both basic and acidic groups.
- (d)  
Polybetaines are zwitterionic, meaning that each structural repeating unit contains both cationic and anionic groups.

Natural polymers that form hydrogels include polysaccharides like starch, alginate, and agarose, as well as proteins like collagen and gelatine. Chemical polymerization techniques are typically used to prepare synthetic polymers that result in hydrogels.

Product made of hydrogel that is environment-sensitive.

Hydrogels are three-dimensional networks of cross-linked hydrophilic polymers swell and contract reversibly in water while holding a significant amount of liquid in the swollen state. When the external environmental conditions change, hydrogels can be engineered to respond in a controlled way by either contracting or expanding.

A wide range of physical and chemical stimuli such as temperature, light and temperature, pressure, electrical or magnetic fields, and sound, as well as solvent composition, ionic strength, and molecular species, can cause them to undergo dramatic volume transitions.

A phenomenon known as volume or phase decay transition may occur when the hydrogel experiences Such inflation or deflation in response to changes in its external environment. Over the past forty years, synthetic hydrogels have been the subject of much research, and this field is still very active today (Ahmed, 2015).

## 14. Hydrogel 4D printing

Personalized medicine or medical care adapted to each patient's needs, has gained a lot of attention in the US thanks to the Precision Medicine Initiative. One of the possible approaches for personalized medicine is 3D printing, which makes use of materials that can change in response to stimulation. Recent research has looked into the possibility of using 3D and 4D printing in conjunction with medicines, which could result in the creation of individualized delivery of medication systems and formulations. Spritam®, the first medication to be 3D printed, is currently available in pharmacies. Personalized medicine has emerged as a result of the field of diagnostics, and it considers individual differences in the course and effects of disease. The US National Institutes of Health's Precision Medicine Initiative, launched in 2015, emphasized its importance. Of personalized medicine even more. However, there are difficulties in producing personalized medications, such as how to routinely make them and customize them to each patient's needs. Charles Hull originally described 3D and 4D printing technologies in 1986, and they may aid in the advancement of personalized medicine.

Because of its extreme flexibility, 3D printing may be the perfect tool for creating drug delivery systems that can be customized to deliver personalized medications. For instance, it would be simple and regular to print pills and tablets with different therapeutic agents and customized dosages. Articles with this term are still based on the trend of research articles published in the field of 4D and 3D printing drug delivery. However, in the previous ten years, only sixteen research papers on the subject have been published, implying that this area will develop soon (Jacob et al., 2020).

While many techniques have been developed over the past 20 years, their low throughput when compared to traditional medicine fabrication methods remains a limitation for many of them. Limitations associated with biomaterials include the possibility that drug formulations within the material may not be optimal at high temperatures. Innovative biomaterials, like those derived from collagen or fibrin, exhibit excellent biocompatibility and minimal immunogenicity, capacity helping to develop implantable drug delivery systems. By adding a fourth dimension, 4D printing enables the transformation of virtual data into real objects such as organs, tissues and cells. High sensitivity, selectivity, controlled drug release, clinical safety, drug and biomaterial effectiveness, and real-time control over response to 4D stimuli are some areas where 4D bioprinting still has room to improve. Reformable hydrogels that can adapt and transform form in response to outside stimuli and may find use in medicine. Overall, the fields of drug delivery are opened up by 3D and 4D bioprinting, but commercialization and clinical application of these technologies still have a ways to go.

A promising method for producing customized biomedical devices with exact forms and delicate structures is 3D printing. A promising biomaterial, Self-healing hydrogel based on chitosan has the ability of injection, biocompatibility and controlled mobility. Li et al., a self-healing hydrogel based on oxidized chondroitin sulfate hydroxy-butyl chitosan that was loaded with mesenchymal stem cells and demonstrated excellent capacity for cartilage tissue engineering. For self-healing hydrogels used in 3D printing, stable rheological properties and cross-linking are very important after printing. Using DF-PEG and phenol-functionalized chitosan (Chi-pH) crosslinked by visible light, Liu et al. developed a self-healing hydrogel. After undergoing intense shaking, the hydrogel was printed in modular form as a three-dimensional structure, and blue light was then applied to reinforce it. A more complex lattice structure was printed using 3D bioprinting, and the filled cell demonstrated a high rate of survival. For 3D bioprinting, however, more work needs to be done on the self-healing hydrogel's biostability and printing resolution. Medical soft robots, which require biocompatibility and biodegradability, can be created through the 4D printing of hydrogels with chitosan as the basis for self-healing capabilities. Jang et al. used a 3D printer and ink made of a biocompatible and biodegradable chitosan hydrogel to create a 4D printed untethered milli-gripper. Superparamagnetic iron oxide nanoparticles (SPIONs) coated in citric acid were added to this ink to enable the milli-gripper to change shape after printing. Under the influence of the magnetic field, the untethered milli-gripper can move cargo to the desired location while being driven by the electric field. Solvent triggers can also modify the shape of hydrogels based on chitosan that self-heal after 3D printing demonstrating promise as a medical robot (Willemen et al., 2022).

Minzimo Song et al. examined how modified chitosan linked amorphous regions in PLA/PCL blends to toughen and compatibilize them: This study correctioned modified chitosan (mCS) which can crosslink the amorphous phase of PLA and PCL, thereby toughening and compatibilizing the PLA/PCL blends. This was demonstrated by 4D printing and shape retention procedures. Under thermal stimulation, the 4D printed mCS/PLA/PCL model exhibited reined shape retention behavior. The following qualities of PLA/PCL blends can be improved by adding mCS: 1) the hydrophilic PLA/PCL blend, which may be biodegradable in the environment, replaced the hydrophobic blend after the addition of mCS. 2) By adding  $\geq 0.5$  g of mCS to 10 g PLA/PCL blends, the blends may acquire two T<sub>g</sub> and T<sub>m</sub>, which would enable them to be

printed in four dimensions and retain their shape under heat. (3) By serving as a bridge between PLA and PCL in mCS/PLA/PCL blends, the mCS has significantly increased Interaction force in shape stabilization and deformation during shape memory of mixtures. These findings demonstrated that, at 60 °C and 90 °C, respectively, mCS/PLA/PCL spring models may be 4D printed rapidly and effectively transformed autonomously between their original and temporary shapes. Applications such as aerospace, smart manufacturing, bionic Parts, activated robotics, and others find mCS/PLA/PCL 4D printing materials promising because of their unique toughness, water-soluble, degradability, and shape memory functionality (George et al., 2020).

#### 14.1. Time-Dependent changes in shape and properties of 4D printed structures for improved wound healing

4D printing technology, which integrates 3D printing with intelligent materials capable of time-dependent shape modifications, has emerged as a game-changer across various industrial sectors. This innovative approach enables the creation of structures that can adapt and transform over time, offering enhanced flexibility and versatility in design. By combining 4D printing with bioprinting technologies, a new frontier in tissue engineering and wound healing is being unlocked, paving the way for groundbreaking advancements in regenerative medicine. The advent of 4D printing technology has introduced a dynamic dimension to tissue engineering, particularly in the development of wound healing solutions. Unlike traditional 3D printing, which produces static structures, 4D printing incorporates time as a fourth dimension, allowing printed materials to undergo shape changes in response to external stimuli such as temperature, pH, or moisture levels. This capability can significantly enhance the functionality of wound dressings and scaffolds. One of the primary advantages of 4D printed structures is their ability to conform to the dynamic architecture of human tissues. These structures can react to specific physiological conditions, facilitating intelligent tissue restoration by mimicking the natural behavior of skin during the healing process3. For instance, when exposed to changes in temperature or moisture, 4D printed hydrogels can expand or contract, adapting to the wound environment and promoting better integration with surrounding tissues. Moreover, the time-dependent deformation of 4D printed materials can influence cell behavior, including adhesion, proliferation, and differentiation. By modulating these cellular responses, 4D printed scaffolds can enhance tissue regeneration and improve the overall healing process3. The ability to create scaffolds that dynamically change their properties over time allows for a more tailored approach to wound care, addressing the specific needs of each patient and the unique characteristics of their wounds. Additionally, the integration of bioactive compounds into 4D printed chitosan-based materials can facilitate controlled drug delivery at the wound site. This controlled release of therapeutic agents can further accelerate healing by providing localized treatment, reducing inflammation, and preventing infection. In the realm of tissue engineering, bioprinting technologies have made significant strides in creating biomimetic constructs with strong bioactivity and biocompatibility. The key to success in bioprinting lies in selecting optimal bio-inks that exhibit high printability while maintaining essential biological properties. Among the array of materials gaining popularity in bioprinting, chitosan has emerged as a frontrunner due to its compatibility with biological systems and favorable characteristics. The synergy between 4D printing and bioprinting technologies presents exciting opportunities for optimizing wound healing processes. Dynamic wound dressings created through 4D printing can adapt their shape or functionality in response to changing wound conditions, providing tailored and optimal healing environments. Additionally, 4D printed scaffolds for tissue engineering applications can undergo controlled shape transformations and release bioactive factors over time, eliciting targeted cellular responses to accelerate tissue repair. Through the integration of chitosan and other innovative materials in bioprinting processes, the field of regenerative medicine is witnessing a paradigm

shift, with the potential to create intricate and biologically relevant structures that mimic natural tissues with precision. Leveraging the temporal dimension of 4D printing and the bioactive properties of chitosan, healthcare professionals can develop personalized interventions for wound healing that promote faster recovery, reduced scarring, and improved patient outcomes. This convergence of technologies is poised to revolutionize wound care, offering transformative solutions for complex medical challenges and ushering in a new era of regenerative medicine. In conclusion, the incorporation of time-dependent changes in shape and properties through 4D printing presents a promising avenue for improving wound healing applications. By leveraging the dynamic capabilities of 4D printed structures, healthcare providers can develop more effective and personalized wound care solutions that enhance tissue regeneration and improve patient outcomes. However, further research is needed to optimize these technologies for clinical use and address challenges related to scalability and regulatory approval (Nguyen et al., 2023; Aldawood, 2023).

#### *14.2. Mechanisms and practical applications of 4D printing compared to traditional 3D printing*

##### *14.2.1. Understanding 4D printing mechanisms*

###### *14.2.1.1. Definition and overview of 4D printing.*

- **Mechanism Advantage Explanation:** 4D printing introduces the concept of time as a fourth dimension, allowing printed objects to change shape or function in response to environmental stimuli. This dynamic capability surpasses traditional 3D printing by enabling the creation of structures that can self-assemble, adapt, or repair themselves, thus offering significant advantages in practical applications such as healthcare, aerospace, and consumer products where adaptability and functionality are crucial.

###### *14.2.1.2. Key differences between 3D and 4D printing.*

- **Pros:** Enhanced adaptability, allows for self-assembly, dynamic responses to stimuli, potential for complex repairs, innovative applications in various fields, improved functionality over time
- **Cons:** Higher complexity in design, increased material costs, longer production times, limited current technology, requires advanced understanding, potential for unpredictable outcomes

###### *14.2.1.3. Computational folding in 4D printing.*

- **Dynamic Shape Transformation:** Computational folding techniques enable 4D printed objects to change their shape in response to environmental factors, enhancing their functionality and adaptability compared to static 3D printed items.
- **Algorithmic Design Integration:** The use of advanced algorithms in computational folding allows for precise control over the folding patterns, leading to innovative designs that can perform complex tasks or adapt to various conditions.
- **Real-World Applications:** Practical applications of computational folding in 4D printing include self-repairing materials, deployable structures in aerospace, and responsive medical devices that adjust to patient needs, showcasing the technology's transformative potential.

###### *14.2.1.4. The role of smart materials in 4D printing.*

- **Smart Material Characteristics:** Smart materials possess the ability to respond to external stimuli such as temperature, light, or moisture,

enabling 4D printed objects to change their shape or function dynamically, which is a significant advancement over traditional 3D printing methods.

- **Applications in Various Fields:** The integration of smart materials in 4D printing facilitates innovative applications across sectors like healthcare, where implants can adapt to body conditions, and aerospace, where components can adjust to environmental changes for improved performance.
- **Future Research Directions:** Ongoing research into the development of new smart materials and their properties is crucial for enhancing the capabilities of 4D printing, potentially leading to breakthroughs in self-repairing structures and multifunctional products that can revolutionize manufacturing processes.

##### *14.2.2. Advantages of 4D printing over traditional 3D printing*

###### *14.2.2.1. Ability to create larger objects as single components.*

- **Single Component Creation:** 4D printing enables the fabrication of larger objects as cohesive units, eliminating the need for assembly of multiple parts, which enhances structural integrity and reduces production time, thereby streamlining manufacturing processes in various industries.

###### *14.2.2.2. Dynamic structures and self-assembly capabilities.*

- **Self-Assembly Mechanisms:** 4D printing utilizes smart materials that can autonomously reconfigure in response to environmental stimuli, allowing for the creation of dynamic structures that can adapt their shape and function without manual intervention.
- **Practical Applications:** The ability to self-assemble opens new avenues in fields such as robotics, where components can form complex structures on demand, and in healthcare, where implants can adjust to physiological changes for improved patient outcomes.
- **Advantages Over Traditional Methods:** Unlike traditional 3D printing, which produces static objects, 4D printing's dynamic capabilities enable the development of systems that can repair themselves or change functionality, significantly enhancing the utility and lifespan of printed products.

###### *14.2.2.3. Enhanced flexibility and adaptability of printed objects.*

- **Dynamic Response Mechanism:** The mechanism of 4D printing allows printed objects to respond dynamically to environmental changes, such as temperature or moisture, thereby enhancing their flexibility and adaptability compared to traditional 3D printed items, which remain static and unresponsive.

###### *14.2.2.4. Potential for complex deformations and repairs.*

- **Mechanism for Repairs:** 4D printing enables the creation of materials that can undergo complex deformations and self-repair, utilizing smart materials that respond to environmental stimuli, thus providing significant advantages in practical applications such as infrastructure maintenance and medical devices.

##### *14.2.3. Practical applications of 4D printing*

###### *14.2.3.1. 4D printing for skin wound repair.*

- **Mechanism of Advantage:** 4D printing offers a significant advantage over traditional 3D printing by utilizing smart materials that can respond dynamically to environmental changes, such as moisture and temperature, which enhances the healing process of skin wounds through adaptive wound dressings.

- **Practical Applications:** The practical applications of 4D printing in skin wound repair include the development of self-adjusting dressings that promote optimal healing conditions, reduce infection risks, and provide real-time monitoring of wound status, ultimately improving patient outcomes and recovery times.

#### 14.2.3.2. Case studies and research findings.

- **Dynamic Response Mechanism:** Recent studies highlight the effectiveness of 4D printed wound dressings that adapt to moisture levels and temperature changes, significantly improving healing rates compared to traditional methods.
- **Real-World Applications:** Case studies demonstrate successful implementations of 4D printing in clinical settings, showcasing its potential to create personalized wound care solutions that enhance patient recovery and reduce complications.

#### 14.2.3.3. Future potential in medical applications.

- **Advancements in Smart Materials:** Continued research into smart materials will enhance the capabilities of 4D printing, allowing for the development of more sophisticated medical applications that can respond to a wider range of physiological conditions and improve patient care.
- **Integration with Bioprinting:** The combination of 4D printing with bioprinting technologies holds promise for creating complex tissue structures that can adapt and grow, potentially revolutionizing regenerative medicine and organ transplantation.
- **Personalized Medicine Solutions:** The future of 4D printing in healthcare lies in its ability to create customized medical devices and treatments tailored to individual patient needs, leading to improved outcomes and more efficient healthcare delivery.

#### 14.2.3.4. Integration with other technologies.

- **Synergistic Advancements:** The integration of 4D printing with technologies such as IoT and AI can enhance the functionality of adaptive wound dressings by enabling real-time monitoring and data analysis, allowing for personalized treatment plans that respond dynamically to patient needs and environmental conditions, ultimately improving healing outcomes and patient care efficiency.

#### 14.2.4. Future directions and challenges in 4D printing

##### 14.2.4.1. Research and development trends in 4D printing.

- **Need for Mechanism Clarity:** Recent studies highlight the necessity to elucidate the mechanisms that enable 4D printing to outperform traditional 3D printing, particularly in practical applications. Understanding these mechanisms is crucial for advancing the technology and maximizing its potential across various industries.
- **Focus on Practical Applications:** Emphasizing practical applications of 4D printing can drive research efforts, as industries seek innovative solutions. This focus will facilitate the development of

adaptive materials and structures that respond dynamically to environmental changes, enhancing functionality in fields such as healthcare, aerospace, and consumer products.

##### 14.2.4.2. Overcoming technical and material limitations.

- **Understanding Mechanisms:** A comprehensive understanding of the mechanisms behind 4D printing is essential to leverage its advantages over traditional 3D printing, particularly in creating adaptable and responsive structures for practical applications.
- **Material Innovations:** The development of advanced smart materials is crucial for overcoming current limitations in 4D printing, enabling the production of objects that can dynamically change shape and function in response to environmental stimuli.
- **Practical Application Focus:** Emphasizing practical applications in various industries will help clarify the benefits of 4D printing, guiding research towards solutions that address technical challenges and enhance material performance for real-world use.

##### 14.2.4.3. The role of industry collaboration in advancing 4D printing.

- **Enhancing Research Through Partnerships:** Collaborative efforts between academia and industry can accelerate the understanding of 4D printing mechanisms, facilitating the development of innovative applications. By pooling resources and expertise, stakeholders can address technical challenges and drive advancements in smart materials and adaptive structures.
- **Driving Practical Applications:** Industry collaboration is essential for translating theoretical advancements in 4D printing into practical applications. Joint ventures can lead to the creation of prototypes and pilot projects that demonstrate the real-world benefits of 4D printing, fostering wider adoption across sectors such as healthcare, aerospace, and consumer products.
- **The Future of 4D Printing in Healthcare:** Mechanism Clarification Needed: Further exploration is required to elucidate the specific mechanisms by which 4D printing enhances practical applications in healthcare, particularly in skin wound repair, where adaptive materials can significantly improve healing outcomes compared to traditional 3D printing methods (Alves & Santana, 2022; Kuang et al., 2019; Haleem et al., 2021; Shinde et al., 2023; Antezana et al., 2023; Goehrke, 2024; Pei, 2014; Mahmood et al., 2022).

#### 15. Challenges in scaling up the production of chitosan-based wound dressings via 3D/4D printing

Chitosan-based wound dressings have gained attention for their biocompatibility and antibacterial properties. However, scaling up their production using 3D/4D printing technologies poses unique challenges. This paper discusses the specific obstacles associated with this transition, including material characteristics, printing precision, scalability of processes, regulatory hurdles, economic factors, post-processing requirements, and market acceptance. The increasing demand for advanced wound care solutions has led to the exploration of 3D/4D printing technologies for the production of chitosan-based dressings. While these technologies offer customization and potential for improved healing, the scaling up of production presents several challenges that must be addressed to facilitate widespread clinical use.

##### 15.1. Material challenges

**Viscosity and Printability:** Chitosan's high viscosity can hinder its

flow through printers, necessitating the development of optimal formulations. Adjusting the molecular weight and using plasticizers can help, but these modifications may alter the material's desired properties.

**Degradation:** Chitosan is susceptible to environmental conditions. Moisture and temperature fluctuations can affect the material during production, compromising the integrity and effectiveness of the final product.

### 15.2. Precision in printing

**Resolution and Layer Thickness:** Achieving the desired resolution for intricate designs is a challenge. Thicker layers can result in compromised structural integrity and reduced effectiveness in wound healing applications.

**Mechanical Properties:** Ensuring that the printed dressings maintain their mechanical properties under physiological conditions is crucial. Variability in printing parameters can lead to inconsistencies in performance.

### 15.3. Scalability of processes

**Printer Limitations:** Most current 3D/4D printers are not designed for high-throughput production. Upgrading to industrial-scale printers that can deliver consistent quality is essential but may require significant investment.

**Batch Consistency:** Maintaining uniformity across batches poses a challenge, as variations in printing conditions can lead to discrepancies in material properties and performance.

### 15.4. Regulatory and compliance issues

**Regulatory Landscape:** The medical device sector is heavily regulated, requiring extensive testing and documentation to meet compliance standards. Navigating this landscape can be resource-intensive and slow down the scaling process.

**Quality Assurance Protocols:** Developing standardized quality assurance protocols is essential for ensuring safety and efficacy, but this adds complexity to production and increases costs.

### 15.5. Economic considerations

**Material Costs:** The cost of high-quality chitosan and any necessary additives can be significant, impacting the overall cost-effectiveness of production.

**Investment in Technology:** Transitioning to advanced 3D/4D printing technologies involves substantial capital investment, which may deter small to medium-sized enterprises from scaling up.

### 15.6. Post-Processing challenges

**Sterilization Techniques:** Effective sterilization methods must be established to ensure that wound dressings are safe for use. This can complicate the production workflow and extend lead times.

**Functionalization:** Enhancing the properties of chitosan-based dressings (e.g., incorporating antimicrobial agents) may require additional processing steps, increasing production complexity.

### 15.7. Market acceptance

**Healthcare Provider Education:** Gaining acceptance from clinicians and healthcare providers requires robust educational initiatives to demonstrate the benefits and efficacy of 3D/4D printed dressings.

**Clinical Validation:** Conducting clinical trials to validate the safety and effectiveness of these innovative dressings is essential, yet resource-intensive and time-consuming.

Consequently, the transition to scalable production of chitosan-based

wound dressings using 3D/4D printing faces several obstacles, from material and process challenges to regulatory and market acceptance issues. Addressing these challenges requires a multidisciplinary approach, leveraging advances in materials science, engineering, regulatory expertise, and healthcare to realize the potential of these innovative wound care solutions (Shokrani et al., 2023; Yang et al., 2022).

## 16. Degrees of freedom in 4D printing

### 16.1. Overview of 4D printing

4D printing is an advanced manufacturing process that extends the capabilities of traditional 3D printing by incorporating the dimension of time. In essence, 4D printing involves creating objects that can autonomously change their shape or properties in response to environmental stimuli such as heat, moisture, or light. This transformative capability is achieved through the use of smart materials that can undergo programmed changes, allowing for dynamic responses that are not possible with conventional static 3D printed objects. The implications of 4D printing are vast, ranging from biomedical applications to aerospace engineering, where adaptability and functionality are paramount.

### 16.2. Importance of degrees of freedom in modern manufacturing

Degrees of freedom (DoF) refer to the number of independent movements or transformations that an object can undergo. In the context of 4D printing, degrees of freedom are crucial as they determine how effectively a printed object can respond to external stimuli. The greater the degrees of freedom, the more complex and versatile the transformations an object can achieve. This adaptability is essential for practical applications, enabling innovations in various fields, including healthcare, robotics, and architecture. Understanding and optimizing degrees of freedom in 4D printing is vital for advancing the technology and expanding its applications.

## 17. Definition and importance of degrees of freedom

### 17.1. Explanation of degrees of freedom in 4D printing

In 4D printing, degrees of freedom can be defined as the number of independent ways in which a printed object can change its configuration or state in response to environmental factors. This can include movements such as bending, twisting, expanding, or contracting. For instance, a 4D printed structure designed to respond to temperature changes may have the ability to bend in multiple directions, thereby exhibiting multiple degrees of freedom. The concept is rooted in mechanical engineering and physics, where it is used to describe the motion capabilities of mechanical systems.

### 17.2. Significance in response to environmental stimuli

The significance of degrees of freedom in 4D printing lies in their direct correlation with the functionality and adaptability of printed objects. Objects with higher degrees of freedom can perform more complex transformations, making them suitable for a wider range of applications. For example, in biomedical applications, a 4D printed scaffold with multiple degrees of freedom can adapt to the dynamic environment of the human body, promoting better integration with biological tissues. Similarly, in aerospace, structures that can morph in response to changing aerodynamic conditions can enhance performance and safety.

## 18. Degrees of freedom in 4D printing mechanisms

### 18.1. Mechanisms enabling self-assembly

Self-assembly is a critical mechanism in 4D printing that leverages degrees of freedom to create complex structures autonomously. This process involves the spontaneous organization of components into ordered structures without external guidance. By designing 4D printed objects with specific degrees of freedom, engineers can enable self-assembly processes that respond to environmental cues. For instance, a 4D printed material that expands when exposed to moisture can self-assemble into a predetermined shape, facilitating applications in areas such as tissue engineering and environmental remediation.

### 18.2. Dynamic responses to stimuli

Dynamic responses to stimuli are another essential aspect of degrees of freedom in 4D printing. The ability of a printed object to react to changes in its environment—such as temperature, humidity, or light—depends on its design and the materials used. For example, shape memory polymers can be engineered to change shape when subjected to specific stimuli, allowing for dynamic functionality. This capability is particularly valuable in applications where adaptability is crucial, such as in soft robotics, where robots must navigate unpredictable environments.

### 18.3. Enhancing adaptability and functionality

The enhancement of adaptability and functionality through degrees of freedom is a key advantage of 4D printing. By optimizing the design of printed objects to maximize their degrees of freedom, manufacturers can create products that are not only more versatile but also more efficient. For instance, a 4D printed device that can adjust its shape based on the surrounding temperature can improve energy efficiency in buildings by optimizing insulation properties. This adaptability can lead to significant advancements in sustainable design and energy conservation.

## 19. Examples of applications

### 19.1. Innovative applications in healthcare

In the healthcare sector, 4D printing has the potential to revolutionize patient care through the development of responsive medical devices. For example, 4D printed stents that can expand or contract in response to changes in blood flow or temperature can provide better support for blood vessels. Additionally, scaffolds for tissue engineering that adapt to the growth of cells can enhance the integration of implants with surrounding tissues, leading to improved healing outcomes.

### 19.2. Aerospace applications

The aerospace industry stands to benefit significantly from the advancements in 4D printing. Aircraft components that can change shape in response to aerodynamic forces can improve fuel efficiency and performance. For instance, wings that morph during flight to optimize lift and drag can lead to more efficient aircraft designs. Furthermore, 4D printed materials that can repair themselves in response to damage can enhance the safety and longevity of aerospace structures.

### 19.3. Complex repairs and adaptive structures

4D printing also enables the creation of adaptive structures that can perform complex repairs autonomously. For example, a 4D printed bridge that can adjust its shape in response to environmental conditions, such as temperature fluctuations or load changes, can enhance structural integrity and safety. Similarly, buildings equipped with 4D printed

components that can adapt to seismic activity can improve resilience against earthquakes.

## 20. Challenges and future directions

### 20.1. Material limitations

Despite the promising applications of 4D printing, several challenges remain, particularly concerning material limitations. The development of smart materials that can exhibit the desired degrees of freedom while maintaining structural integrity is a significant hurdle. Current materials may not possess the necessary properties to achieve the complex transformations required for advanced applications.

### 20.2. Need for advanced smart materials

The need for advanced smart materials is critical for the future of 4D printing. Researchers are exploring new materials that can respond to a broader range of stimuli and exhibit greater durability. Innovations in nanotechnology and polymer science may lead to the development of materials that can undergo more complex transformations, thereby enhancing the degrees of freedom in 4D printed objects.

### 20.3. Future research directions

Future research directions in 4D printing should focus on optimizing the design of printed objects to maximize their degrees of freedom while addressing material limitations. Collaborative efforts between material scientists, engineers, and designers will be essential to develop innovative solutions that push the boundaries of what is possible with 4D printing. Additionally, exploring the integration of artificial intelligence and machine learning in the design process may lead to more efficient and effective 4D printed structures.

## 21. Degrees of freedom in 3D/4D printing of chitosan-based materials for wound repair

The advent of 3D and 4D printing technologies has revolutionized various fields, particularly in biomedical applications. Among these, the use of chitosan-based materials for wound repair presents a compelling case for exploring the degrees of freedom inherent in this innovative approach. Degrees of freedom, in this context, refer to the various parameters and design choices available to researchers and practitioners when creating custom scaffolds and wound dressings. This discussion will delve into the multifaceted aspects of 3D/4D printing of chitosan-based materials, highlighting the flexibility and versatility that these technologies offer in the realm of wound healing.

### 21.1. Material properties and customization

Chitosan, a biopolymer derived from chitin, is known for its biocompatibility, biodegradability, and antimicrobial properties. These characteristics make it an ideal candidate for wound repair applications. The degrees of freedom in this context begin with the selection and modification of chitosan itself. Researchers can manipulate the molecular weight, degree of deacetylation, and even blend chitosan with other materials to enhance its properties. This customization allows for the creation of scaffolds that can be tailored to specific wound types, whether they are chronic, acute, or infected. Moreover, the incorporation of bioactive agents, such as growth factors or antimicrobial agents, into the chitosan matrix during the printing process further expands the degrees of freedom. This enables the development of scaffolds that not only support cell growth but also actively promote healing and prevent infection. The ability to fine-tune these properties is crucial for optimizing the performance of wound dressings.

## 21.2. Design flexibility in 3D/4D printing

The transition from traditional manufacturing methods to 3D/4D printing introduces significant design flexibility. In 3D printing, the ability to create complex geometries and structures that mimic the natural extracellular matrix is a key advantage. This capability allows for the production of scaffolds with varying porosity, surface topography, and mechanical properties, all of which can be tailored to the specific requirements of the wound environment. 4D printing, which incorporates the dimension of time into the design process, adds another layer of complexity and functionality. By utilizing stimuli-responsive materials, 4D printing enables scaffolds to change shape or properties in response to environmental triggers such as temperature, pH, or moisture. This dynamic behavior can be particularly beneficial in wound healing, where the scaffold can adapt to the physiological changes occurring during the healing process. For instance, a scaffold may initially provide structural support and then gradually release therapeutic agents as the wound heals, thereby optimizing the healing trajectory.

## 21.3. Manufacturing techniques and scalability

The degrees of freedom also extend to the manufacturing techniques employed in 3D/4D printing. Various printing methods, such as extrusion-based printing, inkjet printing, and laser-assisted printing, offer distinct advantages and limitations. Each technique allows for different resolutions, material compatibilities, and production speeds. The choice of printing method can significantly influence the final properties of the chitosan-based scaffold, including its mechanical strength and porosity. Furthermore, scalability is a critical consideration in the transition from laboratory-scale production to clinical applications. The ability to produce large quantities of customized scaffolds efficiently is essential for widespread adoption in clinical settings. Advances in printing technology and automation are continuously improving the scalability of 3D/4D printing processes, thereby enhancing the degrees of freedom in terms of production volume and cost-effectiveness.

## 21.4. Regulatory and ethical considerations

While the technical degrees of freedom in 3D/4D printing of chitosan-based materials are substantial, regulatory and ethical considerations also play a crucial role. The development of new biomedical products must adhere to stringent regulatory frameworks to ensure safety and efficacy. This regulatory landscape can impose constraints on the design and manufacturing processes, thereby influencing the degrees of freedom available to researchers and manufacturers. Ethical considerations, particularly regarding the use of biomaterials and the implications of advanced manufacturing technologies, must also be addressed. Ensuring that the materials used are sourced sustainably and that the manufacturing processes do not pose risks to human health or the environment is paramount. These factors can shape the direction of research and development in the field, ultimately affecting the degrees of freedom in the design and application of chitosan-based wound repair solutions.

In summary, the degrees of freedom in the 3D/4D printing of chitosan-based materials for wound repair are extensive and multifaceted. From material customization and design flexibility to manufacturing techniques and regulatory considerations, each aspect contributes to the potential of this innovative approach in advancing wound healing applications. As research continues to evolve, the ability to harness these degrees of freedom will be crucial in developing effective, personalized, and adaptive wound care solutions that meet the diverse needs of patients. The integration of advanced printing technologies with biocompatible materials like chitosan heralds a new era in regenerative medicine, offering promising avenues for future

exploration and application degrees of freedom play a critical role in the functionality and application of 4D printing technologies. By understanding and optimizing these degrees of freedom, manufacturers can create objects that are not only more adaptable but also more efficient in responding to environmental stimuli. The implications of this technology span various fields, including healthcare, aerospace, and structural engineering.

Final Thoughts on the Future of 4D Printing and Degrees of Freedom, As 4D printing continues to evolve, the exploration of degrees of freedom will be essential for unlocking new applications and enhancing existing technologies. The challenges associated with material limitations and the need for advanced smart materials present opportunities for innovation and research. Ultimately, the future of 4D printing holds great promise, with the potential to transform industries and improve the quality of life through responsive and adaptive technologies (Pei & Loh, 2018; Sossou et al., 2019; Hu et al., 2020; van Manen et al., 2021; Zolfagharian et al., 2020).

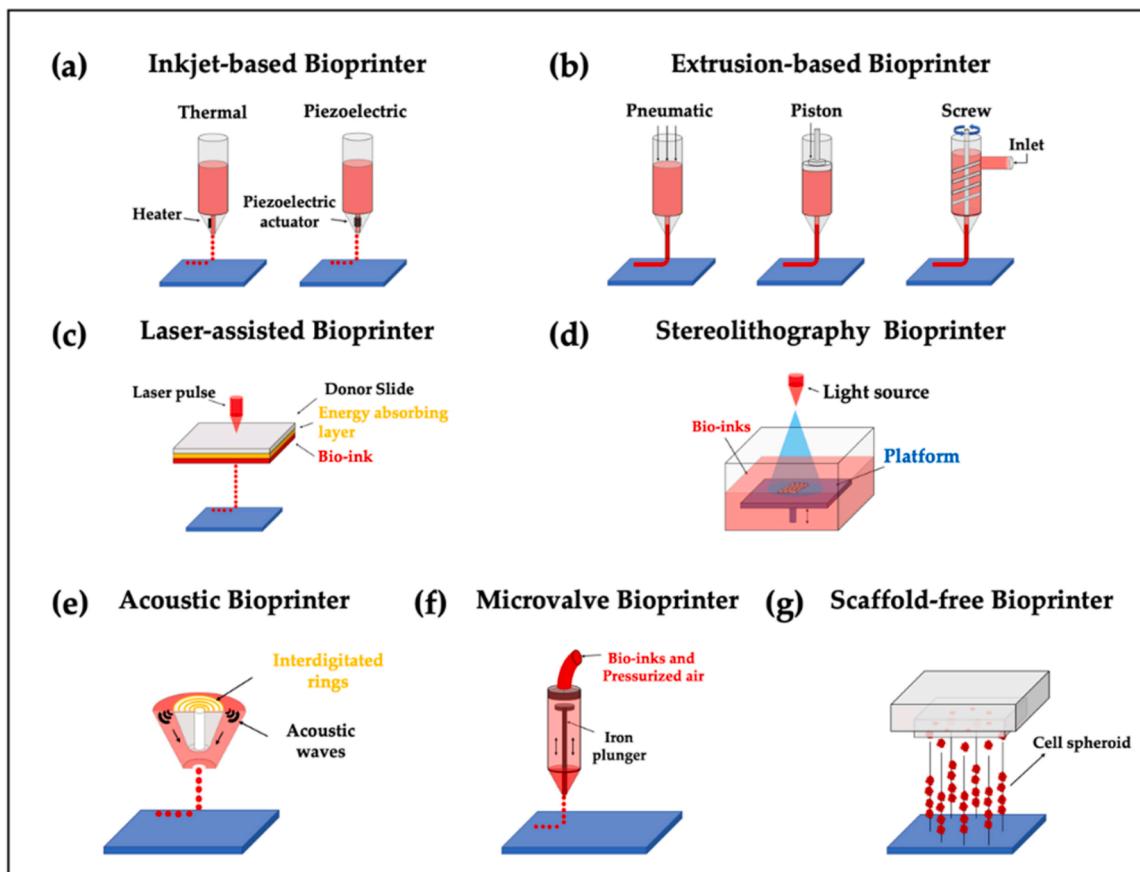
## 22. 4D bioprinting

A new bioprinting method called 4D bioprinting adds time as a fourth dimension. To overcome the static nature of 3D bioprinting, it entails creating a sophisticated bioink that can shape and function changes over time when exposed to an external stimulus. This method of simulating tissues and generating functional vasculature in tissue-engineered constructs is becoming more and more popular. The dynamic component can help printed tissues work better and offer ways to make the vasculature in tissue-engineered constructs function. This can be accomplished through the use of responsive materials or cell-encapsulated or self-organizing bioprinting construct maturation. Responsive bioink changes morphologically in response to external stimuli, including changes in pH, humidity, temperature, ions, and acoustic, electrical, or magnetic fields. In 4D bioprinted constructs, cell maturation can be accomplished by coatings, cellular spheroids, matrix deposition, or self-organization dependent on cell location. 4D bioprinting techniques based on stereolithography have demonstrated promise; however, they require a photocrosslinkable material whose shape is malleable in response to external triggers. The most significant advantage of the lies of 4D bioprinting in its capacity to facilitate gradual structural modifications to a construct, leading to enhanced applicability and customized medicine. Nonetheless, there are difficulties due to the bioink's intricate design and the high cost of the bioink and bioprinter (Chu et al., 2020; Yu et al., 2020). (Fig. 6) shows a schematic of different polymer bioprinting methods (Yu et al., 2020).

4D-printed scaffolds are beneficial for conforming to the dynamic architecture of human organs and tissues, rendering them appropriate for minimally invasive surgical procedures. They can react to particular environmental or physiological conditions, such as solvent, temperature, and pH, to achieve time-dependent physical alterations or mimic native tissue function, facilitating intelligent tissue restoration. These 4D dynamic supports facilitate cell adhesion, orientation, proliferation, and differentiation, rendering them optimal for tissue repair and functional tissue substitutes. Their time-dependent deformation affects cell shape, modulates cell behaviors, and governs cell activities. In a cell-rich 4D framework, dynamic manipulation of these variables may facilitate spatiotemporal management of cellular responses, signaling pathways, and gene expression patterns (Agarwal et al., 2023).

External stimuli encompass physical elements such as temperature, humidity, force, sound, photoelectricity, time, pH, acidity and alkalinity, catalysts, as well as biological parameters like sugar concentration, salinity, and enzymes. These alterations, which are spontaneous and evolve over time, may utilize energy that is stored or transformed from external situations. Advanced technologies have been created to unify product design, manufacturing, and assembly, facilitating a more efficient utilization of energy (Han et al., 2023).

In comparison to 3D printing, 4D printing presents several



**Fig. 6.** Schematic of different polymer bioprinting methods (Gudapati et al., 2016; Kacarevic et al., 2018; Keriquel et al., 2017; LaBarge, Morales, Pretorius, Kahn-Krell, & Kannappan, 2019; Malda et al., 2013; Yu et al., 2020a).

advantages, including the rapid development of intelligent multi-materials, more adaptable and deformable structures, and the ability to expand applications for both 4D and 3D printing. It provides superior efficiency, quality, and performance relative to conventional methods, as the 4D printed structures may autonomously enhance their attributes and behavior. The minimal use of materials in 4D printing aids in promoting sustainable development. F. Momeni and J. Ni have established three principles that dictate the shape-altering behavior of all 4D printed structures. The first law asserts that all shape-altering activities, including coiling, curling, twisting, and bending, result from the differential expansion between active and passive materials. The second law elucidates that four physical elements underlie the shape-changing capability of all multi-material 4D structures: mass diffusion, thermal expansion, molecular transformation, and organic development. Mass alteration transpires due to the absorption or adsorption of stimuli, such as water or ions, resulting in a change in the structure's mass and consequent shape distortion. Thermal expansion can induce deformations in structures owing to variations in temperature, and may also occur when stimuli such as electrical, light, and UV alter the structure's temperature. Molecular transformation can induce relative expansion in structures while mass and temperature remain constant. Examples encompass electric or magnetic fields orienting dipoles, mechanical strain aligning polymer chains, and ultraviolet radiation inducing *trans*-to-*cis* isomerization. Organic growth denotes the augmentation in size and mass of a living organism over time. These principles elucidate the physics underlying the shape-altering capability of 4D printed structures. Organic growth, induced by stimuli including electrical, thermal, hydric, pH, and mechanical forces, characterizes the morphogenic behavior of cells, tissues, scaffolds, stents, and organs in 4D bioprinting, as they undergo expansion due to augmented mass and

length. The third law of 4D printing delineates the shape-morphing characteristics of multi-material structures regulated by two categories of temporal constants, which may be equivalent, substantial, or nonexistent based on the stimulus and material employed. A mathematical bi-exponential equation for the fourth dimension was also formulated (Aldawood, 2023; Ahmed et al., 2021).

The fundamental distinction between 3D and 4D printing lies in the static characteristic of the former method. In contrast to 3D printing, 4D printing enables the base material to undergo shape transformation over time in response to external triggers (Joshi et al., 2020).

Smart structures may be stiff or incorporate expandable components that alter their shape in response to stimuli. These materials may be hydrogels, which absorb water and expand, or polymeric materials, which can revert to their original forms. In 3D printing, the printer's capacity limits the dimensions of an object, but in 4D printing, the object's dimensions may exceed the printer's limitations. Biomaterials that respond to stimuli can be used in 4D bioprinting, where 3D printed scaffolds change over time in response to outside factors. This technique employs stimulus-responsive multimedia that can dynamically alter characteristics when exposed to appropriate triggers. Scalability poses a considerable challenge in 4D printing within biomedical engineering, as structures must be fabricated in substantial quantities or at varying scales to satisfy patient requirements. Existing methodologies are labor-intensive and have restricted scalability, rendering them inappropriate for extensive manufacturing. Researchers must devise novel printing techniques that yield structures more rapidly and with minimal material waste, while also investigating automation methods and their integration with other manufacturing technologies, such as injection molding or additive manufacturing, to enhance production capacity and decrease costs (Ramezani & Mohd Ripin, 2023).

## 23. Future perspective and outlook

**Enhanced Customization:** By using chitosan-based materials for 3D/4D printing, wound dressings that are specifically customized to meet the needs of each patient can be made, improving the healing rate.

**Controlled Drug Delivery:** These printing mechanisms cause controlled release of therapeutic agents at the wound site, capacity speeding up the healing process, by integrating bioactive compounds into the chitosan matrix.

**Scaffold Design:** Using chitosan-based materials, intricate 3D and 4D structures can be designed, opening the door to the possibility of building scaffolds that mimic the body's extracellular matrix to promote tissue regeneration, cell adhesion, and proliferation.

All things considered, encouraging advances in tissue engineering and controlled drug delivery in the application of 3D/4D printing in chitosan-based materials for wound healing, and personalized medicine.

## 24. Conclusion

A major advancement in the string of applications for wound conglutination is the result of 3D/4D printing technologies with chitosan-based materials, which provide a fresh method for creating customized scaffolds and wound dressings. The manufacturing sector has undergone a revolution thanks to 3D/4D printing technology, which makes it possible to efficiently and precisely construct complex architectures. This technology can be used to develop highly customized solutions for a variety of medical applications. One such area is wound healing, where materials based on chitosan have shown promising results. With its unique characteristics, Chitosan, a biocompatible polymer derived from chitin, is ideal for application in wound-healing applications. It has antibacterial and anti-inflammatory strengthens the properties of cell adhesion and proliferation and accelerates tissue regeneration. In conjunction with 3D/4D printing technology, materials based on chitosan can be precisely designed to fit particular wound characteristics, improving the effectiveness of treatment. According to the principles of 3D/4D printing, the material is deposited layer by layer using digital models as a guide, giving exact control over the finished structure. This degree of personalization is especially helpful in wound care, as each patient's needs can differ greatly from the next. Healthcare providers can employ 3D/4D printing techniques to produce customized scaffolds or dressings made of chitosan, which can expedite healing and lower the risk of infection. In the future, studies are being conducted to maximize the use of 3D/4D printing for materials based on chitosan in wound healing applications. Notwithstanding its capacity advantages, issues with cost-effectiveness, scalability, and regulatory barriers must be resolved to encourage broader use in clinical settings. Future advancements might concentrate on creating bioactive additives or intelligent materials that dynamically adapt to the state of wounds, thereby improving the course of treatment for patients with severe or chronic wounds.

## CRediT authorship contribution statement

**Seyed Morteza Naghib:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization. **Seyedeh Neda Hosseini:** Writing – original draft, Investigation. **Anahita Beigi:** Investigation, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## References

- Abbasipour, M., Mirjalili, M., Khajavi, R., & Majidi, M. M. (2014). Coated Cotton Gauze with Ag/ZnO/chitosan Nanocomposite as a Modern Wound Dressing. *Journal of Engineered Fibers and Fabrics*, 9(1), Article 155892501400900114. <https://doi.org/10.1177/155892501400900114>.
- Agarwal, T., Chiesa, I., Costantini, M., Lopamarda, A., Tirelli, M. C., Borra, O. P., et al. (2023). Chitosan and its derivatives in 3D/4D (bio) printing for tissue engineering and drug delivery applications. *International Journal of Biological Macromolecules*, 246, Article 125669. <https://doi.org/10.1016/j.ijbiomac.2023.125669>.
- Ahmed, A., Arya, S., Gupta, V., Furukawa, H., & Khosla, A. (2021). 4D printing: Fundamentals, materials, applications and challenges. *Polymer*, 228, Article 123926. <https://doi.org/10.1016/j.polymer.2021.123926>.
- Ahmed, E. M. (2015). Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research*, 6(2), 105–121. <https://doi.org/10.1016/j.jare.2013.07.006>.
- Ahmed, S., & Ikram, S. (2016). Chitosan Based Scaffolds and Their Applications in Wound Healing. *Achievements in the Life Sciences*, 10(1), 27–37. <https://doi.org/10.1016/j.jals.2016.04.001>.
- Aleme, D., Getachew, E., & Mondal, A. K. (2023). Study on the Physicochemical Properties of Chitosan and their Applications in the Biomedical Sector. *International Journal of Polymer Science*, (1), Article 5025341. <https://doi.org/10.1155/2023/5025341>.
- Alves, J. L., & Santana, L. (2022). Chapter 20 - 3D printing trends and perspectives. In J. Izdebska-Podsiadly (Ed.), *Polymers for 3D printing* (pp. 369–383). William Andrew Publishing.
- Amiryaghoubi, N., Fathi, M., Safary, A., Javadzadeh, Y., & Omidi, Y. (2024). In situ forming alginate/gelatin hydrogel scaffold through Schiff base reaction embedded with curcumin-loaded chitosan microspheres for bone tissue regeneration. *International Journal of Biological Macromolecules*, 256, Article 128335. <https://doi.org/10.1016/j.ijbiomac.2023.128335>.
- Antezana, P. E., Municoy, S., Ostapchuk, G., Catalano, P. N., Hardy, J. G., Evelson, P. A., et al. (2023). 4D Printing: The Development of Responsive Materials Using 3D-Printing Technology. *Pharmaceutics*. <https://doi.org/10.3390/pharmaceutics15122743>
- Apelqvist, J., Armstrong, D. G., Lavery, L. A., & Boulton, A. J. M. (2008). Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds. *The American Journal of Surgery*, 195(6), 782–788. <https://doi.org/10.1016/j.amjsurg.2007.06.023>.
- Archana, D., Singh, B. K., Dutta, J., & Dutta, P. K. (2013). In vivo evaluation of chitosan-PVP-titanium dioxide nanocomposite as wound dressing material. *Carbohydrate Polymers*, 95(1), 530–539. <https://doi.org/10.1016/j.carbpol.2013.03.034>.
- Arjun, B., Krishnendu, P. R., Anishma, P. N., & Zachariah, S. M. (2023). 5 - Chitin in drug delivery. In R. Jayakumar, & V. P. Murali (Eds.), *Natural biopolymers in drug delivery and tissue engineering* (pp. 101–125). Woodhead Publishing.
- Atiyeh, B. S., Costagliola, M., Hayek, S. N., & Dibo, S. A. (2007). Effect of silver on burn wound infection control and healing: Review of the literature. *Burns : journal of the International Society for Burn Injuries*, 33(2), 139–148. <https://doi.org/10.1016/j.burns.2006.06.010>.
- Auböck, J. (1999). *Synthetic dressings, management of leg ulcers*. S.Karger AG, 010.1159/000060633.
- Badhe, R. V., Chatterjee, A., Bijukumar, D., & Mathew, M. T. (2023). Current advancements in bio-ink technology for cartilage and bone tissue engineering. *Bone*, 171, Article 116746. <https://doi.org/10.1016/j.bone.2023.116746>.
- Bahavarnia, F., Hasanzadeh, M., Bahavarnia, P., & Shadjou, N. (2024). Advancements in application of chitosan and cyclodextrins in biomedicine and pharmaceuticals: Recent progress and future trends. *RSC Advances*, 14(19), 13384–13412. <https://doi.org/10.1039/D4RA01370K>, 10.1039/D4RA01370K.
- Balavigneswaran, C. K., & Muthuvijayan, V. (2021). Biomaterials for Soft Tissue Engineering: Concepts, Methods, and Applications. *Biomaterials in Tissue Engineering and Regenerative Medicine: From Basic Concepts to State of the Art Approaches*, 381–422.
- Bell, Denise, & Dot, Hyam (2007). Choosing an appropriate dressing for chronic wounds. *Prescriber*, 18(11), 65–70.
- Bento, C. S. A., Gaspar, M. C., Coimbra, P., de Sousa, H. C., & Braga, M. E. M. (2023). A review of conventional and emerging technologies for hydrogels sterilization. *International Journal of Pharmaceutics*, 634, Article 122671. <https://doi.org/10.1016/j.ijpharm.2023.122671>.

- 10.1016/j.ijpharm.2023.122671. <https://www.sciencedirect.com/science/article/pii/S0378517323000911>
- Biswal, A., Purohit, S. S., & Swain, S. K. (2023). Chitosan based composite scaffolds in skin wound repair: A review. *Journal of Drug Delivery Science and Technology*, 84, Article 104549. <https://doi.org/10.1016/j.jddst.2023.104549>. <https://www.sciencedirect.com/science/article/pii/S177322472300401X>
- Bryant, R., & Nix, D. (2015). *Acute and chronic wounds: Current management concepts*. Elsevier Health Sciences.
- N.J. Buote, Wound Dressings, Techniques in Small Animal Wound Management 2024, pp. 127–154.
- Calaval, A. (2024). Efficacy of Hyaluronic Acid/Collagenase Ointment in the Treatment of Chronic Wounds: A Retrospective Observational Study. *The International Journal of Lower Extremity Wounds*, , Article 15347346241243102. <https://doi.org/10.1177/15347346241243102>
- Catanzano, O., & Boateng, J. (2020). Local Delivery of Growth Factors Using Wound Dressings. *Therapeutic Dressings and Wound Healing Applications*, 291–314.
- Catanzano, O., Quaglia, F., & Boateng, J. S. (2021). Wound dressings as growth factor delivery platforms for chronic wound healing. *Expert Opinion on Drug Delivery*, 18(6), 737–759. <https://doi.org/10.1080/17425247.2021.1867096>
- Chamkouri, H., & Chamkouri, M. (2021). A review of hydrogels, their properties and applications in medicine. *Am. J. Biomed. Sci. Res.*, 11(6), 485–493.
- CHI, D., Berchuck, A., Dizon, D. S., Yashar, C. M., & Khabele, D. (2024). *Principles and Practice of Gynecologic Oncology*. Lippincott Williams & Wilkins.
- Chimisso, V., Aleman Garcia, M. A., Yorulmaz Avsar, S., Dinu, I. A., & Palivan, C. G. (2020). Design of Bio-Conjugated Hydrogels for Regenerative Medicine Applications: From Polymer Scaffold to Biomolecule Choice. *Molecules* (Basel, Switzerland). <https://doi.org/10.3390/molecules25184090>
- Choudhary, P., Ramalingam, B., & Das, S. K. (2020). Fabrication of Chitosan-Reinforced Multifunctional Graphene Nanocomposite as Antibacterial Scaffolds for Hemorrhage Control and Wound-Healing Application. *ACS Biomaterials Science & Engineering*, 6 (10), 5911–5929. <https://doi.org/10.1021/acsbiomaterials.0c00923>
- Chu, H., Yang, W., Sun, L., Cai, S., Yang, R., Liang, W., et al. (2020). *4D Printing: A review on recent progresses*. *Micromachines*. <https://doi.org/10.3390/mi11090796>
- Clarissa, W. H., Chia, C. H., Zakaria, S., & Eyyan, Y. C. (2022). Recent advancement in 3-D printing: Nanocomposites with added functionality. *Prog Addit Manuf*, 7(2), 325–350. <https://doi.org/10.1007/s40964-021-00232-z>
- Colmenares, J. C., & Kunz, E. (2017). Photoactive Hybrid Catalysts Based on Natural and Synthetic Polymers: A Comparative Overview. *Molecules* (Basel, Switzerland). <https://doi.org/10.3390/molecules22050790>
- Cutting, K. F., & White, R. J. (2002). Maceration of the skin and wound bed 1: Its nature and causes. *Journal of Wound Care*, 11(7), 275–278. <https://doi.org/10.12968/jowc.2002.11.7.26414>
- Dealey, Carol. (2008). *The care of wounds: a guide for nurses*. John Wiley & Sons.
- Derby, B. (2010). Inkjet Printing of Functional and Structural Materials: Fluid Property Requirements, Feature Stability, and Resolution. *Annual Review of Materials Research*, 40, 395–414. <https://doi.org/10.1146/annurev-matsci-070909-104502> (Volume 40, 2010) <https://www.annualreviews.org/content/journals/10.1146/annurevmatsci-070909-104502>.
- Ding, Y.-W., Zhang, X.-W., Mi, C.-H., Qi, X.-Y., Zhou, J., & Wei, D.-X. (2023). Recent advances in hyaluronic acid-based hydrogels for 3D bioprinting in tissue engineering applications. *Smart Materials in Medicine*, 4, 59–68. <https://doi.org/10.1016/j.smaim.2022.07.003>. <https://www.sciencedirect.com/science/article/pii/S2590183422000357>
- Di Prima, M., Coburn, J., Hwang, D., Kelly, J., Khairuzzaman, A., & Ricles, L. (2016). Additively manufactured medical products – the FDA perspective. *3D Printing in Medicine*, 2(1), 1. <https://doi.org/10.1186/s41205-016-0005-9>
- Diyashri, G., Badhe, R. V., Sadanandan, B., Vijayalakshmi, V., Kumari, M., Ashrit, P., et al. (2022). Applications of hydrogel-based delivery systems in wound care and treatment: An up-to-date review. *Polymers for Advanced Technologies*, 33(7), 2025–2043. <https://doi.org/10.1002/pat.5661>
- Dykes, P. J., Heggie, R., & Hill, S. A. (2001). Effects of adhesive dressings on the stratum corneum of the skin. *Journal of Wound Care*, 10(2), 7–10. <https://doi.org/10.12968/jowc.2001.10.2.26054>
- Edwards, J. V., Yager, D. R., Cohen, I. K., Diegelmann, R. F., Montante, S., Bertoniere, N., et al. (2001). Modified cotton gauze dressings that selectively absorb neutrophil elastase activity in solution. *Wound Repair and Regeneration*, 9(1), 50–58. <https://doi.org/10.1046/j.1524-475x.2001.00050.x>
- Eivazzadeh-Keihan, R., Radinekiyan, F., Aliabadi, H. A. M., Sukhtezari, S., Tahmasebi, B., Maleki, A., et al. (2021). Chitosan hydrogel/silk fibroin/Mg(OH)<sub>2</sub> nanobiocomposite as a novel scaffold with antimicrobial activity and improved mechanical properties. *Scientific Reports*, 11(1), 650. <https://doi.org/10.1038/s41598-020-80133-3>
- Fansler, R. F., Taheri, P., Cullinane, C., Sabates, B., & Flint, L. M. (1995). Polypropylene mesh closure of the complicated abdominal wound. *The American Journal of Surgery*, 170(1), 15–18. [https://doi.org/10.1016/S0002-9610\(99\)80244-X](https://doi.org/10.1016/S0002-9610(99)80244-X). <https://www.sciencedirect.com/science/article/pii/S000296109980244X>
- Froelich, A., Jakubowska, E., Wojtylko, M., Jadach, B., Gackowski, M., Gadziński, P., et al. (2023). Alginate-Based Materials Loaded with Nanoparticles in Wound Healing. *Pharmaceutics*. <https://doi.org/10.3390/pharmaceutics15041142>
- Gaspar-Pintilieescu, A., Stanciu, A.-M., & Craciunescu, O. (2019). Natural composite dressings based on collagen, gelatin and plant bioactive compounds for wound healing: A review. *International journal of biological macromolecules*, 138, 854–865.
- George, J., Hsu, C.-C., Nguyen, L. T. B., Ye, H., & Cui, Z. (2020). Neural tissue engineering with structured hydrogels in CNS models and therapies. *Biotechnology Advances*, 42, Article 107370. <https://doi.org/10.1016/j.biotechadv.2019.03.009>. <https://www.sciencedirect.com/science/article/pii/S073497501930045X>
- Goehrke, S. (2024). *4D PRINTING the next dimension of advanced manufacturing: Researchers envisage 4D printing technology will have significant application potential for healthcare, automotive, aerospace and consumer industries. but what is it exactly?* (p. 16 +) Machine Design.
- Gudapati, H., Dey, M., & Ozbolat, I. (2016). A comprehensive review on droplet-based bioprinting: Past, present and future. *Biomaterials*, 102, 20–42.
- Hackert, B., Stürmer, E. K., & Weger, U. (2024). Empowerment in chronic wound care—Exploring the scope for patient contribution. *Frontiers of Nursing*, 11(1), 1–16.
- Haleem, A., Javaid, M., Khan, R. H., & Suman, R. (2020). 3D printing applications in bone tissue engineering. *Journal of Clinical Orthopaedics & Trauma*, 11, S118–S124. <https://doi.org/10.1016/j.jcot.2019.12.002>
- Haleem, A., Javaid, M., Singh, R. P., & Suman, R. (2021). Significant roles of 4D printing using smart materials in the field of manufacturing. *Advanced Industrial and Engineering Polymer Research*, 4(4), 301–311. <https://doi.org/10.1016/j.aiapr.2021.05.001>. <https://www.sciencedirect.com/science/article/pii/S2542504821000282>
- Han, X., Saiding, Q., Cai, X., Xiao, Y., Wang, P., Cai, Z., et al. (2023). Intelligent Vascularized 3D/4D/5D/6D-Printed Tissue Scaffolds. *Nano-Micro Letters*, 15(1), 239. <https://doi.org/10.1007/s40820-023-01187-2>
- Hannen, R., Connolly, J., Myers, S., & Ojeah, N. (2023). Chapter 15 - Skin tissue engineering and keratinocyte stem cell therapy. In J. De Boer, C. A. V. Blitterswijk, J. A. Uquillas, & N. Malik (Eds.), *Tissue engineering (Third edition)* (Eds., pp. 491–532). Academic Press.
- Heras, K., Las, Igartua, M., Santos-Vizcaino, E., & Hernandez, R. M. (2020). Chronic wounds: Current status, available strategies and emerging therapeutic solutions. *Journal of Controlled Release*, 328, 532–550. <https://doi.org/10.1016/j.jconrel.2020.09.039>. <https://www.sciencedirect.com/science/article/pii/S0168365920305538>
- Hossain, M. R., Mallik, A. K., & Rahman, M. M. (2020). Chapter 7 - Fundamentals of chitosan for biomedical applications. In S. Gopi, S. Thomas, & A. Pius (Eds.), *Handbook of chitin and chitosan* (pp. 199–230). Elsevier.
- Hu, Y., Wang, Z., Jin, D., Zhang, C., Sun, R., Li, Z., et al. (2020). Botanical-Inspired 4D Printing of Hydrogel at the Microscale. *Advanced Functional Materials*, 30(4), Article 1907377. <https://doi.org/10.1002/adfm.201907377>
- Huang, Y., Leu, M. C., Mazumder, J., & Donmez, A. (2015). Additive Manufacturing: Current State, Future Potential, Gaps and Needs, and Recommendations. *Journal of Manufacturing Science and Engineering*, 137(1). <https://doi.org/10.1115/1.4028725>
- Idumah, C. I., Nwuzor, I. C., Odera, S. R., Timothy, U. J., Ngenegbo, U., & Tanjung, F. A. (2024). Recent advances in polymeric hydrogel nanoarchitectures for drug delivery applications. *International Journal of Polymeric Materials and Polymeric Biomaterials*, 73(1), 1–32. <https://doi.org/10.1080/00914037.2022.2120875>
- Intini, C., Elviri, L., Cabral, J., Mros, S., Bergonzi, C., Bianchera, A., et al. (2018). 3D-printed chitosan-based scaffolds: An in vitro study of human skin cell growth and an in-vivo wound healing evaluation in experimental diabetes in rats. *Carbohydrate Polymers*, 199, 593–602. <https://doi.org/10.1016/j.carbpol.2018.07.057>. <https://www.sciencedirect.com/science/article/pii/S0144861718308488>
- Islam, M. A., Mobarak, M. H., Rimon, M. I. H., Al Mahmud, M. Z., Ghosh, J., Ahmed, M. M. S., et al. (2024). Additive manufacturing in polymer research: Advances, synthesis, and applications. *Polymer Testing*, 132, Article 108364. <https://doi.org/10.1016/j.polymertesting.2024.108364>. <https://www.sciencedirect.com/science/article/pii/S0142941824000412>
- Jacob, S., Nair, A. B., Patel, V., & Shah, J. (2020). 3D Printing Technologies: Recent Development and Emerging Applications in Various Drug Delivery Systems. *AAPS PharmSciTech*, 21(6), 220. <https://doi.org/10.1208/s12249-020-01771-4>
- Järbrink, K., Ni, G., Sonnergren, H., Schmidtchen, A., Pang, C., Bajpai, R., et al. (2016). Prevalence and incidence of chronic wounds and related complications: A protocol for a systematic review. *Systematic Reviews*, 5(1), 152. <https://doi.org/10.1186/s13643-016-0329-y>
- Jayakumar, R., Prabharan, M., Sudheesh Kumar, P. T., Nair, S. V., & Tamura, H. (2011). Biomaterials based on chitin and chitosan in wound dressing applications. *Biotechnology Advances*, 29(3), 322–337. <https://doi.org/10.1016/j.biotechnoladv.2011.01.005>. <https://www.sciencedirect.com/science/article/pii/S0734975011000061>
- Joshi, S., Rawat, K., C, K., Rajamohan, V., Mathew, A. T., Koziol, K., et al. (2020). 4D printing of materials for the future: Opportunities and challenges. *Applied Materials Today*, 18, Article 100490. <https://doi.org/10.1016/j.apmt.2019.100490>. <https://www.sciencedirect.com/science/article/pii/S2352940719306092>
- Kabir, S. M. F., Sikdar, P. P., Haque, B., Bhuiyan, M. A. R., Ali, A., & Islam, M. N. (2018). Cellulose-based hydrogel materials: Chemistry, properties and their prospective applications. *Progress in Biomaterials*, 7(3), 153–174. <https://doi.org/10.1007/s40204-018-0095-0>
- G.S. Kaliaraj, D.K. Shanmugam, A. Dasan, K.K. Mosas, Hydrogels—A Promising Materials for 3D Printing Technology, *Gels*, 2023, 10.3390/gels9030260.
- Kacarevic, Z. P., Rider, P. M., Alkildani, S., Retnasingh, S., Smeets, R., ... Jung, O. (2018). *An introduction to 3D bioprinting: possibilities, challenges and future aspects*. *Materials*, 11, 2199.
- Kalogeropoulou, M., Díaz-Payno, P. J., Mirzaali, M. J., van Osch, G. J. V. M., Fratila-Apachitei, L. E., & Zadpoor, A. A. (2024). 4D printed shape-shifting biomaterials for tissue engineering and regenerative medicine applications. *Biofabrication*, 16(2), Article 022002. <https://doi.org/10.1088/1758-5090/ad1ef>
- Kamoun, E. A., Kenawy, E.-R. S., & Chen, X. (2017). A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings. *Journal of Advanced Research*, 8(3), 217–233. <https://doi.org/10.1016/j.jare.2017.01.005>. <https://www.sciencedirect.com/science/article/pii/S2090123217300243>
- Kearney, J. N. (2001). Clinical evaluation of skin substitutes. *Burns : journal of the International Society for Burn Injuries*, 27(5), 545–551. <https://doi.org/10.1016/>

- S0305-4179(01)00020-1. <https://www.sciencedirect.com/science/article/pii/S0305417901000201>
- Kerquel, V., Oliveira, H., Rémy, M., Ziane, S., Delmond, S., Rousseau, B., Rey, S., et al. (2017). In situ printing of mesenchymal stromal cells, by laser-assisted bioprinting, for in vivo bone regeneration applications. *Scientific Reports*, 7(1), 1778.
- Kolimi, P., Narala, S., Nyavanand, D., Youssef, A. A. A., & Dudhipala, N. (2022). Innovative treatment strategies to accelerate wound healing: Trajectory and recent advancements. *Cells*, 11(15), 2439.
- Kuang, X., Roach, D. J., Wu, J., Hamel, C. M., Ding, Z., Wang, T., et al. (2019). Advances in 4D Printing: Materials and Applications. *Advanced Functional Materials*, 29(2), Article 1805290. <https://doi.org/10.1002/adfm.201805290>
- Lai, J., Liu, Y., Lu, G., Yung, P., Wang, X., Tuan, R. S., et al. (2024). 4D bioprinting of programmed dynamic tissues. *Bioactive Materials*, 37, 348–377. <https://doi.org/10.1016/j.bioactmat.2024.03.033> <https://www.sciencedirect.com/science/article/pii/S2452199X24001245>
- La Monica, F., Campora, S., & Gherzi, G. (2024). Collagen-Based scaffolds for chronic skin wound treatment. *Gels*. <https://doi.org/10.3390/gels10020137>
- Landén, N. X., Li, D., & Stähle, M. (2016). Transition from inflammation to proliferation: A critical step during wound healing. *Cell Mol Life Sci*, 73(20), 3861–3885. <https://doi.org/10.1007/s00018-016-2268-0>
- LaBarge, W., Morales, A., Pretorius, D., Kahn-Krell, A. M., & Kannappan, R. (2019). Scaffold-free bioprinter utilizing layer-by-layer printing of cellular spheroids. *Micromachines*, 10(9), 570.
- Lendlein, A., & Kelch, S. (2002). Shape-Memory Polymers. *Angewandte Chemie International Edition*, 41(12), 2034–2057. [https://doi.org/10.1002/1521-3773\(20020617\)41:12<2034::AID-ANIE2034>3.0.CO;2-M](https://doi.org/10.1002/1521-3773(20020617)41:12<2034::AID-ANIE2034>3.0.CO;2-M)
- Li, N., Liu, W., Wang, Y., Zhao, Z., Yan, T., Zhang, G., et al. (2021). Laser Additive Manufacturing on Metal Matrix Composites: A Review. *Chinese Journal of Mechanical Engineering*, 34(1), 38. <https://doi.org/10.1186/s10033-021-00554-7>
- Li, Z., & Lin, Z. (2021). Recent advances in polysaccharide-based hydrogels for synthesis and applications. *Aggregate*, 2(2), e21. <https://doi.org/10.1002/agt2.21>
- Liu, C., Xu, N., Zong, Q., Yu, J., & Zhang, P. (2021). Hydrogel prepared by 3D printing technology and its applications in the medical field. *Colloid and Interface Science Communications*, 44, Article 100498. <https://doi.org/10.1016/j.colcom.2021.100498> <https://www.sciencedirect.com/science/article/pii/S2215038221001382>
- Madni, A., Kousar, R., Naeem, N., & Wahid, F. (2021). Recent advancements in applications of chitosan-based biomaterials for skin tissue engineering. *Journal of Bioresources and Bioproducts*, 6(1), 11–25. <https://doi.org/10.1016/j.jobab.2021.01.002> <https://www.sciencedirect.com/science/article/pii/S2369969821000037>
- Mahmood, A., Akram, T., Chen, H., & Chen, S. (2022). On the Evolution of Additive Manufacturing (3D/4D Printing) Technologies: Materials, Applications, and Challenges. *Polymers*. <https://doi.org/10.3390/polym14214698>
- Malda, J., Visser, J., Melchels, F. P., Jüngst, T., Hennink, W. E., ... Dhert, W. J. A. (2013). 25th anniversary article: engineering hydrogels for biofabrication. *Advanced Materials*, 25(36), 5011–5028. Harvard.
- Mariani, F., Mattaliano, V., Mosti, G., Gasbarro, V., Bucalossi, M., Blättler, W., et al. (2008). The treatment of venous leg ulcers with a specifically designed compression stocking kit. *Phlebologie*, 37(04), 191–197.
- Marsili, L., Dal Bo, M., Berti, F., & Toffoli, G. (2021). Chitosan-Based Biocompatible Copolymers for Thermoresponsive Drug Delivery Systems: On the Development of a Standardization System. *Pharmaceutics*. <https://doi.org/10.3390/pharmaceutics13111876>
- Metwally, W. M., El-Habashy, S. E., El-Hosseiny, L. S., Essawy, M. M., Eltaher, H. M., & El-Khordagui, L. K. (2024). Bioinspired 3D-printed scaffold embedding DDAB-nano ZnO/nanofibrous microspheres for regenerative diabetic wound healing. *Biofabrication*, 16(1), Article 015001. <https://doi.org/10.1088/1758-5090/acfd60>
- Mironov, V., Reis, N., & Derby, B. (2006). Review: Bioprinting: A Beginning. *Tissue Engineering*, 12(4), 631–634. <https://doi.org/10.1089/ten.2006.12.631>
- Mogoșanu, G. D., & Grumezescu, A. M. (2014). Natural and synthetic polymers for wounds and burns dressing. *International Journal of Pharmaceutics*, 463(2), 127–136. <https://doi.org/10.1016/j.ijpharm.2013.12.015> <https://www.sciencedirect.com/science/article/pii/S0378517313010831>
- Molan, P. C. (2006). The Evidence Supporting the Use of Honey as a Wound Dressing. *The International Journal of Lower Extremity Wounds*, 5(1), 40–54. <https://doi.org/10.1177/1534734605286014>
- Nagano, H., Mizuno, N., Sato, H., Mizutani, E., Yanagida, A., Kano, M., et al. (2024). Skin graft with dermis and appendages generated in vivo by cell competition. *Nature Communications*, 15(1), 3366. <https://doi.org/10.1038/s41467-024-47527-7>
- Nguyen, H. M., Ngo Le, T. T., Nguyen, A. T., Thien Le, H. N., & Pham, T. T. (2023a). Biomedical materials for wound dressing: Recent advances and applications. *RSC Advances*, 13(8), 5509–5528. <https://doi.org/10.1039/D2RA07673J>
- Nguyen, H. T. T., Do, N. H. N., Lac, H. D., Nguyen, P. L. N., & Le, P. K. (2023b). Synthesis, properties, and applications of chitosan hydrogels as anti-inflammatory drug delivery system. *Journal of Porous Materials*, 30(2), 655–670. <https://doi.org/10.1007/s10934-022-01371-6>
- Nguyen, T. K., Le, B. T., Nguyen, M. T. H., Pham, V.-S., Do, T., Tran, P., et al. (2023c). Development of a novel direct powder screw extruder for 3D scaffold printing of PCL-based composites. *The International Journal of Advanced Manufacturing Technology*, 128(7), 3161–3182. <https://doi.org/10.1007/s00170-023-12076-8>
- Nie, L., Wei, Q., Sun, M., Ding, P., Wang, L., Sun, Y., et al. (2023). Injectable, self-healing, transparent, and antibacterial hydrogels based on chitosan and dextran for wound dressings. *International Journal of Biological Macromolecules*, 233, Article 123494. <https://doi.org/10.1016/j.ijbiomac.2023.123494> <https://www.sciencedirect.com/science/article/pii/S0141813023003860>
- Noori, S., Kokabi, M., & Hassan, Z. M. (2015). Nanoclay Enhanced the Mechanical Properties of Poly(Vinyl Alcohol)/Chitosan /Montmorillonite Nanocomposite Hydrogel as Wound Dressing. *Procedia Materials Science*, 11, 152–156. <https://doi.org/10.1016/j.prosm.2015.11.023> <https://www.sciencedirect.com/science/article/pii/S221181281500365X>
- Obagi, Z., Damiani, G., Grada, A., & Falanga, V. (2019). Principles of Wound Dressings: A Review. *Surgical technology international*, 35, 50–57.
- Okay, O. (2010). General properties of hydrogels. *Hydrogel sensors and actuators: Engineering and technology*, 1–14.
- Oprea, A.-M., Ciocalu, D., Neamtu, A., Mungiu, O. C., Stoica, B., & Vasile, C. (2010). Cellulose/chondroitin sulfate hydrogels: Synthesis, drug loading/release properties and biocompatibility. *Cellulose Chemistry & Technology*, 44(9), 369.
- Pan, S., Zhu, C., Wu, Y., & Tao, L. (2023). Chitosan-Based Self-Healing Hydrogel: From Fabrication to Biomedical Application. *Polymers*. <https://doi.org/10.3390/polym15183768>
- Paradowska-Stolarz, A., Wieckiewicz, M., Owczarek, A., & Wezgowiec, J. (2021). Natural Polymers for the Maintenance of Oral Health: Review of Recent Advances and Perspectives. *International Journal of Molecular Sciences*. <https://doi.org/10.3390/ijms21910337>
- Parimi, J. L. (2024). 8 - Role of scaffolds in wound care and management. In P. R. Solanki, A. Kumar, R. Pratap Singh, J. Singh, & K. Rb Singh (Eds.), *Nanotechnological aspects for next-generation wound management* (Eds., pp. 169–192). Academic Press.
- Pei, E. (2014). 4D printing – revolution or fad? *Assembly Automation*, 34(2), 123–127. <https://doi.org/10.1108/AA-02-2014-014>
- Pei, E., & Loh, G. H. (2018). Technological considerations for 4D printing: An overview. *Progress in Additive Manufacturing*, 3(1), 95–107. <https://doi.org/10.1007/s40964-018-0047-1>
- Percival, S. L., Woods, E., Nutekpor, M., Bowler, P., Radford, A., & Cochrane, C. (2008). Prevalence of silver resistance in bacteria isolated from diabetic foot ulcers and efficacy of silver-containing wound dressings. *Ostomy/wound management*, 54(3), 30–40.
- Piekarska, K., Sikora, M., Owczarek, M., Józwik-Pruska, J., & Wiśniewska-Wrona, M. (2023). *Chitin and chitosan as polymers of the future—Obtaining, modification, Life Cycle Assessment and Main Directions of Application*. *Polymers*. <https://doi.org/10.3390/polym15040793>
- Rajabi, M., McConnell, M., Cabral, J., & Ali, M. A. (2021). Chitosan hydrogels in 3D printing for biomedical applications. *Carbohydrate Polymers*, 260, Article 11768.
- Ramezani, M., & Mohd Ripin, Z. (2023). 4D Printing in Biomedical Engineering: Advancements, Challenges, and Future Directions. *Journal of Functional Biomaterials*. <https://doi.org/10.3390/jfb14070347>
- Rezanejad Bardjee, G., Ghavami, S., & Hosseini, S. S. (2020). A Review on pH and Temperature Responsive Gels in Drug Delivery. *Journal of Chemical Reviews*, 2(2), 80–89. <https://doi.org/10.33945/SAMI/JCR.2020.2.1> <https://www.jchemrev.com/article/99440.html>
- Rezvani Ghomi, E., Khalili, S., Nouri Khorasani, S., Esmaily Neisiany, R., & Ramakrishna, S. (2019). Wound dressings: Current advances and future directions. *Journal of Applied Polymer Science*, 136(27), 47738. <https://doi.org/10.1002/app.47738>
- S, S., R, G, A, P, Bajaj, G, John, A, E, Chandran, S, Kumar, V, V, et al. (2023). A review on the recent applications of synthetic biopolymers in 3D printing for biomedical applications. *Journal of Materials Science: Materials in Medicine*, 34(12), 62. <https://doi.org/10.1007/s10856-023-06765-9>
- Sahoo, D. R., & Biswal, T. (2021). Alginic acid and its application to tissue engineering. *SN Applied Sciences*, 3(1), 30.
- Saroia, J., Yanen, W., Wei, Q., Zhang, K., Lu, T., & Zhang, B. (2018). A review on biocompatibility nature of hydrogels with 3D printing techniques, tissue engineering application and its future prospective. *Bio-Design and Manufacturing*, 1(4), 265–279. <https://doi.org/10.1007/s42242-018-0029-7>
- Schultz, G. S., & Wysocki, A. (2009). Interactions between extracellular matrix and growth factors in wound healing. *Wound Repair and Regeneration*, 17(2), 153–162. <https://doi.org/10.1111/j.1524-475X.2009.00466.x>
- Selimović, S., Piraino, F., Gauvin, R., & Bae, H. (2015). New Biomaterials in Drug Delivery and Wound Care. *BioMed research international*, (2015), Article 320496. <https://doi.org/10.1155/2015/320496>
- Sheokand, B., Vats, M., Kumar, A., Srivastava, C. M., Bahadur, I., & Pathak, S. R. (2023). Natural polymers used in the dressing materials for wound healing: Past, present and future. *Journal of Polymer Science*, 61(14), 1389–1414. <https://doi.org/10.1002/pol.20220734>
- Shinde, S., Mane, R., Vardikar, A., Dhumal, A., & Rajput, A. (2023). 4D printing: From emergence to innovation over 3D printing. *European Polymer Journal*, 197, Article 112356. <https://doi.org/10.1016/j.eurpolymj.2023.112356> <https://www.sciencedirect.com/science/article/pii/S0014305723003596>
- Shokrani, H., Shokrani, A., Seidi, F., Mashayekhi, M., Kar, S., Nedeljkovic, D., et al. (2023). Polysaccharide-based biomaterials in a journey from 3D to 4D printing. *Bioengineering & Translational Medicine*, 8(4), e10503. <https://doi.org/10.1002/btm2.10503>
- Sikdar, P., Uddin, M. M., Dip, T. M., Islam, S., Hoque, M. S., Dhar, A. K., et al. (2021). Recent advances in the synthesis of smart hydrogels. *Materials Advances*, 2(14), 4532–4573.
- Sikka, M. P., Bargir, J. A., & Garg, S. (2024). Modern developments in burn wound dressing. *Research Journal of Textile and Apparel ahead-of-print(ahead-of-print)*. <https://doi.org/10.1108/RJTA-08-2023-0084>

- Sossou, G., Demoly, F., Belkebir, H., Qi, H. J., Gomes, S., & Montavon, G. (2019). Design for 4D printing: Modeling and computation of smart materials distributions. *Materials & Design*, 181, Article 108074. <https://doi.org/10.1016/j.matdes.2019.108074>. <https://www.sciencedirect.com/science/article/pii/S026412751930512X>
- Srivastava, G. K., Martinez-Rodriguez, S., Md Fadilah, N. I., Looi Qi Hao, D., Markey, G., Shukla, P., et al. (2024). Progress in Wound-Healing Products Based on Natural Compounds, Stem Cells, and MicroRNA-Based Biopolymers in the European, USA, and Asian Markets: Opportunities, Barriers, and Regulatory Issues. *Polymers*. <https://doi.org/10.3390/polym16091280>
- Stashak, T. S., Farstedt, E., & Othic, A. (2004). Update on wound dressings: Indications and best use. *Clinical Techniques in Equine Practice*, 3(2), 148–163. <https://doi.org/10.1053/j.ctep.2004.08.006>. <https://www.sciencedirect.com/science/article/pii/S154751604000460>
- Suarato, G., Li, W., & Meng, Y. (2016). Role of pH-responsiveness in the design of chitosan-based cancer nanotherapeutics: A review. *Biointerphases*, 11(4).
- Tabrizi, A. G., & Douroumis, D. (2022). Recent advances in 3D printing for wound healing: A systematic review. *Journal of Drug Delivery Science and Technology*, 74, Article 103564. <https://doi.org/10.1016/j.jddst.2022.103564>. <https://www.sciencedirect.com/science/article/pii/S1773224722004750>
- Thang, N. H., Chien, T. B., & Cuong, D. X. (2023). *Polymer-Based hydrogels applied in drug delivery: An overview*. *Gels*. <https://doi.org/10.3390/gels9070523>
- Umur, E., Bayrak, E., Arslan, F., Bulut, S. B., Baysoy, E., Kaleli-Can, G., et al. (2023). Advances in Three Dimensional Bioprinting for Wound Healing: A Comprehensive Review. *Applied Sciences*. <https://doi.org/10.3390/app131810269>
- van Manen, T., Janbaz, S., Jansen, K. M. B., & Zadpoor, A. A. (2021). 4D printing of reconfigurable metamaterials and devices. *Communications Materials*, 2(1), 56. <https://doi.org/10.1038/s43246-021-00165-8>
- Vijayavenkataraman, S., Lu, W. F., & Fuh, J. Y. H. (2016). 3D bioprinting of skin: A state-of-the-art review on modelling, materials, and processes. *Biofabrication*, 8(3), Article 032001. <https://doi.org/10.1088/1758-5090/8/3/032001>
- Vuerstaek, J. D. D., Vainas, T., Wuite, J., Nelemans, P., Neumann, M. H. A., & Veraart, J. C. J. M. (2006). State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *Journal of Vascular Surgery*, 44(5), 1029–1037. <https://doi.org/10.1016/j.jvs.2006.07.030>. <https://www.sciencedirect.com/science/article/pii/S0741521406013036>
- Wang, L., Xu, Z., Zhang, H., & Yao, C. (2023). A review on chitosan-based biomaterial as carrier in tissue engineering and medical applications. *European Polymer Journal*, 191, Article 112059. <https://doi.org/10.1016/j.eurpolymj.2023.112059>. <https://www.sciencedirect.com/science/article/pii/S0014305723002422>
- Willemen, N. G. A., Morsink, M. A. J., Veerman, D., da Silva, C. F., Cardoso, J. C., Souto, E. B., et al. (2022). From oral formulations to drug-eluting implants: Using 3D and 4D printing to develop drug delivery systems and personalized medicine. *Bio-Design and Manufacturing*, 5(1), 85–106. <https://doi.org/10.1007/s42242-021-00157-0>, 10.1007/s42242-021-00157-0.
- Winter, G. D. (1962). Formation of the Scab and the Rate of Epithelialization of Superficial Wounds in the Skin of the Young Domestic Pig. *Nature*, 193(4812), 293–294. <https://doi.org/10.1038/193293a0>, 10.1038/193293a0.
- Winter, G. D. (1963). Effect of Air Exposure and Occlusion on Experimental Human Skin Wounds. *Nature*, 200(4904), 378–379. <https://doi.org/10.1038/200378a0>, 10.1038/200378a0.
- Woo, K. Y., Coutts, P. M., & Sibbald, R. G. (2012). Continuous Topical Oxygen for the Treatment of Chronic Wounds: A Pilot Study. *Advances in Skin & Wound Care*, 25 (12). [https://journals.lww.com/aswcjournal/fulltext/2012/12000/continuous\\_topical\\_oxygen\\_for\\_the\\_treatment\\_of\\_7.aspx](https://journals.lww.com/aswcjournal/fulltext/2012/12000/continuous_topical_oxygen_for_the_treatment_of_7.aspx).
- Yang, W., Tu, A., Ma, Y., Li, Z., Xu, J., Lin, M., et al. (2022). Chitosan and Whey Protein Bio-Inks for 3D and 4D Printing Applications with Particular Focus on Food Industry. *Molecules (Basel, Switzerland)*. <https://doi.org/10.3390/molecules27010173>
- Yang, Y., Campbell Ritchie, A., & Everitt, N. M. (2021). Recombinant human collagen/chitosan-based soft hydrogels as biomaterials for soft tissue engineering. *Materials Science and Engineering C*, 121, Article 111846. <https://doi.org/10.1016/j.msec.2020.111846>. <https://www.sciencedirect.com/science/article/pii/S0928493120337656>
- Yu, J., Park, S., Kim, W., Ha, T., Xin, Y., Lee, J., et al. (2020a). Current Advances in 3D Bioprinting Technology and Its Applications for Tissue Engineering. *Polymers*, 12 (12), 2958.
- Yu, J., Park, S. A., Kim, W. D., Ha, T., Xin, Y.-Z., Lee, J., et al. (2020b). Current Advances in 3D Bioprinting Technology and Its Applications for Tissue Engineering. *Polymers*. <https://doi.org/10.3390/polym12122958>
- Zolfagharian, A., Kaynak, A., Bodaghi, M., Kouzani, A. Z., Gharaie, S., & Nahavandi, S. (2020). Control-Based 4D Printing: Adaptive 4D-Printed Systems. *Applied Sciences*. <https://doi.org/10.3390/app10093020>