Pioneer. Adv. Mater. 2026, 1(4): 1-17 DOI: 10.48308/piadm.2026.244062.1017

Shahid Beheshti University

Pioneering Advances in Materials

Journal homepage: http://piadm.sbu.ac.ir ISSN: 3115-7114

Research paper

Gelatin-Based Smart Nanocomposites: a Mini-Review on Fundamental Properties, Biomedical Applications and 4D Printing

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Article info:

Article history:

Received: 25/04/2026

Accepted: 14/06/2026

Keywords:
Gelatin, Smart nanocomposite, Biomedical, 4D printing

Abstract

Abstract

Gelatin, as a natural biopolymer with properties such as biocompatibility, degradability, chemical modification, and high similarity to biological tissues, has been widely considered in the development of new biomaterials in recent years. Combining gelatin with various nanomaterials not only improves its mechanical properties and stability but also enables the design of smart nanocomposites that are able to respond to physical, chemical, and biological stimuli. These properties have paved the way for extensive applications in biomedical fields, including tissue engineering, targeted drug delivery, and the design of scaffolds with high adaptability to physiological conditions of the body. On the other hand, the high potential of gelatin provides a valuable opportunity for the production of smart biostructures that can change shape or perform specific functions over time and under environmental conditions. In this mini-review, the fundamental properties of gelatin are first reviewed, followed by an examination of its role in stimuli-responsive nanocomposites, 4D printing, and novel biomedical applications.

1. Introduction

Gelatin is an inexpensive combination of polypeptides and proteins obtained from the soft tissues of various animals and is colorless or tasteless. It is the result of partially denatured thermal processing of collagen under acidic or alkaline conditions. When the temperature is reduced below the gelation point, the denatured random coil of collagen can partially recover its original triple helical structure. Gelatin has many useful properties, such as being able to form films, gel, foam, and emulsify better than other materials, and being environmentally and

humanly safe. This makes it useful in the food, pharmaceutical, and medical care industries. Gelatin films provide exceptional barrier properties against the absorption of gases, oxygen, and odors in situations with low to moderate humidity. Furthermore, due to the denatured and distinct amino acid sequence, the phase behavior of dilute and semi-dilute gelatin solutions can be easily altered by external stressors such as temperature, pH, and ionic strength. However, the mechanical strength of gelatin is not very strong, although it can be strengthened by cross-linking using enzymes or chemicals. The addition of reinforcing nanofillers is another technique to improve the mechanical properties of gelatin. Some of the nanofillers used include carbon nanotubes, hydroxyapatite, graphene oxide, clay, calcium carbonate, quantum dots, and nanofibers. To make nanocomposites that can be used in various ways. These composites exhibit superior properties compared to pure matrices and standard composites. Gelatin has recently emerged as a prominent biopolymer candidate for the fabrication of these nanocomposites. Gelatin can be native, chemically crosslinked, enzymatically crosslinked,microspheres, 3D printed, or electrospun. This means that there are various methods for fabricating new materials from gelatin. This review focuses on recent advances in gelatin-based smart nanocomposites, covering their fundamental properties, stimuli-responsive behaviors, and cutting-edge applications in biomedical engineering and 4D printing [1, 2].

2. Structure and properties

Gelatin is produced by breaking down the triple helix structure of collagen into random helical molecules. It is used in various ways in the food and pharmaceutical industries as a gelling and stabilizing agent. Gelatin is mainly obtained from mammalian sources such as skin, bone, tendon, and cartilage of cattle and pigs. Intercalated collagen molecules exist in a triple helix, formed by the intertwining of three α chains through intra- and interchain hydrogen bonding. The collagen monomer (tropocollagen), consisting of three alpha chains, has the similar amino acid sequence Gly-X-Y, where X is often proline and Y is hydroxyproline. Glycine constitutes about 30% of the total amino acid residues. Fish skin and bones, and chicken skin have been prominent sources of gelatin in recent years. To extract gelatin, a series of pre-treatments are required, such as in water at temperatures above 45 °C, to ensure good extraction. In order for collagen to dissolve properly, acidic or alkaline pre-treatments are used to break down the non-covalent bonds in collagen. After that, heat treatment breaks the hydrogen and covalent bonds, transforming the triple helix into a random coil. This converts the collagen into soluble gelatin. Gelatin is prepared in two forms: A and B. Type A gelatin is made by heating it to break down the proteins and then adding acid to it at pH 8-9. Type B gelatin (isoelectric point at pH 4-5) is produced by alkaline treatment, in which the amide groups of glutamine and asparagine are converted to glutamic and aspartic acids, respectively. Gelatin, having various functional groups such as amine, carbonyl, carboxyl, and hydroxyl, can be modified with functional groups of various materials in such a way as to provide structures with special functions such as self-healing and responsiveness to various stimuli [2].

3. Smart nanomatrials: a cutting-edge toolbox in biotechnology

Smart nanomaterials have become a major advance in nanotechnology in the past few years. What makes them different is that they can respond to factors inside the body, such as pH, enzymes, and reactive oxygen species, as well as factors outside the body, such as light and magnetic fields (Figure 1). This unique property allows them to do more than just deliver drugs.

They can also be used in medicine, bioengineering, robotics, and advanced sensing technologies. Smart nanomaterials can be considered a "multi-purpose toolbox" because their size, shape, surface properties, and composition can be modified to suit the needs of a specific study or treatment.

In tissue engineering, these nanomaterials are added to scaffolds that, when placed under physiological conditions in the body, in response to stimuli present in the damaged tissue, such as a temperature of 40 °C, an acidic pH, and a high concentration of metalloproteases, can provide effective bone tissue repair functions, including improved differentiation of stem cells into osteogenic cells, controlled release of growth factors, and elimination of bacteria, which are very effective in bone and cartilage regeneration. In biorobotics, nanoparticles that respond to light or magnets can be used as actuators or guides for microrobots.

These microrobots could one day deliver drugs precisely or perform very delicate surgeries inside the body.

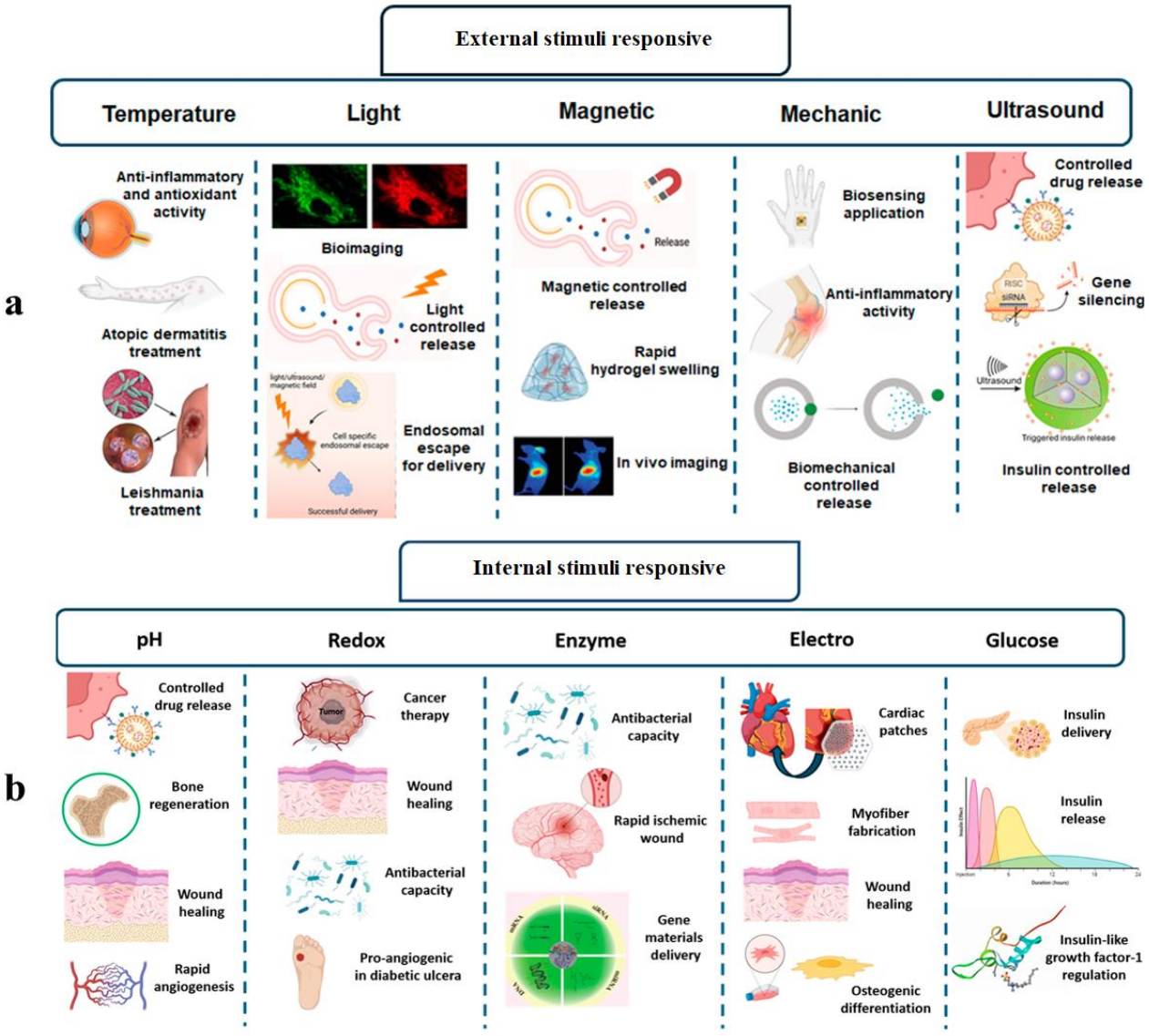

Figure 1. Classification of stimulants based on function in biomedicine.(a) external (b) internal [5]

In diagnostic sensors and analytical tools, changes in the color or fluorescence of nanoparticles upon interaction with specific molecules facilitate rapid disease detection or metabolite monitoring. In drug delivery, they deliver drugs or genes to specific cells, while also enabling imaging to track how well the treatment is working [3, 4]. These systems can now be designed outside the lab. Artificial intelligence and computational modeling are making it easier to choose the right combinations and make accurate predictions about how nanoparticles will behave in the body. Smart nanoparticles are crucial both for treating diseases and for creating new engineering tools and technologies, where their potential applications allow life sciences to combine with the latest technological advances and demonstrate their best performance. A comprehensive comparison of various organic and inorganic nanomaterials, including their specific roles in the gelatin matrix and their responsive stimuli, is summarized in Table 1.

Table 1. Comparison of organic and inorganic nanomaterials integrated into gelatin-based smart nanocomposites

Category	Nanomaterial Type	Primary Role in Gelatin Matrix	Responsive Stimuli	References
Organic	Polymeric NPs/ Nanocellulose	Mechanical reinforcement, rheological control, and sustained drug release	pH, Enzymes	[4, 6]
Organic	Dendrimers	Scaffolds for bone regeneration and carriers for growth factors	pH	[4]
Organic	Liposomes	Targeted delivery of genetic materials and bio-sensing	Light, pH, Ultrasound, Redox	[4, 8]
Organic	Protein Nanoparticles	Enhancing cell adhesion and slow release of vascular growth factors	Biological signals	[8]
Inorganic	Mesoporous Silica (MSNs)	High-capacity drug loading and targeted treatment of cancer	pH, Ionic interactions	[4, 8]
Inorganic	Gold Nanoparticles	Photothermal therapy (PTT), molecular sensing, and photoimaging	Light (NIR), Chemical changes	[9]
Inorganic	Quantum Dots (QDs)	Cell imaging, disease diagnosis, and enhancing photothermal efficiency	Light (NIR)	[10, 11]

4. Smart organic nanomaterials

4.1. Polymeric nanoparticles

Polymeric nanoparticles (NPs) constitute an established and increasingly significant component of nanotechnology, garnering substantial attention for their extensive utility in biomedical applications. Both natural and synthetic polymers serve as highly versatile constituent materials, offering key advantages such as inherent biocompatibility, biodegradability, and favorable non-toxicity profiles. The encapsulation of therapeutic agents within these polymeric nanocarriers facilitates a sustained-release kinetic profile, consequently prolonging the systemic half-life of the payload. This characteristic contributes to enhanced therapeutic efficacy and safety margins, concurrently mitigating the occurrence of adverse drug reactions and thereby improving overall patient adherence and acceptance of the treatment regimen. Loading drugs into polymer nanocarriers protects the drug against physiological conditions of the body and also increases the half-life of the drug. It also improves the solubility in the physiological environment and passes through the body's natural tissues, allowing the drug to be released in a controlled manner and without

wasting in the target tissue. In addition to the controlled release of the drug, polymer nanomaterials play a special role in regulating the rheological and mechanical properties of bioinks in 3D printing [4]. In 3D printing, besides enabling sustained drug release, polymeric nanoparticles (NPs) enhance bioink specifications [4]. According to Wu et al., the addition of nanocellulose to alginate led to improved printing precision and shear thinning for liver tissue structures [6]. Thanks to their RGD motifs for cell targeting and MMP-sensitive sites for enzyme-triggered drug release in tumors, gelatin-based nanoparticles present unique benefits [7, 8]. While Bhattacharyya et al. gelatin engineered nanocarriers for 5-Fluorouracil with pH-sensitive release (6.0–7.4) [7], Vaghasiya et al. developed MMP-2 responsive gelatin nanoparticles for cisplatin to achieving targeted therapy with decreased side effects [8]. The incorporation of gelatin nanoparticles into bioinks has brought about important advancements in the field of 4D bioprinting. According to Omidvari et al., GelMA inks with nanoliposomes have paved the way for precise pore size control for cell migration [9]. When combined with cartilage extracellular matrix, gelatin nanoparticles enabled tunable UV degradation and enhanced printability by 26-fold [10]. As a result, gelatin-based polymeric nanoparticles serve as key agents for 4D printing and smart drug delivery [6, 7].

4.2. Dendrimers

Dendrimers are nanoscale, radially symmetrical, and highly branched spherical polymers. Their unique architecture, consisting of a multivalent surface and an internal cavity, makes them ideal candidates for integration into gelatin-based smart nanocomposites. The functional groups on the outer layer of dendrimers facilitate drug targeting and attachment, while the inner void enables effective encapsulation, reducing toxicity and providing controlled release profiles. When incorporated into a gelatin matrix, dendrimers act as sophisticated nano-fillers or cross-linking agents that significantly enhance the mechanical and biological properties of the resulting hydrogel. These nanostructures are typically synthesized via 'divergent' or 'convergent' iterative methods. In the context of gelatin-based 4D printing, the precise control over dendrimer density allows for the modulation of the hydrogel's responsiveness to external stimuli. In tissue engineering, the synergy between dendrimers and gelatin is particularly evident. For instance, fourth-generation PAMAM dendrimers have been successfully embedded within gelatin hydrogels to serve as carriers for bone cell proliferation, significantly enhancing bone regeneration in animal models compared to pure gelatin scaffolds. Furthermore, PEGylated dendrimers integrated into gelatinous matrices have functioned as reservoirs for growth factors in cardiac tissue engineering, promoting the proliferation of myocardial stem cells. The amino groups on the dendrimer surface can form stable interactions with the gelatin polypeptide chains, allowing for the fine-tuned release of drugs or nucleic acids. Such gelatin-dendrimer nanocomposites also show great promise in advanced immunotherapy and targeted cancer treatments [4].

4.3. Polymeric micelles

Polymer nanomicelles are self-assembling core-shell structures formed through intermolecular hydrogen bonding, electrostatic interactions, and van der Waals forces in amphiphilic polymers. In the design of gelatin-based smart nanocomposites ,these micelles serve as versatile nano-carriers embedded within the gelatinous matrix. During micellization, the hydrophobic core effectively encapsulates proteins and gene-based therapies, which are typically insoluble in water. Integrating these micelles into gelatin hydrogels offers synergistic benefits, such as enhancing drug solubility, minimizing side

effects, and providing a protective environment against proteolytic degradation, a critical factor for the stability of gelatin-based delivery systems. A key feature of these nanocomposites is their dual-responsiveness. While micelles can respond to pH variations (e.g., the acidic microenvironment of tumors), the gelatin matrix contributes its inherent thermo-sensitivity, making the composite a candidate for 4D printing applications .For instance, the pH-responsive release of a targeted payload can be combined with the structural changes of gelatin to create multifunctional platforms for bioimaging or molecular sensing. Advanced synthetic chemistry, such as the covalent grafting of micelles onto methacrylated gelatin (GelMA) ,allows for the creation of smart, multifunctional scaffolds. These systems not only provide therapeutic delivery but also support tissue regeneration and disease diagnosis, leveraging the excellent cell-adhesiveness (RGD sequences) of the gelatin framework [8].

4.4. Liposomes

Liposomes are nanoparticles that are both hydrophilic and lipophilic. They are made up of phospholipid bilayers that look like cell membranes.

This unique structure lets them hold a wide range of drugs and biomolecules. Water-soluble compounds are trapped in the internal aqueous core, and lipid-soluble molecules are incorporated into the lipophilic layers. Liposomes can be either small or large unilamellar vesicles or multilamellar vesicles, depending on how many and how big the bilayers are. There are many ways to make liposomes, such as thin-film hydration, solvent injection, detergent dialysis, and reverse-phase evaporation.

In the last few years, new technologies like supercritical fluids and anti-solvent methods have been created to make particles more uniform, more stable, and easier to control their size.

Traditional liposomes had problems like low stability, limited drug loading, and quick release. However, modern changes have mostly fixed these problems. For example, PEGylation makes liposomes stay in the body longer and helps them get past the body's natural defenses [4].

In contemporary research, intelligent liposomes are increasingly being integrated into gelatin-based smart nanocomposites to impart multi-stimuli responsiveness, including light, redox reactions, pH alterations, and enzymatic activity.

This integration allows the gelatinous matrix to function as a structural framework that stabilizes liposomes and regulates their release kinetics. These liposome-incorporated gelatin scaffolds are capable of transporting genetic materials, imaging agents, and chemotherapeutic drugs, positioning them as advanced multifunctional platforms for precision medicine [9].

A significant advancement in this field is the development of gelatin-lipid nanoparticle (LNP) hybrids, which are utilized in genome editing and gene delivery, such as CRISPR-Cas9 technology.

In tissue engineering, the synergy between liposomes and gelatin is crucial; for instance, gelatin hydrogel scaffolds embedded with liposomes containing bone growth factors have been shown to expedite bone fracture healing by providing a sustained, localized release. In the domain of biosensing, liposomes containing enzymes or fluorescent dyes can be encapsulated within gelatin-based diagnostic kits, where the thermal and pH sensitivity of gelatin enhances the signal detection in response to bacterial infections. Furthermore, in the context of 4D printing and bio-robotics, liposomes serve as actuating components within gelatin-based microrobots.

For example, light-sensitive liposomes embedded in a photo-crosslinkable gelatin matrix (e.g., GelMA) can release their payload or trigger shape-memory effects upon laser exposure at designated locations. These examples illustrate that when combined with gelatin, liposomes transcend their

traditional role as mere carriers, becoming instrumental in the advancement of cutting-edge, smart biotechnological applications [4, 10].

4.5. Protein nanoparticles

Protein-based nanoparticles are a great way to make smart nanomaterials because they are naturally found in soy, milk, cereals, egg whites, and human or cow serum. These nanoparticles have a lot of good things about them. For example, they are easy to make, can hold a lot of stuff, are safe for living things, break down easily, have a long plasma half-life, and are not very toxic or immunogenic. They have a lot of different functional groups on their surfaces that let ligands attach and change the surface. This makes them great for making systems that respond to biological signals. Abraxane is a medicine that contains albumin nanoparticles that carry anticancer drugs. It works much better than other treatments. But they can do more than just give out drugs. In tissue engineering, protein nanoparticles are used to control how scaffolds release growth factors. For instance, gelatin nanoparticles have made it possible for vascular growth factors to be released slowly. This speeds up the growth of new blood vessels in engineered tissues. In biosensing, protein nanoparticles carry enzymes or diagnostic molecules. This makes systems that can quickly find diseases more sensitive and accurate. Adding them to biopolymer matrices has made microrobots more mobile and able to respond to stimuli, even in soft robotics. These examples show that protein nanoparticles can do more than just carry drugs. They are biologically diverse and easy to change, which makes them useful in many areas of life sciences and advanced technologies [10]. Gelatin-based protein nanoparticles are characterized by enzyme-responsive potentials without chemical crosslinkers. To deal with spinal cord injuries, Guo et al. designed gelatin/silk fibroin nanoparticles with ~72% drug loading and enzyme-triggered release [11]. While the gelatin-based implants developed by Jiang et al. degrade in response to MMP enzymes for cancer immunotherapy [12], Bian et al. used gelatin-gellan composites to generate 3D-printed biodegradable soft robotic actuators [13]. The above instances indicate that gelatin-based protein nanoparticles function as smart platforms for implants, 4D printing, and drug delivery.

5. Smart inorganic nanomaterials

5.1. Mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) have become a pivotal platform for the development of smart nanomaterials due to their homogeneous pores with tunable widths (2–6 nm), variable particle sizes (50–300 nm), extremely high surface area, significant pore volume, and outstanding biocompatibility. A smart nanocarrier should have tunable pore sizes and particle sizes to carry drugs of different molecular weights and optimally release them into the target tissue. To achieve this goal, nanopores can be modified with stimuli-responsive polymers and smart materials to protect the drug when exposed to the chemical and biological environment of the body and to optimize drug release in response to environmental stimuli. One of the novel approaches to improve the performance of these nanoparticles is their surface functionalization with negatively charged groups such as carboxylate (–COOH), sulfonate ($–SO_3^-$), or phosphate ($–PO_4^-$). This surface modification changes the physicochemical properties of the particle, increases colloidal stability in physiological environments, and reduces nonspecific adsorption of plasma proteins. On the other hand, the negative surface charge, by taking advantage of the difference in electrical charge between the surface of cancer cells and healthy cells, increases the tendency of nanoparticles to interact with HCC cells, because liver cancer cells usually have a relatively positively charged

surface. This feature provides more selective cellular uptake and greater accumulation of nanoparticles in tumor tissue. In addition, ionic bonds between the negative groups on the nanoparticle surface and the positively charged drugs allow for controlled and pH-sensitive release, such that in the acidic environment of the tumor, the bonds are broken and the drug is released in a targeted manner. The results of cellular and animal studies have shown that these systems increase antitumor efficacy, reduce systemic toxicity, and improve drug biodistribution. Overall, negatively charged mesoporous silica nanoparticles are a promising approach for the development of smart drug delivery systems in the treatment of liver cancer [4, 10]. The combination of mesoporous silica nanoparticles with gelatin matrices generates smart nanocomposites for 4D printing and biomedical purposes [14]. Cui et al. combined gelatin methacrylate with Sr^{2+}/Zn^{2+} co-doped MSNs to develop injectable photo-crosslinked hydrogels for osteoporotic osseointegration [14]. Also, by fabricating electrospun PLGA/gelatin dressings with strontium-doped mesoporous silicon, Li et al. achieved 96.1% wound closure [15]. The above investigations approve the use of gelatin-MSN hybrid systems for drug delivery and tissue engineering purposes.

5.2. Gold nanoparticles

Gold nanoparticles (AuNPs) have significant potential for cancer diagnosis and drug delivery due to their ease of synthesis, high specific surface area, surface plasmon resonance (SPR), and multi-functionality. However, to enhance their stability and biocompatibility in physiological environments, gelatin is frequently employed as a natural polymer matrix or capping agent. Gelatin-coated AuNPs exhibit improved non-toxic and non-immunogenic profiles, alongside enhanced permeability and retention (EPR) effects, which are critical for tumor targeting. Various morphologies, including gold nanorods, nanostars, and nanocages, can be successfully stabilized within gelatin-based nanocomposites, preserving their unique optical and physical properties for photothermal therapy (PTT), photodynamic therapy (PDT), and biosensing. The presence of gelatin provides abundant functional groups (like amine and carboxyl groups) that facilitate the attachment of drugs, targeting ligands, or proteins onto the AuNP surface [16]. For instance, gelatin-gold nanocomposites functionalized with specific amino acids or isoDGR labels can achieve superior targeted delivery and localized photothermal effects. Furthermore, the thermo-responsive nature of gelatin adds a "smart" dimension to these platforms, allowing for controlled drug release or shape-memory behavior in 4D printing applications, making them powerful tools in bioengineering and smart technologies [17, 18].

5.3. Quantum dots (QDs)

Quantum dots (QDs) are semiconductor nanoparticles (2 to 10 nm) that exhibit unique quantum-confined optical properties. When integrated into gelatin-based smart nanocomposites, they provide excellent platforms for cell imaging, disease diagnosis, and targeted drug delivery. Among various QDs, carbon quantum dots (CQDs) have gained significant attention due to their superior biocompatibility and the ease of being grafted onto the gelatin backbone. Depending on the precursors, CQDs possess various hydrophilic functional groups (carboxyl, hydroxyl, and amine) that facilitate stable covalent or electrostatic interactions with the polypeptide chains of gelatin [19].

The functionalization of QDs within gelatinous matrices significantly enhances their biological effectiveness. For instance, incorporating PEGylated QDs into gelatin hydrogels facilitates their penetration into cancerous tissues under

physiological conditions. Moreover, the synergy between QDs and gelatin is pivotal for 4D printing and photothermal therapy. By modifying gelatin-based scaffolds with near-infrared (NIR) light-sensitive QDs, the photothermal conversion efficiency is optimized to maintain temperatures in the range of 39–41°C.

This localized heating, supported by the thermo-responsive nature of gelatin, triggers-controlled drug release and shape-transformation in 4D-printed constructs, making them highly effective for advancing clinical goals in regenerative medicine [20, 21].

5.4. Black phosphorus (BP)

Black phosphorus (BP), first synthesized in 1914, has garnered significant interest for its unique properties. As a layered semiconductor similar to graphene, BP consists of phosphorus atoms in six-membered rings.

However, BP's high sensitivity to light and temperature leads to rapid oxidation in air. In the development of gelatin-based smart nanocomposites, the gelatin matrix serves as a crucial protective barrier, encapsulating BP nanoparticles to prevent oxidation while maintaining their biocompatibility. Each phosphorus atom in BP is sp3 hybridized, and the layers are held together by weak van der Waals forces.

A key advantage of integrating BP into gelatinous scaffolds is its exceptional ability to absorb and emit NIR radiation. This makes BP-reinforced gelatin nanocomposites ideal for photothermal therapy and photoacoustic (PA) imaging of cancer. To enhance stability and solubility, PEGylated BP nanoparticles can be fabricated and subsequently embedded within gelatin hydrogels. These BP-gelatin hybrids exhibit high photothermal conversion efficiency, where the heat generated by BP under NIR light can trigger the thermo-responsive shape-memory effect of gelatin, a fundamental mechanism in 4D printing.

These features position the BP-incorporated gelatin system as a promising nanotheranostic agent for combined therapy and advanced tissue engineering [4, 22].

5.5. Smart nanocomposite response to stimuli

Smart hydrogels, or stimuli-responsive polymers, appeared later than conventional hydrogels, with the term “smart” coined by Kuhn and colleagues in 1948. Unlike traditional hydrogels, these polymers respond to external stimuli, gaining enhanced properties and broader applications. Their behavior is reversible: the macroscopic changes revert once the stimulus is removed. The swelling properties of smart hydrogels have attracted significant interest, driving applications in drug delivery, separation processes, sensors, contact lenses, and many other areas [23, 24]. The hydrogels containing gelatin-based smart nanocomposites present multi-stimuli responsiveness [25]. By employing gelatin methacrylate with ROS- and pH-responsive nanoparticles, Li et al. designed a double network hydrogel for self-regulating Cu^{2+} release [25]. Moreover, another research combined PNIPAM, alginate, and carbon nanotubes responding to H_2O_2, pH, NIR-II light, and temperature to design a multi-responsive hydrogel [26]. In addition, smart gelatin-based hydrogels have been designed with pH, H_2O_2, and glucose responsiveness for neural tissue engineering [27]. The above-mentioned studies confirm the use of gelatin-based smart nanocomposites as adaptive platforms for tissue engineering, 4D printing, and drug delivery.

5.5.1. pH-responsive

Gelatin-based smart hydrogels exhibit inherent pH-responsiveness due to the presence of ionizable functional groups (amino and carboxyl groups) along the gelatin polypeptide backbone. This pH-sensitivity can be further tuned by

incorporating acidic or basic monomers such as PAAc or PMAA into the gelatin network, creating sophisticated gelatin-based nanocomposites [28]. The protonation and deprotonation of these groups in response to environmental pH modulate the charge density, swelling ratio, and mechanical properties of the gelatinous scaffold [29]. OS/Donan osmotic pressure from mobile counterions drives swelling at high pH (deprotonation increases fixed charge), while low pH reduces charge and swelling [30]. In these systems, OS/Donan osmotic pressure, driven by mobile counterions, induces swelling at high pH as deprotonation increases the fixed charge density within the gelatin matrix, while low pH environments typically reduce charge and swelling. For 4D printing and biomedical applications, design choices such as the degree of gelatin methacrylation (GelMA), crosslink density, and the integration of pH-sensitive nanofillers allow for precise control over the pH range and biodegradation rates. A key advantage of using gelatin as the primary matrix is its superior biocompatibility compared to purely synthetic pH-responsive polymers. Furthermore, to overcome structural integrity trade-offs at high swelling ratios, gelatin can be combined with zwitterionic components or dual-responsive designs [31]. Tuning the pH response of these gelatin nanocomposites enables targeted delivery to the GI tract or colon, the development of smart wound dressings, and the creation of 4D-printed scaffolds that adapt their shape and release profiles to the acidity of diseased or inflamed tissues.

5.5.2. *Temperature-responsive*

Thermo-sensitive hydrogels are water-filled polymer networks that swell or deswell with temperature changes, driven by a balance shift between hydrophilic/hydrophobic interactions and water [8]. These polymers are categorized into LCST-type and UCST-type systems. LCST polymers (like NIPAM) deswell above a critical temperature, while UCST systems exhibit gelation or increased solubility upon heating. Gelatin is a prominent example of a natural UCST-based polymer in terms of its sol-gel transition; it forms a triple-helix structured gel at lower temperatures and undergoes a transition to a random-coil sol state upon heating above its gelation temperature (typically ~30–35°C). In the context of gelatin-based smart nanocomposites, this inherent thermal responsiveness is crucial for 4D printing, where temperature-induced phase changes allow for shape-memory effects and precise structural control. By incorporating nanoparticles into the gelatin matrix, the tunable thermal responsiveness enables applications like controlled drug release and tissue engineering, where the hydrogel's mechanical properties and swelling behavior are modulated by physiological temperature shifts. The synergy between gelatin's UCST behavior and other smart components allows for the design of dually-responsive or complex 4D structures [32, 33].

5.5.3. *Electro-responsive*

Electro-sensitive polymers are smart polymers that react to external electric fields, allowing electrically driven swelling or deswelling for actuation and sensing in hydrogel systems [10, 11]. They fall into two main categories: ionic (conductive) polymers and dielectric polymers. Ionic electro-sensitive polymers rely on mobile ions and electrochemical processes like redox reactions to alter charge storage and osmotic/electrostatic interactions, with oxidation inserting ions into the polymer and reduction releasing them, driving volume changes as the environment shifts from acidic to basic [12]. Dielectric electro-sensitive polymers use the electric field to induce deformation via Coulombic forces without significant ion migration or redox chemistry, affecting crosslinking tension and network polarization. These materials offer high-speed, low-voltage actuation and are useful for

sensing and dynamic mechanical applications [34]. In a study conducted by Zhang et al., a conductive gelatin methacrylate–poly(aniline) (GelMA–PANI) hydrogel was developed for cell encapsulation. In this system, gelatin methacrylate provided a biocompatible and photocrosslinkable matrix supporting cell adhesion and proliferation, while the incorporation of poly(aniline) imparted electrical conductivity. Thus, gelatin contributed to both the biological functionality and structural integrity of the hydrogel, enabling its application in electrically responsive tissue engineering, particularly for cardiac and neural regeneration [35].

6. Applications in drug delivery system

According to the 2011 IUPAC recommendations, polymeric particles with a diameter of approximately 0.1–100 μm are referred to as polymeric microparticles, while those with diameters of about 1–100 nm are called polymeric nanoparticles. These systems can each be categorized into two morphological classes: spheres and capsules. Spherical particles are polymeric and have a uniform, spherical form in which the drug is physically and homogeneously dispersed within the polymer matrix. Capsule-like particles, on the other hand, consist of at least two-phase domains in which a drug nucleus (whether fluid or solid) is embedded inside a polymeric envelope that forms the outer layer and can subsequently release the drug. Various methods have been developed to prepare gelatin-based micro- and nano-drug delivery systems (DDSs), as described in multiple reviews, and these can be grouped into physico-chemical and mechanical approaches. Physico-chemical processes rely on precipitation or flocculation of the colloidal material and include desolvation, precipitation, and coacervation. In contrast, mechanical processes involve specialized equipment to generate particles, such as electrospray, spray drying, and emulsification [34]. In order to generate multifunctional systems of drug delivery, gelatin integrates with other nanomaterials and polymers. Sultana et al. used PEG-functionalized graphene to design a gelatin-chitosan film. They achieved 95% cell viability, antimicrobial activity, and pH-responsive release at pH 4.5, 7.0, and 8.0 [36]. In a PVA-gelatin-montmorillonite hydrogel developed by Sanjabi et al. for clindamycin, release rate and swelling were controlled by clay content through Fickian transport [37]. Also, using phenytoin-loaded PLGA nanoparticles, a temperature-responsive GelMA/NIPAm hydrogel was designed by Daaboul et al. The hydrogel showed release rates of ~20% and ~34% at 37°C and 40°C over 7 days, respectively [38]. The mentioned examples underline the use of gelatin-based nanocomposites as versatile, stimuli-responsive platforms for the purpose of controlled drug delivery, which is in alignment with the scope of the present mini-review on gelatin-based smart nanocomposites.

In the synthesis of micrometer- and nanometer-scale devices, there are no essential restrictions on the gelatin type used; numerous studies employ both Type A and Type B gelatin to achieve the desired release kinetics of biologically active molecules. Regarding the gelatin source, porcine- and bovine-skin-derived gelatins are among the most commonly used. A few studies have reported using gelatin from beef nails, camel skin, and fish skin for the development of gelatin-based drug delivery systems (DDSs) [39]. However, several works did not specify the animal source or gelatin type. Across synthesis techniques, the common feature is the use of chemical crosslinkers necessary to tune DDS degradation and drug release kinetics.

The most frequently used crosslinkers include glutaraldehyde, followed by formaldehyde, genipin, dialdehyde carboxymethyl cellulose, methylenebisacrylamide, formalin, diisopropylcarbodiimide, and calcium chloride

[39]. Less common are physical crosslinking by heat and enzymatic crosslinking mediated by enzymes such as transglutaminase. Gelatin-based DDSs have demonstrated the ability to encapsulate a wide range of compounds, spanning growth factors (e.g., TGF-β1, bFGF, VEGF, BMP-2), vitamins (e.g., α-tocopherol, vitamin D3), and plant extracts (e.g., Phyllanthus urinaria extract, cocoa-derived polyphenolic extract, capsaicin, curcumin) [40].

These systems have been studied in various cellular contexts, including L929 fibroblasts, human bone marrow stromal cells, and human adipose-derived stem cells [41].

Stimuli-responsive biomaterials, especially nanocomposite hydrogels, offer transformative potential beyond passive drug-eluting systems by enabling multi-stimuli control over therapeutic delivery.

Internal, intrinsic cues such as pH, redox potential, enzymes, glucose, and temperature can be harnessed, with some becoming dysregulated in disease to enable targeted, self-regulated treatments.

External stimuli including heat, magnetic fields, ultrasound, and light provide on-demand activation while maintaining stability in physiological environments. Other cues like electric fields or mechanical forces can be leveraged for tissue electrochemistry or biomechanical activation, offering opportunities for on-demand responses integrated with bodily processes.

By tuning threshold sensitivities and designing orthogonal responsive motifs, researchers can tailor platforms to physiological or pathological contexts and achieve precise, programmable release.

The review outlines biomedical applications of current stimuli-responsive nanocomposite hydrogels across these internal and external inputs, highlighting how stimulus type and delivery strategy shape therapeutic outcomes [42].

7. Applications in tissue engineering

Gelatin is increasingly important in tissue engineering, especially in the development of 3D scaffolds for tissue repair and regeneration. Given the increasing demand for donated bone and cardiac tissues, scaffold-based strategies are advancing towards clinical application, drawing attention to key factors such as reproducibility, cost-effectiveness, and scalability [25]. Modern 3D bioprinting enables loading scaffolds with biologics and cells, enabling complex, cost-effective, reproducible constructs for skeletal muscle, bone, and neural tissues. 4D bioprinting adds time- and stimulus-responsive behavior to better mimic native tissue dynamics [26]. Biomaterials must balance biocompatibility, biodegradability, and low toxicity. Gelatin, derived from collagen, is prominent due to orthopedic relevance and widespread use in drug delivery, hydrogels, scaffolds, and wound dressings. FDA-regulated examples like DBX Strips and absorbable gelatin sponges illustrate translational potential [27].

Gelatin is biocompatible, biodegradable, low-toxicity, and promotes cell adhesion, differentiation, and proliferation, while being degraded by body enzymes without triggering immunogenicity and offering cost-effective options across bone, skeletal, and neural applications (from bone regeneration microparticles to wound dressings and hydrogel-based chemotherapeutic delivery) [43]. Its main drawbacks include poor thermostability, often mitigated by physical or chemical crosslinking; however, physical methods offer limited crosslink density control, chemical methods can introduce cytotoxic byproducts, and enzymatic approaches, though more benign, add complexity and can hinder in situ gel formation. High water uptake can create porous structures that jeopardize cell survival if pore size and geometry are not optimized, posing a major design challenge for

high cell viability. Additionally, gelatin is typically animal-derived (commonly porcine skin), raising reproducibility and scalability concerns, especially since mechanical stability is modest and often requires reinforcement with other materials, which can complicate design, reduce reproducibility, and impact cost-efficiency and translational potential [44].

Time-enhanced 3D bioprinting with gelatin enables targeted application to injury sites, while 4D bioprinting combining a gelatin-based hydrogel with electrical stimulation induces cellular alignment and the formation of fibrous, muscle-like structures; gelatin acts as a smart biomaterial that reshapes under changing conditions (wettability, electric or magnetic fields), with promising implications for bone tissue engineering, including potential for targeted drug delivery and biosensing. Additionally, incorporating inorganic molecules into gelatin via 3D bioprinting improves homogeneity and mechanical properties, as demonstrated by scaffolds with varying gelatin and β-tri-calcium phosphate that effectively disseminate calcium phosphate nanoparticles and support enhanced in vivo bone formation. Nanoclays further augment gelatin hydrogels by strengthening mechanics, enabling controlled release of bioactive agents, and creating configurations that better mimic native tissue when combined with printing; proof-of-concept studies using VEGF-releasing gelatin methacrylate scaffolds with embedded laponite nanoparticles show rapid crosslinking, seamless blending, and steadier growth-factor release, consistent with broader evidence that nanoclays enhance protein absorption and hydrogel integrity [45]. Collectively, integrating inorganic components and nanoclays with gelatin in 3D (and 4D) bioprinting yields constructs with improved mechanical properties, controlled bioactive delivery, and closer recapitulation of tissue architecture, advancing bone tissue engineering and regenerative applications [46].

8. Applications in 4D printing

Since its inception in 2013, the domain of 4D printing has undergone considerable progress. Researchers are diligently exploring diverse techniques and materials to create objects capable of dynamically altering their texture, functionality, and form over time. The ability to translate abstract ideas into versatile prototypes has propelled advancements across multiple sectors, including healthcare and conventional manufacturing. Tissue engineering focuses on employing cell-based therapies and biological materials to restore or substitute damaged tissues and organs. The main objective in this domain is to develop synthetic scaffolds capable of effectively substituting damaged tissues. Materials exhibiting bio-mimetic characteristics and bio-responsive properties are in high demand for their capacity to enhance tissue reconstruction. Recent research milestones regarding the use of gelatin-based smart constructs in 3D/4D bioprinting and their specific biomedical applications are detailed in Table 2. 4D printing has emerged as a significant asset in this domain, facilitating the fabrication of intricate scaffolds with regulated property alterations over time. A notable advantage of 4D printing in medical applications is its ability to produce tiny implants that minimize the necessity for extensive surgical incisions [47]. gelatin served as a key component of the 3D-printed hydrogel/bioceramic core/shell scaffolds, primarily functioning as the drug-carrying core material. Owing to its excellent biocompatibility, hydrophilicity, and abundant functional groups, gelatin provided an ideal matrix for the encapsulation and controlled release of doxorubicin (DOX). The DOX-loaded gelatin core enabled effective chemo-photothermal therapy by allowing drug release in response to the NIR-II-induced thermal effect. Thus, gelatin not only contributed to the structural integrity of the scaffold but also played a crucial role in achieving

synergistic therapeutic efficacy through its dual function in drug delivery and biological compatibility. In an investigation carried out by Zhang et al. [48], gelatin was utilized as an essential constituent in the formulation of the 4D-printed hydrogel/bioceramic core–shell scaffold architecture, primarily functioning as the drug-entrapped core matrix. Due to its remarkable biocompatibility, hydrophilicity, and the presence of numerous reactive functional groups, gelatin established an appropriate microenvironment conducive to the encapsulation and regulated release of doxorubicin (DOX). The incorporation of DOX-embedded gelatin facilitated a near-infrared II (NIR-II) responsive drug release mechanism, thereby accomplishing synergistic chemo-photothermal therapeutic outcomes. Beyond its function in drug delivery, gelatin augmented the structural robustness and biological efficacy of the scaffold, underscoring its dual role in enhancing therapeutic effectiveness and promoting bone tissue regeneration.

Table 2. Applications of gelatin-based smart constructs in 3D/4D bioprinting and tissue engineering.

system Type	Composite Composition	Stimulus / Trigger	4D Response / Functionality	Biomedical Application	Ref
4D Bioprinting	GelMA-Poly(aniline) (PANI)	Electric Field	Cellular alignment and muscle-like fiber	Cardiac and Neural regeneration	[21]
4D Printing	Hydrogel/Bioceramic (Gelatin core)	NIR-II Light	Controlled drug release (DOX) via thermal effect	Chemo-photothermal therapy of bone tumors	[31]
3D/4D Printing	Gelatin/ Nanoclay (Laponite)	Chemical / Physical	Improved mechanical integrity and steady growth factor release	Bone tissue engineering	[28, 29]
4D Printing	Stimuli-responsive Gelatin	Temperature / pH	Reversible shape transformation and adaptive structure	Smart scaffolds and Soft robotics	[2, 30]
4D Bioprinting	Nanocellulose/ Alginate-Gelatin	Shear stress	Improved rheological properties and honeycomb-like tissue patterning	Liver tissue engineering	[6]

9. Conclusion

In summary, it can be said that gelatin-based nanocomposites with the ability to respond to various stimuli form a new generation of bio-smart materials that can, in addition to maintaining the biological properties of gelatin, improve its physical and chemical properties in a way that can play an important role in various biomedical and 4D printing applications. These materials not only largely overcome the challenges of mechanical weakness and stability of gelatin, but also enable the design of structures whose behavior changes dynamically and in accordance with environmental conditions; a feature that will directly lead to the creation of adaptive and intelligent systems in future medicine.

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