

REVIEW ARTICLE

Beyond structure: A review of intelligent, bioresponsive, and sustainable design paradigms for three-dimensional-printed metamaterials in drug delivery

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Abstract

Drug administration involves the precise delivery of therapeutic agents to targeted sites in a controlled manner, maximizing efficacy while minimizing adverse effects. This goal is pursued through drug delivery systems (DDSs), built from synthetic, natural, or hybrid biomaterials, that encapsulate and release drugs via diverse administration routes and mechanisms. Their core purpose is to localize pharmacological activity, reduce systemic toxicity, and protect surrounding healthy tissues. Despite advances, persistent challenges remain, including poor bioavailability, instability in drug loading and release profiles, limited targeting accuracy, undesirable systemic persistence, and inadequate spatiotemporal control. Additional concerns include inadequate chemical stability, patient compliance, and risks of long-term toxicity, all of which hinder clinical translation. To overcome these obstacles, metamaterials—engineered structures with geometry-driven properties—have emerged as promising platforms. By leveraging additive manufacturing and nanoscale design, metamaterials offer tunable architectures and unconventional physicochemical properties, enabling precise control over release dynamics, spatial specificity, and therapeutic outcomes. This review highlights the integration of metamaterials into DDSs, focusing on material selection, structural design strategies, fabrication challenges, and the novel possibilities enabled by three-dimensional printing. We also examine their applications in sustained, pulsatile, and stimuli-responsive release, targeted therapy, theranostics, and regenerative medicine. Finally, we discuss unresolved issues such as biocompatibility, scalability, and translational barriers, emphasizing the transformative potential of metamaterial-enabled DDSs in advancing precision medicine and healthcare innovation.

Keywords: Bioprinting; Drug delivery; Metamaterials

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1. Introduction

Drug administration plays a crucial role in directing therapeutic compounds precisely to diseased tissues, thereby enhancing their pharmacological effectiveness while minimizing systemic harm. This goal is often achieved through drug delivery systems

(DDSs), which are engineered constructs designed to transport active molecules selectively to pathological regions, ensuring minimal impact on adjacent healthy cells, tissues, and organs.^{1–3} Their functionality arises from the controlled encapsulation,⁴ storage,⁵ and release dynamics of the therapeutic agents.⁶ Historically, DDSs were relatively rudimentary, involving the incorporation of medicines into natural matrices such as carbohydrates,⁷ lipids,⁸ or proteins for oral administration.⁹ Modern biomedical innovations, however, have catalyzed rapid expansion in pharmaceutical strategies to achieve targeted release with fewer adverse effects by employing a wide spectrum of advanced natural and synthetic carriers. Examples include membrane-cloaked nanostructures,¹⁰ extracellular vesicles,¹¹ liposomal formulations,¹² aerosolized nanosprays,¹³ biodegradable scaffolds,¹⁴ polymer-based nanocarriers,¹⁵ monoclonal antibodies and antibody–drug conjugates,^{16,17} and multifunctional hydrogels.¹⁸ Moreover, hybrid DDSs exhibiting multiple modes of responsiveness have been engineered to achieve superior precision, often by integrating hydrogels with nanoscale or macroscale delivery modules.^{19–21} Despite their diversity, many of these platforms are unified by shared physicochemical traits, including porosity,²² biodegradability,²³ injectability,²⁴ adaptability,²⁵ and self-repairing capacity.²⁶ Beyond these intrinsic features, several can be designed to respond to external or endogenous stimuli, such as changes in temperature,²⁷ pH,²⁸ enzymatic activity,²⁹ or light exposure,³⁰ thereby enabling modulation of their release kinetics. Nonetheless, persistent barriers remain, particularly in attaining high loading efficiency,³¹ achieving precise site selectivity,³² minimizing chronic toxicity,³³ and realizing extended release profiles,³⁴ all of which pose considerable challenges for their clinical translation.

Recent scientific progress has increasingly emphasized the engineering of artificial materials that exhibit behaviors absent in nature. Among the most striking outcomes of this effort is the creation of metamaterials, sometimes referred to as architected materials, whose unique characteristics are derived from carefully arranged geometries and microstructural designs rather than their chemical composition.^{35,36} Originally introduced in 1968 within the context of materials science, the concept of metamaterials has since extended to biomedical domains, including drug delivery, where their unusual physical features are being explored for therapeutic benefit. At dimensions smaller than the wavelength of incoming stimuli, metamaterials exhibit extraordinary interactions with electromagnetic radiation and acoustic waves. Such subwavelength control enables these materials to serve as “intelligent” carriers that respond selectively to environmental or externally applied triggers, ranging from pH fluctuations

and thermal changes to magnetic fields, ultrasound, and microwaves, thereby releasing their therapeutic payload only at the intended pathological site while reducing off-target toxicity.^{37–41} Through controlled interactions with electromagnetic radiation, metamaterials can generate localized thermal effects or photonic activation, enabling externally regulated drug release triggered by infrared or microwave energy.⁴² Moreover, many exhibit negative refractive indices, which enhance optical manipulation and facilitate the precise stimulation of delivery systems through targeted light exposure, a capability particularly advantageous for oncology, where spatial accuracy is critical. In addition, their inherent flexibility and design adaptability permit adjustment to complex physiological environments, improving penetration and distribution within tissues. Despite these advantages, manufacturing metamaterials with reproducible precision remains a substantial challenge. To achieve their intricate architectures, researchers increasingly employ additive manufacturing strategies,⁴³ such as advanced three-dimensional (3D) printing, which builds carriers layer by layer with programmable geometries capable of adapting dynamically to biological conditions, including pH shifts or temperature variations.^{36,44–47}

Certain classes of materials possess the intrinsic ability to undergo self-assembly as a result of their chemical and molecular characteristics. Nevertheless, to broaden or optimize these self-assembling behaviors, researchers have introduced a variety of complementary fabrication approaches. Among them, 3D printing has emerged as a particularly powerful tool in biomaterials and bioengineering research. Using extrusion-based strategies, materials with distinct mechanical and physicochemical properties can be deposited through specialized nozzles to create hierarchical composites with tailored architectures. The ability to achieve finely tuned spatial and temporal control during the printing process enables the engineering of metamaterials that better emulate the structural and functional intricacies of natural biological tissues, thereby enhancing the effectiveness of therapeutic DDSs.^{48,49} A further advantage of 3D bioprinting lies in its ability to incorporate functional biomolecules, including growth factors,⁵⁰ enzymes,⁵¹ or active pharmaceutical agents,⁵² directly into scaffold matrices, which facilitates controlled and localized release while simultaneously promoting tissue repair and regeneration.⁵³ By engineering concentration gradients of these bioactive substances within a scaffold, researchers can create biomimetic environments highly beneficial for regenerative medicine. In addition, these printed constructs can be designed to degrade at tunable rates, allowing for programmed therapeutic release over clinically relevant time scales. The

versatility of bioprinting also enables the integration of multiple materials with distinct physical and mechanical properties within a single construct, providing structural robustness alongside efficient delivery performance.^{54,55} Collectively, these advances underscore the unique capabilities of 3D printing in producing metamaterials with sophisticated, customizable geometries that are ideally suited for biomedical applications. 3D-printed metamaterials have recently emerged as a transformative class of engineered architectures with extraordinary structural, mechanical, and functional tunability, enabling sophisticated control over drug transport and release. While prior reviews, including Singh *et al.*,⁵⁶ have systematically summarized the physical properties and fabrication strategies of these systems, the field is rapidly shifting toward a new era emphasizing biological intelligence, adaptive responsiveness, and sustainability. These emerging paradigms extend beyond structural optimization, incorporating living components, real-time feedback mechanisms, and eco-conscious design philosophies. In this context, the present review redefines the landscape by exploring intelligent, biohybrid, and sustainable metamaterial-based DDSs, addressing how advanced computation, responsive bioprinting, and circular manufacturing approaches can together accelerate the translation of metamaterials from structural novelty to clinical reality.

This review critically examines the most recent progress in the development and application of printed metamaterials for drug delivery, offering a comprehensive overview of their distinctive attributes—encompassing structural, mechanical, electromagnetic, and functional properties—as well as key considerations in design, material selection, fabrication methodologies, and optimization approaches. In doing so, we highlight how these engineered systems are being integrated into drug delivery platforms to achieve higher therapeutic efficiency with reduced adverse effects. By integrating the core principles of metamaterials with recent progress in 3D printing, this review seeks to offer both conceptual understanding and practical guidance that are critical for the development of next-generation DDSs. It is our view that such an overview not only summarizes the current state of the art in this field but also sparks continued exploration into this rapidly evolving discipline. In particular, by outlining the challenges and opportunities related to biocompatibility, scalability, and translational hurdles, we emphasize how the convergence of metamaterials and additive manufacturing holds the potential to drive transformative advances in precision medicine and next-generation therapeutic delivery systems.

2. Physical properties of metamaterials

The growing attention to metamaterials in recent years stems from their extraordinary ability to display electromagnetic, acoustic, and mechanical behaviors that are seldom observed in natural substances, a property rooted in their distinct structural configurations and engineered 3D architectures.^{57,58} Typically, these materials are constructed from periodic or quasi-periodic arrangements, whose structural organization dictates how they interact with incident electromagnetic radiation. By being engineered at dimensions significantly smaller than the wavelength of the applied electromagnetic field, metamaterials can be characterized in terms of their permittivity (ϵ ; describing the response to electric fields) and permeability (μ ; describing the response to magnetic fields). Under specific conditions, the effective electric permittivity and magnetic permeability can attain negative values, resulting in negative-index or left-handed materials in which wave propagation obeys the left-hand rule of electromagnetism. Such optical and electromagnetic metamaterials enable an unprecedented degree of control over the guidance and transmission of light and electromagnetic waves. In parallel, mechanical metamaterials are deliberately engineered to regulate responses across elastic, nonlinear elastic, plastic, and fracture domains, allowing precise tuning of properties such as isotropy, auxeticity, and fracture resistance. These tailored characteristics hold critical significance not only for biomedical innovations, including drug delivery platforms and implantable systems, but also for aerospace technologies and the advancement of next-generation composite materials.^{59,60} Collectively, these innovations overcome the constraints imposed by naturally available material properties, thereby reshaping the landscape of functional material design and establishing metamaterials as a central focus of modern materials science.

Within the domain of additive manufacturing, and particularly in bioprinting, one of the most persistent hurdles is the commercial-scale fabrication of intricate micro- and nanoscale metamaterial architectures.⁶¹ While microscale constructs have been successfully realized in research environments, the reliable production of large, fully functional metamaterial assemblies remains challenging, continuing to limit broader applications. Consequently, the field increasingly demands advanced 3D and emerging four-dimensional (4D) printing technologies that combine exceptional precision with high throughput and scalability, thereby enabling the fabrication of complex structures at commercially relevant volumes.⁶² Achieving such progress necessitates not only technical innovations in printing methodologies but also a comprehensive

understanding of the mechanical, electromagnetic, structural, and functional characteristics that govern the behavior of metamaterials. Only by bridging these aspects can their immense potential be unlocked across a wide spectrum of applications, particularly in healthcare, where tailored metamaterial-based solutions could address pressing clinical and therapeutic challenges.⁶³

The following discussion highlights the fundamental properties of metamaterials that are essential to their successful integration into biomedical and healthcare technologies.

2.1. Structural properties and transport control strategies in metamaterial-based drug delivery

The structural features of metamaterials—especially those emerging from microgeometry-based design approaches—greatly expand the opportunities for tuning material behavior and enhancing their functionality in the contexts of cell–material interactions and DDSs.⁶⁴ In this framework, factors such as unit cell topology, pore size, and overall porosity are recognized as key regulators of scaffold mechanics, permeability, and biological performance. Consequently, there is a growing demand for materials whose microscopic morphology can be precisely engineered and controlled. Features including porosity,⁶⁵ permeability,⁶⁶ and surface-to-volume ratio exert a significant influence on the mechanical response of metamaterial constructs.^{67,68} Porosity plays a particularly decisive role in modulating cellular behavior as well as in facilitating the transport of nutrients and therapeutic agents. Recent studies have demonstrated that mesenchymal stem cells grown on diamond-derived scaffolds with graded density exhibited markedly elevated alkaline phosphatase activity, a well-established indicator of osteogenic differentiation and lineage specification.⁶⁹ These scaffolds were intentionally designed with lower porosity in the inner regions, which enhanced initial cell adhesion, while higher porosity in the outer layers promoted cell proliferation and reduced the risk of pore blockage. Complementary computational models of gyroid lattice structures further confirmed that greater porosity, together with the resulting increase in permeability, primarily stimulated cellular proliferation. Although scaffolds with larger pore sizes initially displayed diminished adhesion, their superior ability to support oxygen and nutrient transport ultimately led to more rapid cell growth and expansion.

It is worth emphasizing that achieving an appropriate cellular density within scaffolds relies on a delicate balance between available surface area and material permeability, parameters that are particularly important in biomedical contexts such as bone tissue engineering. While high porosity can facilitate fluid penetration and nutrient

diffusion, it typically compromises overall strength, thereby limiting structural stability. Consequently, the design of porous scaffolds requires careful optimization to maintain adequate transport of metabolites while preserving compatibility with native tissue. Moreover, the kinetics of drug release from porous carriers are governed by a variety of factors beyond pore architecture alone, including physicochemical properties of the surrounding fluid, interfacial tension, and molecular interactions between the therapeutic payload and the carrier matrix. Thus, modifications in porosity alone are insufficient to guarantee predictable drug release, especially when exposed to dynamic physiological environments.⁷⁰

Hydrodynamic metamaterials represent a class of engineered structures whose internal architectures are deliberately designed to manipulate fluid transport in controlled and predictable ways.⁷¹ By introducing anisotropy into their microstructural organization, these systems can exhibit unconventional flow behaviors that are not typically achievable in natural porous materials. Such fine-tuned regulation of fluid motion across micro- and macroscales offers opportunities to enhance transport processes and improve the performance of biomedical devices. In the context of drug delivery, porous hydrodynamic metamaterials are particularly attractive for implantable systems, as they can facilitate site-specific administration of therapeutics while reducing systemic exposure and collateral tissue damage. One of their remarkable features lies in their ability to function as “hydrodynamic cloaks,” generating protected zones of minimal fluid velocity that serve as local drug reservoirs. Upon demand, these structures can be reconfigured into “concentrators” or intermediate states, effectively boosting local flow intensity and drug dosage at the target region. This dynamic switching capability offers precise spatiotemporal control over release kinetics, making it adaptable to individual therapeutic requirements. Importantly, unlike conventional scaffold strategies, where release is primarily dictated by pore size and diffusion pathways, hydrodynamic metamaterials achieve regulation through direct modulation of fluid flow patterns.⁷² This distinctive mechanism underscores their promise as a next-generation platform for highly responsive and personalized drug delivery.

The surface-to-volume ratio is also a critical microgeometric parameter that exerts a profound influence on both the loading capacity and the release kinetics of a metamaterial-based DDS, as well as on cell fate. A high surface-to-volume ratio, achievable through intricate nanoscale architectures or highly porous micro-lattices, provides an extensive interface for drug adsorption and cell attachment. In the context of drug delivery, a

large interfacial area can significantly enhance the initial loading efficiency of therapeutic agents, particularly those with high molecular weight or with strong affinity for the scaffold material. Subsequently, during the release phase, a high surface-to-volume ratio facilitates a more rapid initial release (burst release) due to the greater number of drug molecules situated near the interface, while also sustaining a more effective long-term release profile by maintaining a high concentration gradient between the carrier's interior and the surrounding medium.⁷³ From a biological perspective, the surface-to-volume ratio directly modulates cell–material interactions. A higher surface-to-volume ratio presents more anchoring sites for cell adhesion proteins (e.g., fibronectin, vitronectin), thereby potentiating stronger cell adhesion and spreading.^{74,75} This is particularly crucial for guiding stem cell differentiation, as specific lineages are sensitive to adhesion density. For instance, osteogenic differentiation of mesenchymal stem cells is often promoted on surfaces that support robust adhesion and spreading, a condition favored by a high surface-to-volume ratio.⁷⁶ Furthermore, in highly convoluted architectures with a massive surface-to-volume ratio, the local micro-environment—including protein adsorption, ion exchange, and the presentation of biochemical cues—can be finely controlled, making the scaffold itself a potent, active signaling entity rather than a passive physical support. A compelling illustration of this principle is found in nanoscale metamaterials, such as those fabricated via two-photon lithography. These structures can achieve surface-to-volume ratios that are orders of magnitude higher than those of conventional scaffolds. Studies have shown that such nano-architected surfaces can induce significant lipid peroxidation and cytoplasmic membrane blebbing in cancer cells, leading to potent, mechanics-driven cell death—a therapeutic effect

that is intrinsically tied to the extreme surface-to-volume ratio and its direct physical interaction with the cellular membrane, offering a novel mechanism to overcome drug resistance.⁷⁷

Overall, metamaterials provide distinct benefits through their capacity to finely tune key structural features, including porosity, permeability, surface-to-volume ratio, and fluid transport behavior, that are fundamental to the optimization of DDSs.^{22,78,79} Such controllable characteristics not only enable the efficient regulation of molecular diffusion and convective flow but also create a favorable microenvironment for nutrient exchange, cellular adhesion, and metabolic waste clearance. These integrated effects collectively enhance cell viability and functionality while accelerating processes of tissue repair and regeneration, underscoring the potential of metamaterials as versatile platforms for advanced therapeutic delivery. We present the stel nanoscale archeta materials and their corresponding drug delivery functions in Table 1.

2.2. Mechanical properties of metamaterials for improving drug delivery efficiency

The continuous drive to expand the functional limits of materials has fostered the emergence of mechanical metamaterials, a class of architected structures with unconventional elastic responses.^{80–82} A hallmark feature of these systems is their anisotropic elasticity, which governs how they deform under defined loading conditions. Their mechanical responses are generally described by constitutive relationships valid at low strain levels and under near-isothermal environments. Classical elastic constants, including Young's modulus, bulk modulus, shear modulus, and Poisson's ratio, are central in characterizing stiffness, compressibility, and rigidity, thereby providing benchmarks for assessing the performance of structural

Table 1. Structural properties of metamaterials and their drug delivery functions

Structural properties	Mechanism/key physical feature	Relevant drug delivery system scenario	Advantages vs. conventional carriers
Auxetic (negative Poisson's ratio)	Expands laterally under tension; strain redistribution	Expandable stents, wound dressings, adaptive scaffolds	Tunable pore opening under load, improved tissue integration
Gyroid/Triply periodic minimal surface structures	Interconnected continuous pores, high surface area	Oral controlled-release printlets, tissue scaffolds	Geometry-dependent diffusion; enhanced mass transport
Pentamode metamaterials	High bulk modulus but near-zero shear modulus (liquid-like)	Pressure-responsive release systems	Fluid-like stress response for mechanically triggered release
Hydrodynamic metamaterials	Microstructural anisotropy controls local flow	Implantable local infusion devices	Direct regulation of convection-driven release
Acoustic metamaterials	Induce microstreaming and enhance penetration	Transdermal rapid delivery (e.g., epinephrine patch)	On-demand multi-burst dosing, faster systemic uptake
Electromagnetic/terahertz biodegradable metamaterials	Resonance shifts and localized heating/monitoring	Smart patches with real-time theranostics	Simultaneous drug release + monitoring; biodegradable

systems subjected to elastic strain. Unlike conventional materials, mechanical metamaterials utilize rationally designed microarchitectures to tune these constants, resulting in behaviors that would otherwise be inaccessible in natural systems.⁸³ For instance, structures exhibiting negative stiffness can facilitate rather than resist deformation, producing dramatic volume changes under stress. Particularly significant in this context is Poisson's ratio, which quantifies lateral contraction or expansion relative to longitudinal strain under uniaxial loading. While typical materials display positive Poisson's ratios, recent innovations have broadened this design space to include highly negative values. Gao *et al.*⁸⁴ verified this concept by engineering a metamaterial characterized by highly adjustable negative Poisson's ratios (NPRs) together with reduced localized stress accumulation. The architecture, constructed from cylindrical shell-beam modules, was realized through a combination of finite element simulations and stereolithography-based 3D printing, which enabled both fabrication and experimental validation of the system. Experimental validation under tensile and compressive loading confirmed numerical predictions, with NPRs as low as -1.618 in tension and -1.657 in compression. Such architectures offer potential for minimally invasive medical applications, including controlled percutaneous delivery and personalized therapies.⁸⁴

Babae *et al.*⁸⁵ developed kirigami-inspired stents, designed as auxetic mechanical metamaterials with patterned architectures that allow adjustable stiffness, controlled directional expansion, and enhanced compliance. These systems incorporate a kirigami-patterned sheath resembling snake skin in combination with a compliant actuator, enabling controlled distribution of drug reservoirs along both the circumferential and longitudinal orientations of tubular tissues, including the gastrointestinal tract, blood vessels, and respiratory passages. Verification in living porcine models with budesonide confirmed that temporary stent deployment facilitated localized submucosal drug storage, providing a sustained release profile that lasted for approximately 1 week.⁸⁵ However, one limitation of auxetic designs is their inability to maintain structural integrity under significant compressive deformation, where symmetry loss can suppress auxetic effects. Because chirality-induced rotation largely determines this behavior, introducing soft hinges, stiffer cores, or hybrid cell architectures can stabilize deformation. Jiang *et al.*⁸⁶ advanced this concept by embedding re-entrant units within chiral cores, yielding hybrid auxetic lattices capable of sequential cell opening under strains ranging from 2.91% to 52.6%. This hierarchical deformation pathway enabled the controlled release of particles under mechanical stimuli. Both

simulations and experimental analyses revealed that the ratio of cell dimensions (c/b_0) together with the re-entrant angle (θ) serve as key determinants governing stiffness, the magnitude of the NPR, and the kinetics of release behavior.⁸⁶ Reducing c/b_0 or increasing θ shifted the strain threshold for release without markedly affecting other parameters. Collectively, these strategies demonstrate how mechanical metamaterials, through engineered auxetic responses and programmable deformation modes, can be harnessed to create advanced DDSs and multifunctional biomedical devices.⁸⁶

In addition to exhibiting NPR behavior, mechanical metamaterials can display atypical mechanical responses, such as achieving a near-zero shear modulus while maintaining a relatively high bulk modulus. This unusual combination allows the material to withstand compressive forces while exhibiting fluid-like flow characteristics, thereby offering precise opportunities for regulating drug release. A prominent example is the pentamode metamaterial, which retains a solid framework but mechanically mimics a liquid by selectively supporting compression while minimizing resistance to shear deformation.⁸⁷ Such properties make pentamode architectures highly attractive for engineering drug release platforms that respond dynamically to applied mechanical stimuli, enabling sustained and site-specific therapeutic delivery. Applications of pentamode-inspired systems have been proposed for diverse biomedical contexts, including oncology, chronic disease management, and regenerative medicine, where localized and prolonged administration is required. When combined with auxetic designs, these structures further improve spatial targeting, proving especially advantageous for addressing tumor microenvironments or localized infections.

Mechanical metamaterials have also shown particular promise in the gastrointestinal tract, where controlled retention and release are crucial for effective treatment. For instance, a soft, gastric-resident metamaterial was specifically designed for oral drug delivery.⁸⁵ The device was specifically designed with high compressibility and elasticity, permitting its secure transit through the esophagus in a minimized cylindrical configuration. Upon entering the stomach, it reconfigured into an enlarged, porous, spherical shape—a structure that allows for extended retention within the gastric cavity. Fabricated with thermos-responsive materials, the device gradually released encapsulated therapeutics over a 2-week timeframe. Importantly, exposure to an endoscopically applied warm fluid (55°C) triggered disassembly of the structure, ensuring safe elimination without obstruction. This innovative design highlights the potential of mechanical metamaterials to function as minimally

invasive, thermally activated drug delivery vehicles that provide sustained release while maintaining patient safety and comfort.⁸⁵

A deeper understanding of metamaterial-based systems requires first examining their underlying mechanical performance, where achieving an optimal balance between strength and toughness is central to maintaining structural reliability and functionality during drug delivery.⁸⁸ Material strength refers to the ability of a structure to resist external loads without structural collapse, whereas toughness denotes its capacity to dissipate energy and undergo considerable deformation prior to breaking. To optimize these mechanical features, researchers have employed multilayered arrangements and diverse topological designs to reinforce strength, while toughness has been advanced through mechanisms that redistribute strain, including auxetic lattice patterns, tensegrity-inspired networks, and hybrid systems integrating both stiff and flexible elements.⁸⁹ Despite these advances, strength and toughness remain inherently competing attributes, as reinforcing one often diminishes the other.⁹⁰ Consequently, an overarching goal in metamaterial design is to integrate both high strength and toughness, producing materials that remain resilient under stress yet capable of bending without fracturing—an essential property in demanding biomedical environments.

An active acoustic metamaterial patch for minimally invasive, transdermal drug delivery has recently been developed.⁹¹ This compact therapeutic platform enhanced skin permeability by creating micron-scale transport channels and facilitating drug delivery into the dermis and deeper tissue layers through localized acoustic streaming. Additionally, the platform enabled programmable and patient-tailored modulation of drug release kinetics through digital control. When tested in a murine model of anaphylaxis, the transdermal patch successfully administered epinephrine in a multi-pulsatile manner, yielding enhanced therapeutic outcomes relative to traditional self-injection methods. Such acoustic metamaterial systems highlight the potential of combining mechanical robustness with adaptability to create advanced platforms for percutaneous drug administration and real-time pharmacokinetic management.

Overall, by enabling precise adjustment of parameters such as Poisson's ratio, bulk and shear moduli, strength, and toughness, mechanical metamaterials provide versatile platforms for biomedical use.^{92–94} Their unique ability to withstand compression while simultaneously permitting fluid-like behavior makes them particularly promising for advanced DDSs requiring accurate and tunable release profiles.

2.3. Electrical properties

Precise regulation of electromagnetic wave behavior underpins progress in fields such as wireless communication, high-resolution imaging, and advanced sensing.⁹⁵ Yet, the intrinsic atomic-scale characteristics of naturally occurring materials impose inherent limitations, preventing fine-tuned control over wave transmission and propagation. To overcome this limitation, engineered metamaterials are designed with tunable unit cell geometries, sizes, and arrangements, enabling tailored responses such as controlled radiation, scattering, and propagation.⁹⁶ Biodegradable metamaterial platforms have been developed that allow simultaneous control of drug release and real-time monitoring through resonance shifts in reflected terahertz (THz) signals. Antibiotic-loaded silk patches function as resorbable antibacterial systems that do not require retrieval after implantation, making them highly attractive for site-specific therapies.⁹⁷

In addition to programmable degradation and release behaviors, the ability to tailor structural features provides access to unconventional electromagnetic characteristics, including the emergence of a negative refractive index.⁹⁸ Such phenomena occur when both the electric permittivity and magnetic permeability exhibit negative values, producing wave-matter interactions that are absent in naturally existing substances. For example, novel ferrite-based metamaterials composed of permanent magnetic ferrite rods and metal wires have been developed that achieve negative and near-zero refraction without the need for an external magnetic field.⁹⁹ Numerical and experimental analyses confirmed their effectiveness, demonstrating strong potential for waveguiding, imaging, and precise delivery of electromagnetic energy. Such effects could be harnessed to direct electromagnetic waves to targeted tissues, enabling controlled, noninvasive drug release.¹⁰⁰

Overall, electromagnetic metamaterials expand the ability to manipulate radiation in unprecedented ways, unlocking biomedical applications in high-resolution imaging,¹⁰¹ *in vivo* sensing, and implantable or wearable antennas that improve medical device communication.¹⁰²

2.4. Functional properties

Beyond their mechanical, structural, and electrical properties, the functional attributes of metamaterials are increasingly recognized for their pivotal role in drug delivery, as they enable controlled release kinetics, site-specific targeting, and responsiveness to external stimuli. By incorporating therapeutic molecules into their internal frameworks, these platforms enable precise and sustained administration, maintaining therapeutically relevant concentrations over time and enhancing treatment efficacy.

Nano-metamaterials, in particular, leverage multilevel nanoscale architectures to directly influence drug release and therapeutic efficacy at the single-cell level. In tumor models, multilevel nanoscale architectures induced the accumulation of lipid, cytoplasmic, and mitochondrial ROS, driving uncontrolled cell death via severe membrane damage and blebbing, thereby overcoming drug resistance. Such precisely engineered nano-architectures demonstrate how drug delivery can be tuned at the cellular level to modulate biochemical responses and death pathways.¹⁰³ In a related development, Sun *et al.*¹⁰⁴ developed silk-derived THz metamaterial patches loaded with antibiotics, demonstrating their potential for targeted antibacterial treatment. When applied to *Staphylococcus aureus*-infected wounds in rats, these flexible patches adhered firmly to the skin, facilitating both drug delivery and real-time monitoring. Within 48 h, visible wound healing was evident, and colony-forming unit assays confirmed efficient eradication of the infection. Together, these studies highlight the versatility of functional metamaterials in creating intelligent therapeutic platforms that combine controlled kinetics, responsiveness, and diagnostic capabilities for next-generation drug delivery.

In summary, the combined influence of metamaterials' structural, mechanical, electrical, and functional attributes forms the foundation for engineering sophisticated systems optimized for therapeutic use. Features such as negative refraction permit precise control of electromagnetic waves, supporting targeted drug delivery while minimizing off-target interactions, whereas near-zero refractive indices enhance signal transmission, ensuring accurate *in vivo* delivery. Collectively, these integrated properties allow the development of therapeutic platforms that are both highly efficient and dependable. Beyond their mechanical robustness and sensing or actuation capabilities, additional physical attributes, such as optical, acoustic, and electromagnetic responses,

together with biocompatibility, remain essential for driving the continuous innovation and clinical translation of these emerging artificial materials. We summarize the above stimuli-responsive metamaterial systems in Table 2.

3. Beyond static structures: toward intelligent, responsive, and programmable systems

Traditional metamaterial research has focused on harnessing fixed geometries to yield static, predictable mechanical or electromagnetic properties, such as an NPR or negative refractive index. While foundational, this paradigm treats DDSs as passive entities. The inherent complexity and dynamism of biological systems, however, demand a new generation of DDSs capable of active dialogue with their microenvironment. This section moves beyond a mere recitation of these static properties to focus on a more advanced frontier: how the convergence of material selection, architectural design, and manufacturing processes can bestow dynamic, programmable intelligence upon metamaterials. We systematically dissect three core capabilities that define this next generation: (i) responsiveness, the ability to perceive and react to physiological cues; (ii) multifunctional integration, the fusion of delivery, sensing, and actuation within a single architecture, and (iii) shape programmability, the capacity for prescribed morphological evolution post-fabrication. Finally, we highlight how artificial intelligence (AI) and generative design are emerging as central driving forces, fundamentally revolutionizing the way we conceive and realize these sophisticated systems.

3.1. Responsive strategies: from passive diffusion to active targeting

Responsive metamaterials enable DDSs to react to physiological cues rather than relying solely on passive diffusion. For instance, a pH-sensitive hydrogel arranged

Table 2. Stimuli-responsive metamaterial systems in drug delivery

Stimulus	Responsive materials/strategies	Triggered-release mechanism
Temperature	Shape-memory polymers (polylactic acid/polycaprolactone blends), thermosensitive hydrogels	Pore size/volume change, triggered disassembly
pH	Eudragit [®] , alginate, chitosan	pH-induced swelling/degradation
Enzyme	Natural polymers (chitosan, collagen, extracellular matrix)	Enzyme-mediated degradation
Light (visible/near-infrared)	Photothermal agents, photo-crosslinkable groups	Local heating or bond cleavage
Magnetic field	Magnetic nanoparticles, composites	Magnetic hyperthermia or field-induced release
Ultrasound/acoustic	Acoustic metamaterials, cavitation-enhanced hydrogels	Enhanced penetration, fast burst release
Electric field	Conductive polymers, embedded heating wires	Joule heating or electrochemical release

in an auxetic lattice configuration can transform a minor swelling event induced by an environmental pH shift into a dramatic pore opening.¹⁰⁵ This structural amplification facilitates a rapid, burst-like drug release profile not readily achievable with conventional hydrogel spheres, enabling swift therapeutic action in response to specific pathological zones (e.g., acidic tumor microenvironments or inflamed tissues).¹⁰⁶

Metamaterials can be engineered to transduce intrinsic mechanical forces—such as vascular pulsation, muscle contraction, or tumor tissue pressure—into a trigger for drug release. A compressible, helically structured scaffold, for instance, can function as a micro-pump, expelling drug payloads from its internal reservoir upon exposure to cyclic compressive strains.¹⁰⁷ This facilitates pulsatile drug administration synchronized with physiological rhythms, enhancing therapeutic efficacy and reducing off-target effects.

Metamaterials can act as “energy lenses,” concentrating and enhancing the effects of external physical fields (e.g., ultrasound, light, magnetic fields) at precise locations. Acoustic metamaterials, for example, can focus planar ultrasound waves into micron-scale “hotspots” of pressure or microstreaming. This focused energy can transiently permeabilize cell membranes or disrupt the carrier’s internal structure, enabling the release of drugs with exceptional spatial accuracy. This approach minimizes the required energy dose systemically, thereby augmenting safety.

3.2. Multifunctional integration: from single delivery to theranostic platforms

The inherently structured nature of metamaterials provides an ideal platform for integrating diverse functional components at the microscale, elevating them from mere “carriers” to autonomous “therapeutic platforms.” A pivotal advancement involves integrating conductive nano-networks (e.g., graphene, MXene) within the metamaterial scaffold to serve as embedded sensors.¹⁰⁸ These sensors can continuously monitor local biochemical markers (e.g., glucose, hydrogen peroxide, cytokines). The acquired data are then processed by an integrated microfluidic circuit or a wireless module, which in turn commands an actuator (e.g., a microscale heater that triggers a phase-change material, or an electroactive polymer valve) to modulate drug release. This creates a self-regulated, closed-loop therapeutic system that autonomously maintains homeostasis. The concept of theranostics is elevated by pre-programming imaging contrast agents (e.g., superparamagnetic iron oxide nanoparticles for magnetic resonance imaging,¹⁰⁹ gold nanorods for photoacoustic

imaging¹¹⁰) directly into the metamaterial’s lattice. This design ensures that the carrier itself acts as a high-fidelity imaging probe, allowing for real-time and precise tracking of its biodistribution and localization. Subsequently, the same physical properties can be harnessed to initiate on-demand therapy (e.g., magneto-thermal or photo-thermal ablation) alongside controlled chemical release, enabling simultaneous diagnosis, treatment, and monitoring. A frontier in autonomous implants is the integration of energy-harvesting mechanisms. Metamaterials can incorporate triboelectric nanogenerators or piezoelectric elements that convert endogenous mechanical energy (e.g., from heartbeats, respiration, or body movement) into electricity.^{111–116} This harvested power can directly drive drug release mechanisms (e.g., electroosmotic pumps) or sustain the operation of sensing and communication modules. This paradigm paves the way for self-sustaining, battery-free implantable DDSs capable of long-term operation.

3.3. Shape programmability: four-dimensional printing for spatiotemporal control

Four-dimensional printing enables the fabrication of constructs with anisotropic material distribution or internal stresses, allowing them to undergo a predefined, multi-stage morphological transformation sequence *in vivo*.¹¹⁷ A single oral capsule, for example, could be designed to first swell gradually for sustained release, then twist open at a specific intestinal pH for a second pulse of drug, and finally unfold completely to facilitate rapid clearance. This allows for complex, time-dependent release profiles from a single, simple-to-administer dosage form.^{118,119}

3.4. The artificial intelligence-driven paradigm: generative and inverse design

Artificial intelligence excels at managing competing design objectives. A single model can be tasked with simultaneously maximizing drug loading capacity, minimizing initial burst release, ensuring mechanical resilience under physiological loads, and matching a target biodegradation timeline. Through high-throughput virtual screening, AI can evaluate millions of candidate designs *in silico*, identifying the optimal trade-offs and drastically accelerating the research and development cycle from years to days.¹²⁰ Machine learning algorithms can analyze real-time sensor data during 3D printing (e.g., melt pool monitoring in selective laser sintering [SLS]) to predict and correct defects. Furthermore, computer vision can analyze post-fabrication micro-computed tomography scans of a printed metamaterial to non-destructively predict its *in vivo* release performance, creating a robust design–manufacture–verification intelligent loop.¹²¹

4. The convergence of digital manufacturing and biofabrication: toward hybrid and four-dimensional-printed metamaterials

The integration of metamaterials with 3D printing technologies significantly enhances fabrication precision and expands structural versatility, enabling the creation of dynamic and stimulus-responsive platforms for biomedical applications.^{122–124} This synergy enables the production of intricate, patient-specific architectures that can alter their form or function in response to environmental cues, thereby supporting the development of more personalized therapeutic strategies. In contrast to traditional materials, metamaterials derive their distinctive behaviors from carefully designed periodic architectures rather than their chemical composition, endowing them with highly adjustable properties that can be programmed to reshape or deform under specific conditions. However, achieving features such as auxetic behavior (NPR), superelasticity, or tunable stiffness is challenging with traditional fabrication methods, which lack the resolution and adaptability required at the microscale. Incorporating 3D and 4D printing overcomes these limitations by offering precise control over geometry and spatial arrangement. While 3D bioprinting enables the construction of complex biomedical scaffolds using cellularized biomaterials and bioactive factors,^{125,126} 4D printing introduces a temporal dimension, allowing fabricated systems to dynamically reconfigure in response to physiological or external stimuli.¹²⁷ This convergence of metamaterials with advanced bioprinting technologies paves the way for multifunctional platforms tailored to next-generation biomedical applications. While existing literature has meticulously catalogued conventional 3D printing modalities such as extrusion, stereolithography, and SLS, the current frontier lies in hybrid biofabrication and 4D printing, where materials can evolve, heal, and reconfigure over time. This section examines how multi-material bioprinting, cell-laden constructs, and stimuli-responsive inks are being integrated to produce living or adaptive metamaterials. Furthermore, AI- and data-assisted design frameworks now enable predictive optimization of printing parameters, offering unprecedented precision in fabricating hierarchical architectures. We also discuss how additive manufacturing interfaces with microfluidics, nanorobotics, and organ-on-chip systems, illustrating how dynamic and biocompatible metamaterial platforms are enabling programmable drug release and regenerative functionalities previously unattainable by static designs.

4.1. Raw materials for three-dimensional-printed metamaterials

Native tissues are inherently complex heterogeneous structures composed of hierarchically organized building

blocks across multiple length scales, a feature that imparts multifunctionality.¹²⁸ Inspired by this principle, 3D printing, particularly bioprinting, has become a powerful strategy for constructing biomimetic scaffolds that emulate both the architecture and functions of living tissues.¹²⁹ Central to this approach is the development of bioinks—carefully engineered formulations that allow precise spatial positioning of cells, biomolecules, and scaffold materials into organized 3D constructs. In the fabrication of metamaterials for biomedical applications, including drug delivery, optimizing bioink composition is particularly crucial.¹²⁸ Their design must strike a careful balance between printability, biocompatibility, and mechanical integrity to ensure that the resulting structures fulfill both functional and therapeutic objectives.¹³⁰

Bioinks are typically formulated from a mixture of biomaterials, living cells, and bioactive agents, enabling the fabrication of constructs that closely mimic native tissue.¹³¹ Their successful integration with 3D printing platforms is crucial for advancing toward clinical translation. Nonetheless, several barriers remain, including insufficient biocompatibility, inadequate mechanical strength, and poor structural fidelity during fabrication.¹³¹ Furthermore, exposure to harsh processing parameters, including high temperatures or organic solvents, can negatively impact both cell survival and functional integrity of embedded biomolecules. Constructing high-resolution, multilayered architectures that faithfully mimic native physiological behavior remains a significant challenge in this area of research.¹³²

Bioink formulations typically utilize two primary categories of polymers: synthetic materials such as polycaprolactone (PCL), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA),^{133–135} and polyethylene oxide terephthalate-co-butylene terephthalate (PEO/PBT), as well as natural polymers including alginate, hyaluronic acid, gelatin, decellularized extracellular matrix, agarose, and nanocellulose.^{136–138} Incorporating cells and biomolecules tailored to the target tissue further enhances the functional capabilities of the engineered metamaterials. For successful bioprinting, bioinks must possess appropriate rheological characteristics, crosslinking capacity, and biological activity. Through precise adjustment of these characteristics via polymer blending and sophisticated fabrication techniques, bioengineered metamaterials can be customized for diverse tissue-specific applications, increasingly serving as programmable, localized DDSs with promise in regenerative medicine and individualized therapeutic strategies.

While the microarchitectural design of metamaterials critically shapes their performance and functional

behavior, the choice of constituent bulk materials remains a key determinant of the properties that can ultimately be realized.¹³¹ Although the designed geometries of metamaterials dictate numerous distinctive properties, the inherent traits of the base materials impose essential limitations. Metamaterials are commonly fabricated from metals,¹³⁹ polymers,¹⁴⁰ and ceramics,¹⁴¹ and the advancement of additive manufacturing has significantly expanded opportunities for producing materials with unprecedented functionalities.¹⁴² In some cases, bulk material properties are indispensable for enabling specific behaviors. For instance, shape-morphing systems, including self-folding origami constructs,¹⁴³ exploit the shape-memory properties of specialized polymers or engineered alloys to enable programmable deformation.^{144,145} In biomedical contexts, metallic metamaterials must meet stringent criteria for biocompatibility, bioactivity, and controlled biodegradability. Biocompatibility and bioactivity are comparatively easier to address, as metals like tantalum inherently exhibit compatibility with biological tissues,¹⁴⁶ and standard surface modification techniques—like anodizing and plasma electrolytic oxidation—can further improve cell-material interactions.^{147,148} In comparison, the emphasis on biodegradability within metallic metamaterials has emerged only recently as a research priority. Investigations have largely centered on magnesium,¹⁴⁹ zinc,¹⁵⁰ iron, and their alloys. However, efforts to fabricate biodegradable metallic metamaterials remain limited, mainly due to processing challenges in additive manufacturing.

In drug delivery contexts, auxetic metamaterials can be designed in diverse structural configurations—including rigid frameworks, chiral lattices, honeycomb networks, aerogels, and hydrogels—tailored to meet particular biomedical requirements. Selecting appropriate base materials is crucial for achieving biocompatibility, responsiveness to external stimuli, and effective release kinetics. Biodegradable polymers such as PLGA, polyethylene glycol (PEG), and PCL are particularly advantageous, as they allow controlled degradation and enable environment-triggered release, for instance, in response to changes in pH or temperature.¹⁵¹ Auxetic hydrogels, owing to their NPR, represent promising candidates for biomedical use.¹⁵² Their swelling and release behaviors can dynamically adjust to environmental stimuli.⁹³ Likewise, mechanical metamaterials coated with polymers combine auxetic properties with lightweight construction, adjustable stiffness, and enhanced mechanical durability, rendering them ideal candidates for drug-releasing bone implants. These implants are capable of supporting physiological loads while providing excellent shear resistance, energy absorption, and indentation

tolerance, thereby improving their potential for clinical implementation.¹⁵³ The adaptable nature of metamaterials further enhances their applicability, especially in devices such as vascular stents. These stents can be delivered in a compact, compressed form during minimally invasive procedures and subsequently expanded at the target location, where structural modifications enable controlled, localized drug release. Materials with shape-memory properties—including specific polymers, metals, and alloys—can revert from a deformed “frozen” state back to their original configuration upon exposure to external triggers such as heat, light, magnetic fields, or electrical stimulation. This reversible transformation supports both structural adaptability and on-demand drug release.¹⁵⁴ However, it is worth noting that not all metamaterials are suitable for stent fabrication. Beyond vascular applications, smart wound dressings based on metamaterials are also emerging. For instance, auxetic filament-based bandages can autonomously respond to wound swelling by opening to release therapeutic agents and closing again as the wound heals.¹⁵⁵ Despite these advancements, comprehensive assessments of auxetic hydrogels—such as those based on polyvinyl alcohol and polytetrafluoroethylene—within biological settings remain scarce, underscoring the need for further research.

Looking forward, material selection for metamaterial design is expected to increasingly emphasize the integration of electronics into structural frameworks, coupling physicochemical properties with advanced functions such as sensing, actuation, signal processing, and drug release modulation. A consistent theme across metamaterial research is the synergistic integration of multiple material responses within a single substrate. Many of the most innovative features rely on the coexistence of components with contrasting properties. For instance, electronic systems demand combinations of conductive, semiconductive, and insulating elements, while magnetic functionalities depend on the integration of magnetic and non-magnetic phases.¹⁵⁶ Similarly, achieving mechanical robustness and adaptability often requires combining soft and rigid components,¹⁵⁷ or designing composites that exhibit instantaneous, delayed, or restrained shape transformations depending on application needs. Recent studies have demonstrated the feasibility of such approaches in biomedical systems. For example, Jang *et al.* engineered a polymer-based hydrogel composite incorporating a deployable radio-frequency antenna alongside an integrated Joule-heating component.¹⁵⁸ Upon remote activation, localized heating induced the hydrogel to cross its lower critical solution temperature, causing it to transition from a solid to a liquid state and thereby triggering on-demand drug release. Likewise, auxetic

chiral polymeric combinations have proven effective in drug delivery constructs as well as skin-mounted electrophysiological sensors, due to their flexibility and conformability. Building on this concept, auxetic chiral hybrid metamaterials function as multifunctional platforms for sensing, actuation, and programmable drug delivery.¹⁵⁹ Despite these advancements, a major challenge in additive manufacturing-enabled metamaterials lies in achieving differential material responses within a single construct. Central to this limitation is material selection, as many biomedical applications demand polymers that are simultaneously auxetic, biocompatible, and biodegradable. However, identifying materials that *meet all* three criteria remains difficult, representing a critical barrier to the broader clinical translation of such systems.

4.2. Design principles of three-dimensional-printed metamaterials

The primary objective in metamaterial design is to engineer microscale architectures that elicit targeted properties at the macroscale. This methodology, often referred to as rational design, combines core physical principles with analytical and computational modeling to identify microstructural configurations that maximize overall performance.¹⁶⁰ In the context of biomedical applications, particularly for 3D-printed DDSs, this approach highlights the importance of aligning structural architecture with material composition. The success of such systems depends not only on selecting biocompatible and responsive bulk materials but also on designing interconnected microstructures that can translate these properties into predictable, large-scale therapeutic performance.

Control over geometry lies at the core of metamaterial engineering, with internal architectures—such as gyroid, cubic, or honeycomb lattices—designed to modulate porosity and surface-area-to-volume ratios. Structures with low infill densities accelerate release by maximizing surface exposure, whereas high-density architectures slow release due to reduced permeability.¹⁶¹ Core-shell architectures provide an additional layer of regulation; for instance, pH-responsive shells can protect encapsulated drugs until they encounter the alkaline conditions of the intestinal tract.¹⁶² Layered architectures, such as bilayer systems with segregated drug compartments, also enable the execution of sequential or combined therapeutic strategies. Different additive manufacturing techniques provide unique yet complementary advantages. Fused deposition modeling is widely employed to produce drug-loaded filaments, allowing the fabrication of tablets with controlled-release properties using matrices such as hydroxypropyl cellulose or ethyl cellulose.¹⁶³ Digital light processing (DLP) enables high-resolution hydrogel architectures that incorporate

stimuli-responsive functionalities, while SLS generates mechanically robust gyroid-lattice “printlets” with tunable release kinetics across various polymer blends.¹⁶⁴ Multi-material printing further expands these capabilities by combining structural polymers with functional hydrogels in a single construct, facilitating advanced, personalized, and programmable drug delivery strategies.

Another key consideration is the choice of material, which directly influences functional performance. Synthetic polymers like PLA and PCL provide mechanical robustness and tunable degradation rates, making them essential for long-term implant applications.¹⁶⁵ Thermo-responsive shape-memory polymers, including PCL/PLA blends, undergo deformation at physiological temperatures, modulating pore dimensions and controlling drug release kinetics. Ion-responsive platforms, fabricated from synthetic polyelectrolytes such as [2-(acryloyloxy)ethyl]trimethylammonium-PEG diacrylate (PEGDA), release drugs in response to local ionic fluctuations within target tissues.¹⁶⁶ Natural polymers, such as chitosan and alginate, offer intrinsic bioactivity, enabling enzyme-mediated drug release in the colon through microbial degradation. Dynamic metamaterials can further detect physiological cues to enable on-demand delivery; for example, pH-sensitive hydrogels, such as alginate, swell in the intestinal environment to release encapsulated therapeutics, like simvastatin. Enzyme-responsive systems leverage chitosan’s susceptibility to microbial lysozymes in the colon to achieve localized release.¹⁶⁷ Hybrid constructs, including alginate-PEGDA composites, combine printability with stimulus responsiveness, while Eudragit® polymers (e.g., L100-55) enable pH-triggered, site-specific delivery in the upper gastrointestinal tract.¹⁶⁸

The majority of metamaterial research starts with a design concept rooted in fundamental physical principles, which is then honed through parametric analyses and computational simulations to correlate microscale architectures with their resulting macroscopic properties. A key consideration in this workflow is defining what qualifies as a microarchitectural design. Initial studies concentrated mainly on geometric configuration, largely because additive manufacturing techniques capable of producing complex free-form structures were not yet widely accessible. These early designs typically consisted of a single material interspersed with voids, forming simple material-void composite systems. The key challenge was to identify microstructural geometries that could impart the desired large-scale properties. In the past decade, however, the emergence and growing accessibility of multi-material 3D printing have transformed the design landscape. These advances allow for the fabrication of intricate architectures with precise spatial arrangements, where individual

layers may possess distinct features and functions.¹⁶⁹ This advancement has greatly broadened the design landscape, allowing for the tailored specification of not only unit cell topology and overall geometry but also the mechanical and physical properties of individual voxels (3D pixels) throughout the structure.¹⁷⁰

In recent years, the integration of machine learning and AI has opened up novel avenues for designing metamaterials. Two primary approaches have emerged: (i) deep learning and other AI techniques that facilitate the resolution of inverse design challenges,¹⁷¹ and (ii) generative models, such as generative adversarial networks and variational autoencoders,¹⁷² that are capable of creating candidate designs tailored to specific target properties, thereby extending the scope of rational design.¹⁷³ Simultaneously, mathematical approaches such as topology optimization have demonstrated efficacy in determining the micro- and nanoscale architectures of both single-material and multi-material systems.¹⁷⁴ Despite this progress, several challenges remain. These include reliable quality prediction, development of robust AI models for optical or mechanical properties, data handling and standardization, automation of design processes, and safety assurance in biomedical contexts. Moreover, specifying clear objective functions for gradient-based topology optimization is not always feasible, which limits the efficiency of these methods.¹⁷⁵ Addressing these issues will require the integration of theoretical and experimental approaches to establish unbiased and scalable design methodologies. Such efforts could accelerate the discovery of novel metamaterial concepts beyond those attainable through intuition or traditional physical reasoning.

4.3. Fabrication strategies of three-dimensional-printed metamaterials

As outlined in the previous sections, several fabrication strategies can be employed to produce metamaterials; however, additive manufacturing has emerged as the most transformative approach. Additive manufacturing, widely referred to as 3D printing, allows for the fabrication of intricate and customizable structures spanning macro-, micro-, and nanoscale dimensions.¹⁷⁶ The typical workflow entails creating designs using computer-aided design software, translating them into printer-compatible formats, and producing the structures through precise, layer-by-layer fabrication. The broader adoption of additive manufacturing has been driven by decreasing costs of 3D printers, along with ongoing improvements in both hardware and software platforms that support the technology.¹⁷⁷ A wide spectrum of additive manufacturing techniques is now available, including extrusion-based printing, fused deposition, SLS, and melt electro-

writing, each offering distinct advantages for tailoring metamaterial architectures.

Three-dimensional-printed mechanical metamaterials enable precise, layer-by-layer construction and offer advantages including improved strength-to-weight ratios, tunable stiffness, customizable mechanical properties, and shape-transforming capabilities, rendering them especially suitable for biomedical applications.¹⁷⁸ Masoumi *et al.*¹⁷⁹ examined the compressive performance of 3D-printed bone scaffolds composed of metamaterial architectures with discrete porosities organized in cubic unit cells. Their results indicated that, although the metamaterial bone scaffolds exhibited a 5.97 % reduction in weight compared to solid bone samples, the compressive strength of vertically oriented solid standard samples remained superior to that of horizontally oriented counterparts.¹⁷⁹

Fina *et al.*¹⁶⁴ introduced a novel hybrid multi-material 3D printing platform that integrates top-down DLP with direct ink writing to fabricate composite structures and multifunctional devices within a single printing workflow. The vat photopolymerization-based DLP module enabled high-speed, high-resolution printing of complex material matrices, while the material extrusion-based direct ink writing module allows deposition of functional materials, including liquid crystal elastomers and conductive silver inks. This hybrid system offered a broad selection of inks and resins, facilitating the fabrication of functional composites with tunable mechanical properties, enhanced interfacial bonding, and multifunctional capabilities. This platform provided a versatile and robust strategy for the 3D printing of multifunctional devices applicable to soft robotics, electronics, active metamaterials, and biomedical applications. Mohammadi *et al.*¹⁸⁰ investigated soft robotic hands inspired by the biomechanics of human finger joints, constructed from auxetic metamaterials. These architectures offer increased flexibility and an extensive bending range, enabling the precise handling of delicate components, such as wires and cables. These characteristics indicate significant potential for the advancement of site-specific, minimally invasive DDSs.¹⁸⁰ Flamourakis *et al.*¹⁸¹ fabricated 3D auxetic scaffolds for tissue engineering applications, employing a re-entrant hexagonal geometry constructed from the organic-inorganic photopolymer SZ2080, which supported mouse fibroblast proliferation and guided directional cellular growth.¹⁸¹

Unlike traditional 3D printing, 4D printing enables materials to undergo predetermined shape and structural transformations in response to external stimuli, such as electric or magnetic fields, temperature fluctuations, pH shifts, or other environmental triggers.¹⁸² Conceptually, 4D printing represents a spatiotemporal extension of additive

manufacturing, where the added dimension is time, allowing dynamic adaptation of the printed construct.¹⁸³ This emerging area of 3D printing exploits materials possessing intrinsic shape-memory or energy-responsive behaviors. Hydrogels, polymers, and scaffold materials are commonly utilized in 4D printing within biomedical engineering,¹⁸⁴ facilitating the creation of stimulus-responsive smart DDSs. In a specialized layered Carbopol supporting bath with different water concentrations, Gungor-Ozkerim *et al.*¹³³ printed zein gel in an ethanol–water mixture, where modulation of hydrophobic and hydrogen bonding induced temporal changes in functions. The part of the construct printed in a supporting bath with higher water content exhibits higher drug loading, faster drug release, and a higher degradation rate than those printed in the supporting bath with lower water content. Che *et al.*¹⁸⁵ used hydroxybutyl methacrylated chitosan, which possesses dual temperature- and photo-sensitive properties, to create microneedles. The DLP approach enabled a quick generation of hydroxybutyl methacrylate-based microneedles with high resolution. The microneedles exhibited 4D properties, changing in needle dimensions upon exposure to temperature, which enhances resolution, sharpens the needles, and improves mechanical strength. These microneedles exhibited high mechanical strength,

efficient tissue penetration, and the capability to deliver small-molecule drugs with sustained release profiles.¹⁸⁵

The integration of 4D printing with metamaterials enables the fabrication of highly dynamic, programmable, and stimuli-responsive structures that can undergo controlled deformation or shape transformation in response to external environmental cues. This integration significantly expands the scope of biomedical applications, offering new possibilities for the development of adaptive and intelligent drug delivery platforms, tissue engineering scaffolds, and responsive implantable devices. As shown in Table 3, we summarized common 3D/4D printing techniques for metamaterial-based drug delivery strategies.

4.4. Optimization and development strategies of three-dimensional-printed metamaterials

The production of polymer-based auxetic metamaterials for biomedical purposes presents both notable challenges and opportunities for refinement. A key difficulty arises from the intricate geometries of auxetic architectures, which require precise multi-scale control—from macro- to micro- to nanoscale—to consistently achieve the intended NPR. Conventional manufacturing techniques often fall short in producing such intricate re-entrant or chiral architectures with sufficient fidelity. Another major limitation involves material selection, as these constructs

Table 3. Comparison of common three- and four-dimensional printing techniques for metamaterial-based drug delivery

Printing technique	Typical resolution/feature size	Common materials (examples)	Advantages (relevance to drug delivery systems/metamaterials)	Limitations/considerations
Fused deposition modeling	~100–500 μm	Polylactic acid, polycaprolactone, polyvinyl alcohol, thermoplastic polymers	Low-cost, widely available, suitable for large porous constructs and drug-loaded filaments, enabling controlled-release tablets	Heat may damage thermosensitive drugs; limited resolution
Digital light processing/stereolithography	~10–100 μm	Photopolymer resins, modified hydrogels	High resolution, capable of fabricating complex microstructures (microneedles, micro-reservoirs)	Biocompatibility concerns with photo-initiators; material options are limited
Selective laser sintering	~50–200 μm	Polymer–drug powder blends	Single-step fabrication of porous drug carriers (e.g., gyroid printlets), tunable release profiles	High equipment cost, complex processing parameters
Direct ink writing/extrusion-based bioprinting	~50–500 μm (ink/nozzle dependent)	Hydrogels, bioinks, drug suspensions	Direct printing of cell-laden or drug-loaded hydrogels, versatile formulation design, and bioresponsive scaffolds	Requires rheological optimization and post-crosslinking
Melt electro-writing/multi-photon lithography (high-resolution techniques)	<10 μm (multi-photon lithography: nanoscale)	Biodegradable polymers, functional inks	Ultra-high resolution, ideal for micro- and nanoscale metamaterial units	High cost, low throughput, limited material compatibility
Four-dimensional printing (stimuli-responsive materials)	Method-dependent	Shape-memory polymers, smart hydrogels, responsive composites	Adds temporal dimension; programmable transformation and stimuli-responsive drug release	Requires precise design of response speed and biodegradability

must simultaneously exhibit auxetic behavior and biocompatibility.¹⁸⁶ Identifying polymers that fulfill both requirements, particularly in biodegradable forms, remains a considerable hurdle.¹⁸⁷ Process-related constraints further complicate fabrication; for instance, techniques such as SLS or conventional 3D printing frequently encounter problems with resolution, interlayer adhesion, and material degradation during production. Finally, maintaining the mechanical performance of auxetic metamaterials under physiological conditions presents an additional layer of complexity, demanding careful optimization to balance durability, flexibility, and biofunctionality.

Two major challenges in additive manufacturing must be overcome to further advance metamaterial development. One key limitation stems from the inherently layer-by-layer nature of 3D printing, which results in extended fabrication times for structures that are significantly larger than the printer's resolution. To mitigate this issue, advanced additive manufacturing techniques—such as melt electro-writing and multi-photon lithography—provide promising solutions.¹⁸⁸ These techniques enable precise control over both geometric features and material properties, allowing the fabrication of auxetic architectures with high fidelity. Moreover, additive manufacturing can be used to create molds,¹⁸⁹ lithography masks,¹⁹⁰ or imprinting stamps, facilitating scalable fabrication in both size and quantity by shortening production times. An emerging strategy involves self-assembly methods, such as spinodal decomposition, to create nano-architected metamaterials.¹⁹¹ Despite limitations imposed by the intrinsic dynamics of the fabrication process, recent research has shown that spinodal-inspired metamaterials possess exceptional mechanical and biomechanical properties.¹⁹² A further challenge is the limited ability to process a wide range of materials using high-resolution additive manufacturing techniques. Although indirect additive manufacturing approaches can partially overcome this restriction, they inherently constrain design flexibility relative to direct fabrication methods. Addressing this challenge will require the development of specialized additive manufacturing systems capable of handling multiple material classes with ultrahigh resolution. Examples include machines with multiple laser sources that can accommodate different material chemistries within a single build process. In parallel, computational design and simulation tools will play a vital role in predicting the structure–property relationships of candidate architectures, enabling rational optimization tailored to specific biomedical applications. Moreover, future research should focus on developing innovative material systems specifically designed for compatibility with next-generation, ultrahigh-resolution additive manufacturing platforms.

Progress in material engineering—such as designing novel polymer blends and composites that merge auxetic properties with biocompatibility—can substantially enhance the performance of biomedical metamaterials. At the same time, fine-tuning fabrication parameters, including laser intensity, scanning speed, and layer thickness, is essential to achieve high structural accuracy and reproducibility. Moving forward, research should prioritize the co-development of advanced additive manufacturing techniques and tailored materials to ensure exceptional quality, scalability, and multifunctionality in the fabrication of metamaterials, meta-structures, and meta-devices.

4.5. Toward living and adaptive metamaterials via artificial intelligence-guided biofabrication

Moving beyond conventional lattice-based designs, AI-assisted topology optimization (TO) represents a paradigm shift toward creating highly efficient, functionally graded metamaterial architectures tailored for specific biological outcomes. Unlike parametric studies of unit cells, TO algorithms iteratively distribute material within a defined design domain to meet a set of performance objectives and constraints. When augmented with machine learning, this process is drastically accelerated and can handle highly complex, multi-objective problems inherent to biology. For instance, TO can be employed to design a bone scaffold that simultaneously maximizes permeability for nutrient diffusion and cell migration while maintaining mechanical stiffness to match the native tissue and guiding osteogenic differentiation through controlled local strain fields.¹⁹³ Deep learning models, particularly generative adversarial networks, can learn from TO-generated data to produce novel, non-intuitive architectures that optimally balance these competing demands.¹⁹⁴ Furthermore, TO can design fluidic metamaterial channels that generate specific shear stress profiles to direct endothelial cell organization for pre-vascularization, or create chemical concentration gradients by optimizing the spatial arrangement of diffusion barriers. This computational approach enables the a priori design of metamaterials that are not merely biocompatible but are proactively instructive, actively recruiting and guiding host cells or encapsulated cells towards a desired therapeutic endpoint.

The realization of computationally optimized, biologically active architectures necessitates advanced fabrication strategies that can orchestrate multiple materials and cell types with high spatial precision. Multi-material bioprinting fulfills this role, enabling the fabrication of “living metamaterials”—constructs where the engineered microarchitecture and the living cellular component are inseparable and co-manufactured.

Techniques such as extrusion-based printing with switching nozzles and DLP with dynamic photomasks allow for the deposition of distinct bioinks within a single construct. This capability is pivotal for creating complex, biomimetic tissue microenvironments. For example, a single print can combine a soft, cell-laden gelatin methacryloyl bioink to mimic the parenchyma of an organ with a stiffer, PEGDA bioink patterned into a reinforcing auxetic lattice, providing mechanical support while supporting tissue maturation.¹⁹⁵ Crucially, this allows for the precise spatial patterning of different cell types (e.g., hepatocytes & endothelial cells) and biochemical cues (e.g., growth factors tethered to specific regions of the scaffold) in accordance with the topological design. The resulting living metamaterials are therefore not passive implants but dynamic, metabolically active tissues engineered from the ground up, with their global mechanical behavior and mass transport properties dictated by the synergism between the living cells and the rationally designed, non-living metamatrix.

5. Drug delivery applications of three-dimensional-printed metamaterials and bioresponsive, self-regulated, and personalized drug delivery systems

Owing to their exceptional structural, spatial, and temporal characteristics, metamaterials hold considerable promise for advancing precision and personalized strategies in drug delivery. In the following sections, we highlight the key design aspects and material strategies that can be integrated into additive manufacturing processes to establish their role as next-generation platforms for controlled and patient-specific therapeutic applications. The next generation of metamaterial-based DDSs transcends traditional controlled-release paradigms, entering the realm of autonomous, self-regulated, and patient-specific therapy. Instead of acting as passive carriers, these smart systems integrate real-time sensing, feedback control, and actuation to achieve precise temporal and spatial regulation of drug kinetics. This section examines cutting-edge applications in closed-loop drug delivery, implantable and wearable bioresponsive devices, and 4D metamaterial scaffolds that can adapt to pathological microenvironments. Special attention is given to personalized metamaterial platforms, where computational modeling, patient-derived bioinks, and AI-guided fabrication jointly enable tailored drug dosing and on-demand release strategies. Such innovations bridge the gap between digital healthcare and advanced materials engineering, marking a decisive step toward precision medicine.

5.1. Controlled drug release

The application of metamaterials fabricated through 3D printing presents significant promise for advancing DDSs, capitalizing on the adaptability and exactitude of this manufacturing approach to improve treatment outcomes. Illustratively, auxetic structures, characterized by an NPR, have been integrated into therapeutic dressings that mechanically react to edema, thus permitting the regulated administration of medicinal compounds. The treatment of critical medical events, including anaphylactic shock, remains particularly difficult due to the necessity for both swift intervention and exact control over drug behavior in the body. In response to this challenge, recent scientific inquiry has investigated the use of sonically activated metamaterials, which employ acoustic energy to facilitate the passage of pharmaceuticals through physiological obstructions, such as the dermal layer. Through the deliberate design of their resonant properties, such platforms achieve improved tissue penetration and accurate tuning of the drug release profile, substantially augmenting the performance of cutaneous delivery methodologies. Azithromycin-loaded contact lenses were fabricated using PEGDA as the cross-linking reagent, PEG-400 as a solvent, and a photoinitiator to enable polymerization, with azithromycin incorporated as the therapeutic agent.¹⁹⁶ The resulting lenses demonstrated sustained antimicrobial activity *in vitro* against both Gram-positive and Gram-negative bacteria. These findings highlight the potential of 3D-printed drug-loaded contact lenses as a platform for effective localized ocular drug delivery. By enabling controlled and prolonged release of antibiotics directly at the infection site, this approach provides a promising strategy for treating bacterial eye infections while reducing systemic side effects and improving patient compliance.¹⁹⁶

A 3D-printed bento box model was fabricated by Kraist *et al.*¹⁹⁷ with either one chamber or two chambers to achieve controlled drug release of propranolol hydrochloride at varying time intervals, following the United States Pharmacopeia dissolution guidelines.¹⁹⁷ Commercially available extruded polyvinyl alcohol filament was employed as the polymeric printing material. As shown in Figure 1, the structure of the printed bento boxes (Figure 1B) closely matched the digital design generated by the modeling software (Figure 1A). The final models appeared yellowish brown in color, slightly darker than the original filament, likely due to the thermal effects of the printing process. The printed surfaces exhibited minor roughness, arranged in the programmed rectilinear pattern.

The one-chamber design contained both propranolol hydrochloride powder and matrix tablets in a single chamber, whereas the two-chamber design separated the two forms of the drug, with powders occupying one

compartment and the tablet in the adjacent compartment (Figure 1C). For comparison, Figure 1D shows that the size of the 3D-printed bento box was similar to that of a commercial capsule, though the bento boxes exhibited

greater width, while the capsule was slightly longer. These results demonstrate that 3D-printed bento boxes can be tailored for multi-modal drug loading, presenting a versatile strategy for controlled and sequential drug

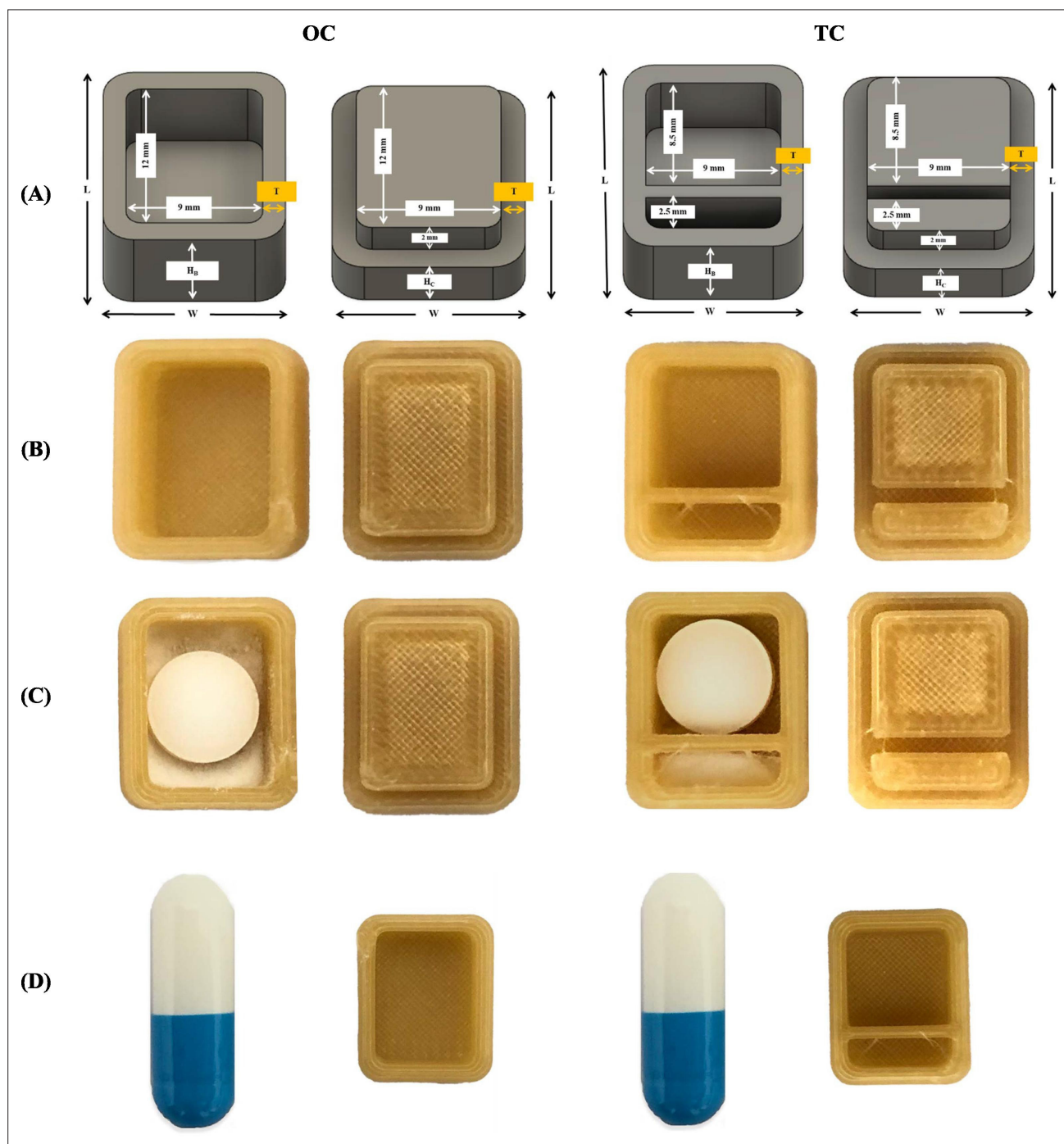


Figure 1. Schematic representations and images of a three-dimensional (3D)-printed bento box for controlled drug release. (A) Images of the 3D-printed bento box model. (B) A fabricated bento box produced by 3D printing. (C) Bento box loaded with propranolol hydrochloride powder and matrix tablets. (D) Comparison of the size between a commercial capsule No. 0 and the 3D-printed bento box.¹⁹⁷ Adapted with permission from Kraissit *et al.*¹⁹⁷ Copyright © 2022, Elsevier.

delivery. The similarity in size to conventional capsules further supports their feasibility as a future dosage form for patient-specific therapies.¹⁹⁷

Sun *et al.*¹⁰⁴ designed a biodegradable antibacterial skin patch using a silk-derived, antibiotic-loaded flexible THz metamaterial platform. By incorporating THz metamaterial resonators, the silk fibroin construct was engineered for programmable disintegration, adhering to a pre-established timeline and velocity. The liberation of the pharmaceutical agent was intrinsically coupled to this structural breakdown, a relationship that was quantitatively monitored through shifts in the metamaterial's resonant signature. Validation in a rodent model of dermal infection confirmed that this antibacterial silk-based patch possesses considerable promise for enabling synchronized drug administration and ongoing surveillance of treatment efficacy.¹⁰⁴

In another study, Jiang *et al.*⁸⁶ engineered a novel class of chiral mechanical metamaterials with a hybrid architecture. This was accomplished through the strategic incorporation of re-entrant unit cells into a matrix composed of conventional chiral cellular structures.⁸⁶ This novel design enabled sequential particle release, suggesting its applicability in DDSs requiring multi-stage delivery. Moreover, the structural adaptability of these metamaterials points toward broader applications in multifunctional composites, sensors, and actuators responsive to environmental cues.⁸⁶ Together, these examples illustrate how metamaterial-enabled DDSs can be engineered to achieve spatiotemporal control, multifunctionality, and responsiveness, offering promising pathways toward next-generation precision therapeutics.

Metamaterials provide a highly tunable and large surface area, making them excellent candidates for biofunctionalization via coatings and surface modifications to support drug delivery applications. Such strategies have been applied to enhance osseointegration and reduce bacterial colonization on implants.^{198,199} Common approaches include electrochemical modification,²⁰⁰ chemical surface treatments,²⁰¹ and advanced coating techniques.²⁰² In orthopedic surgery, where unmet clinical needs often involve both infection control and bone regeneration, surface-engineered metamaterials hold particular promise. For instance, Yavari *et al.*²⁰³ developed additively-manufactured porous metallic scaffolds that were sequentially coated with multiple functional layers, specifically designed to simultaneously suppress implant-associated microbial colonization and stimulate bone regeneration. The layered surfaces served as reservoirs for controlled delivery of vancomycin together with bone morphogenetic protein 2, releasing these agents

gradually over a period of approximately 2–3 weeks. This strategy produced strong antibacterial effects, eliminating planktonic organisms and adherent bacteria on the implant by nearly eight orders of magnitude and preventing biofilm establishment. In parallel, the modified coatings enhanced the osteogenic potential of mesenchymal stem cells, as indicated by a two-fold elevation in alkaline phosphatase activity and mineral deposition levels reaching up to four times those observed in controls. *In vivo* subcutaneous implantation for 8 weeks revealed no signs of foreign body response, while the coatings facilitated connective tissue ingrowth. Collectively, these results highlight the potential of surface-functionalized metamaterials to address dual challenges in orthopedic applications by enabling both localized drug delivery and enhanced tissue integration.²⁰³

These developments suggest that integrating additive manufacturing with metamaterial design may open avenues for constructing customizable drug delivery platforms that can finely tune the timing and localization of therapeutic release to enhance overall treatment outcomes. By harnessing the structural adaptability of metamaterials alongside the versatile fabrication capabilities of additive manufacturing, these platforms can be customized to individual patient requirements, supporting applications that include infection-resistant implants, wound-healing scaffolds, and stimuli-responsive oral or transdermal delivery devices. The integration of design flexibility, functional materials, and advanced fabrication techniques points toward a promising route for next-generation precision medicine. Metamaterials produced through additive manufacturing offer significant promise for pharmaceutical applications, enabling the design of smart nanoscale architectures that facilitate advanced diagnostic strategies and next-generation treatment modalities. By combining programmable architectures with responsive materials, these systems can support highly personalized treatment approaches, ultimately bridging the gap between next-generation drug delivery platforms and precision medicine. We summarize representative studies in Table 4.

5.2. Targeted delivery for cells and tissues

A key goal in tissue engineering is to develop metamaterials that not only facilitate cell homing but also direct specific cellular activities. Mechanical metamaterials offer a versatile platform for modulating mechanical cues, making them attractive for scaffolds that precisely control tissue and cell behaviors.²⁰⁴ Cellular responses to high-aspect-ratio nanostructured surfaces are heavily dependent on features such as spacing, sharpness, and height, which govern membrane-material interactions and subsequent intracellular signaling pathways.²⁰⁵ Importantly, the Poisson's ratio of metamaterials has been shown to affect

Table 4. Representative case studies of metamaterial-based drug delivery systems

Study	Architecture/material	Fabrication method	Application	Key findings
Finá <i>et al.</i> ²¹²	Gyroid-lattice printlets	Selective laser sintering	Oral controlled-release tablets	Tunable dissolution via geometry; versatile dosage design
Xu <i>et al.</i> ⁹¹	Acoustic metamaterial patch	Microstructured acoustic units + electronics	Transdermal epinephrine for anaphylaxis	Multi-burst, on-demand dosing; superior to injections in mice
Sun <i>et al.</i> ¹⁰⁴	Silk-based terahertz resonator patch + antibiotics	Printable degradable metamaterial	Antibacterial wound patch	Combined drug release and real-time monitoring; accelerated healing
Babae <i>et al.</i> ⁸⁵	Gastric-resident structures	Multi-material three-dimensional printing	Long-term gastric devices	Safe retention in the stomach; foundation for a prolonged oral drug delivery system
Yarali <i>et al.</i> ²¹⁰	Auxetic bone scaffolds	Stereolithography/bioinspired design	Orthopedic implants	Tunable porosity and mechanical modulus; enhanced osteogenic activity

cellular characteristics.²⁰⁶ Among these, auxetic constructs have gained particular attention in tissue engineering, as their NPR imparts unique mechanical cues that can direct cellular responses and promote functional tissue development.⁶⁹

As shown in Figure 2, Jia *et al.*²⁰⁷ utilized the potential of a generative computational framework to regulate stress distributions across multiple predefined values, measurement parameters, control zones, and loading scenarios. As an illustration, a femoral support structure was optimized with tailored, irregularly architected materials designed to enhance orthopedic healing following a fracture (Figure 2A–D). The customized femur

support was shown to accurately reproduce the intended stress distribution (Figure 2B), thereby reducing the risks of aseptic loosening and peri-prosthetic fractures, while simultaneously preserving an adequate level of shear stress on the fractured site to promote bone regeneration. This design was fabricated using a commercial masked stereolithography 3D printer (Figure 2D), which required fewer fabrication steps compared with other multi-scale structural design methodologies. This advantage arises because the generated material architectures consist of self-supporting assemblies of building blocks that inherently comply with the minimum feature size required for manufacturability.²⁰⁷ Due to their ability to redistribute mechanical loads while simultaneously

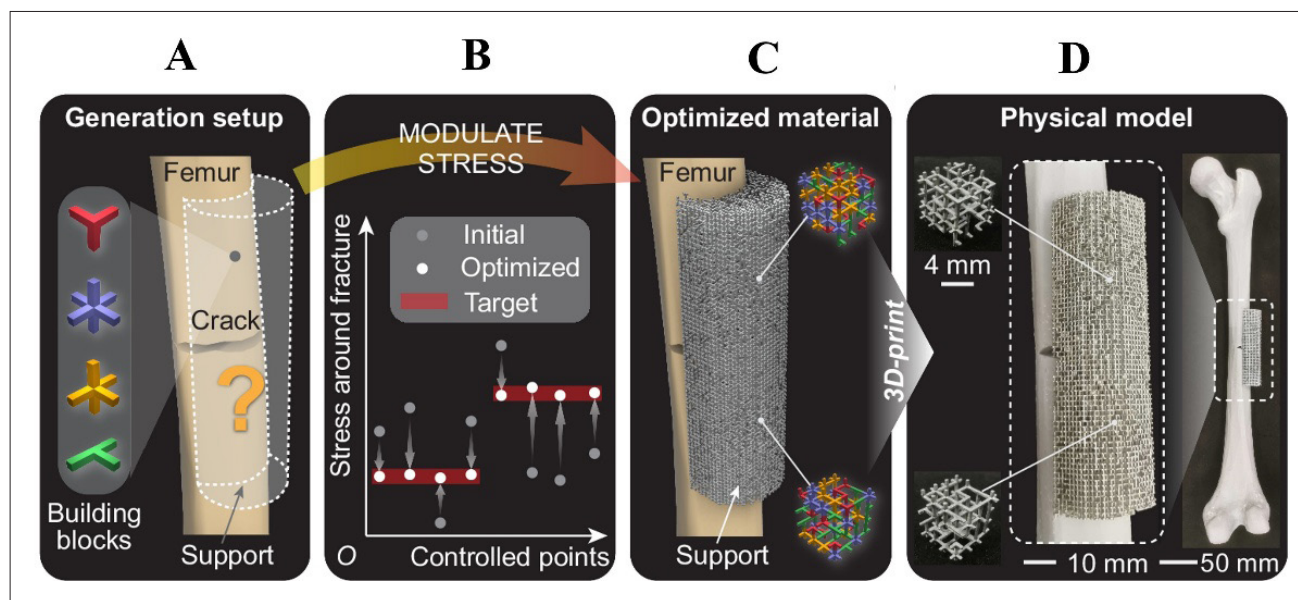


Figure 2. Generation and application of irregular architected materials with optimization-enabled stress modulation. (A) Schematic representation of the construction setup, consisting of a fractured femur stabilized by a support designed from four fundamental unit types. (B) Comparison of the stress distribution in the control region adjacent to the fracture, showing the homogeneous state at the start, the computationally optimized profile, and the desired target stress. (C) Resulting support structure composed of irregularly optimized materials, with disordered microarchitectures highlighted in the two magnified insets. (D) Additively manufactured samples produced at multiple length scales. Reprinted from Jia *et al.*²⁰⁷

maintaining an appropriate level of stress that targets bone regeneration, Jia *et al.*²⁰⁷ highlighted the prospective use of stress-programmable architected materials as supportive structures in femoral orthopedic repair.

Despite progress in nucleic acid therapeutics, achieving precise delivery to specific tissues remains a significant challenge, often hindered by low transfection rates and difficulties in scaling that vary with both cellular phenotype and anatomical environment. To address this, a recent study reported a controllable, vertically aligned configuration of biodegradable porous silicon nanoneedles, which could directly access the cytoplasm and simultaneously introduce small interfering RNA and DNA with efficiencies exceeding 90%.²⁰⁸ Using this strategy, the nanoneedle system successfully transferred the *VEGF-165* gene in animal models, promoting persistent angiogenesis and resulting in nearly a sixfold increase in blood flow within the affected muscle region. Additionally, the nanoneedles promoted the organized development of new vasculature, indicating potential for precise, site-specific regulation of both physiological function and structural organization in selected tissue regions.

The convergence of bioprinting with metamaterials research in DDSs has driven significant progress in engineering intricate and functional architectures. These emerging technologies enable the realization of geometries that were previously unattainable through conventional means, thereby unlocking novel metamaterial applications with exceptional and unconventional properties.

5.3. Regenerative medicine

A distinguishing merit of metamaterials lies in their inherently large interfacial area, a property that lends itself well to chemical or biological modification. Implementing such surface engineering strategies can substantially augment the functional capacity of these materials, with particular promise for promoting cell growth and tissue restoration in regenerative medicine applications.^{207,209}

To overcome persistent clinical limitations in orthopedic surgery, the use of metamaterials requires the incorporation of additional surface functionalities, which can be achieved through the application of purpose-engineered coating strategies. Yarali *et al.*²¹⁰ developed a bone-regenerative system employing metamaterials, drawing inspiration from the influence of Poisson's ratio on osteogenic cell behavior, as illustrated in the fabrication scheme shown in Figure 3A. They defined pore size as the diameter of the largest sphere that can fit within a unit cell of the meta-biomaterials (the yellow sphere in Figure 3B & C). The resulting metamaterial-based implant exhibited mechanical features aligned with clinical requirements, including controlled porosity and elastic modulus, while

also supporting favorable osteogenic activity of pre-osteoblasts within the micro-structured scaffold (Figure 3D–F).²¹⁰ Such engineered constructs are anticipated to accelerate tissue repair and improve regenerative outcomes.

Barri *et al.*²¹¹ reported a novel approach to constructing self-powered metamaterials. Their work revealed that cage-shaped implants with built-in contact-electrification capability can generate internal voltage signals that reflect the progress of bone regeneration. When subjected to axial compressive loading in spinal models, these devices delivered a voltage of 9.2 V and a current of 4.9 nA. Acting as triboelectric nanogenerators, such metamaterial implants have the potential to energize low-power electronics, thereby advancing surgical outcomes for spinal cord injury patients and reshaping implantable device technologies.²¹¹

Auxetic porous materials can improve the delivery of nutrients and therapeutic agents, as well as the removal of metabolic waste, and have been identified as candidates for the development of adaptable scaffolds for tissue engineering applications. Flamourakis *et al.*¹⁸¹ demonstrated that 3D auxetic structures constructed through multi-photon lithography can serve as scaffolds for cell cultures. Even though SZ2080 is fundamentally a stiff material with a positive Poisson's ratio, the bowtie structures fabricated with it exhibit auxetic behavior and high elasticity due to their architected design. In addition, Flamourakis *et al.*¹⁸¹ showed that mouse fibroblasts can readily penetrate and proliferate in these scaffolds, adapting the scaffold shape to their needs, increasing their proliferation, and promoting aligned, directional growth.

5.4. Autonomous and adaptive therapeutic systems

The ultimate goal of smart drug delivery is a system that self-regulates in real-time based on physiological feedback. Metamaterials are uniquely suited to form the physical core of such closed-loop systems. Their structured nature allows for the seamless integration of sensing and actuating modalities. For instance, a metamaterial scaffold can incorporate microfluidic channels functionalized with biosensing hydrogels that swell in the presence of a specific biomarker (e.g., glucose, tumor necrosis factor alpha). This swelling can mechanically modulate the flow through adjacent drug-loaded microchannels, creating a purely mechanical feedback loop. More advanced systems leverage embedded conductive networks (e.g., based on graphene or liquid metal) within the metamatrix to act as electrochemical sensors. The detected signal is processed by a miniaturized circuit, which then triggers an actuation mechanism—such as the Joule heating of a thermally responsive polymer nanogel reservoir within the metamaterial, causing it to collapse and release a therapeutic dose. This creates a self-correcting, bio-

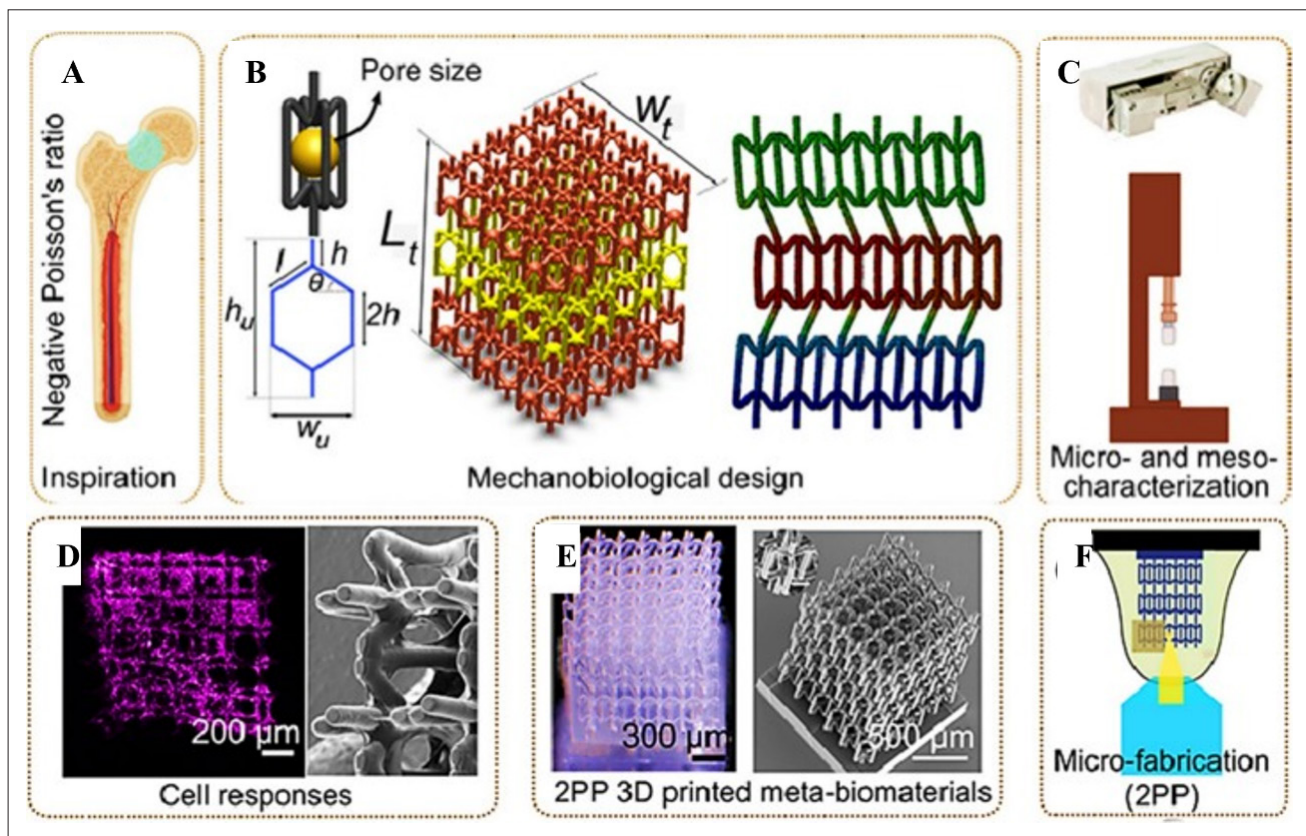


Figure 3. Metamaterial-enabled platforms for therapeutic and diagnostic use. (A) Conceptual inspiration derived from the negative Poisson's ratio of bone. (B) Schematic workflow for metamaterial fabrication. (C) Structural and property characterization. (D) Osteogenic activity of pre-osteoblasts cultured within the metamaterial framework. Scale bar: 200 μm ; magnification: 10 \times . (E) Macroscopic view of the printed scaffolds. Scale bars: 300 μm , 500 μm ; magnifications: 10 \times . (F) Example of microfabricated constructs generated via three-dimensional printing.²¹⁰ Adapted with permission from Yarali *et al.*²¹⁰ Copyright © 2024, Elsevier.

electronic interface that maintains homeostasis without external intervention, representing a monumental leap beyond simple, pre-programmed release kinetics.

Unlike featureless hydrogels, 3D-printed metamaterials can be designed to replicate the mechanical anisotropy and complex porosity of native tissue extracellular matrix. When integrated into a microfluidic chip, these architectures provide a more realistic microenvironment for cultured cells, guiding tissue-level organization and function. A prime application is a “vascularized tumor metamaterial model” for oncology drug screening. A sacrificial metamaterial can be printed to create a perfusable, hierarchical vascular network, which is then seeded with endothelial cells. Tumor cells encapsulated within a surrounding, tissue-specific metamaterial scaffold can be positioned at a defined distance from the vasculature. This setup allows for high-fidelity assessment of drug penetration, efficacy, and toxicity in a human-relevant system that captures key aspects of the tumor microenvironment, including nutrient gradients and

interstitial fluid pressure. This moves drug testing from a static two-dimensional culture to a dynamic, human-specific, and predictive platform.

By precisely controlling the topography, stiffness, and ligand presentation at the cellular level, metamaterials can be designed to direct the fate and function of immune cells. For example, a scaffold with a specific range of pore sizes and surface chemistry can be designed to preferentially recruit M2 macrophages over the M1 phenotype, promoting a healing and regenerative environment instead of a pro-inflammatory one. Furthermore, these scaffolds can serve as localized depots for immunomodulatory agents (e.g., cytokines, checkpoint inhibitors). The release kinetics can be spatially and temporally controlled by the architecture; for instance, an outer layer with fast-release kinetics could deliver an initial signal to recruit specific immune cells, while an inner core with slow-release kinetics provides a sustained polarizing signal. This approach could be transformative for cancer immunotherapy (as an *in*

situ cancer vaccine) and regenerative medicine, where controlled inflammation is crucial for tissue repair.

6. Translational roadmap: from lab-scale design to regulatory and sustainable production

Despite significant progress in functionality and performance, the large-scale translation of metamaterial-based DDSs faces emerging challenges in sustainability, manufacturability, and regulatory compliance. Current research often overlooks the environmental and ethical implications of material selection, energy-intensive printing processes, and post-use biodegradability. This section provides a sustainability-oriented perspective, discussing the use of bio-based inks, low-carbon fabrication strategies, and circular economy principles in the context of metamaterial production. In parallel, it outlines a regulatory roadmap for next-generation biofabricated metamaterials, encompassing safety validation, quality control, and digital traceability frameworks. By integrating green engineering and regulatory governance into material innovation, this section advocates for a holistic approach that aligns scientific advancement with global sustainability and compliance goals.

The intricate and often multi-material nature of 3D-printed metamaterials presents a paradigm shift for regulatory bodies such as the United States Food and Drug Administration and the European Medicines Agency. A primary challenge is the “device–drug combination product” classification. A metamaterial implant that releases a therapeutic agent blurs the traditional lines between a medical device and a pharmaceutical, requiring a hybrid and often complex regulatory submission process. Regulators will require proof that the critical quality attributes of the drug product—such as release kinetics, stability, and sterility—are intrinsically linked to the print fidelity, architectural parameters (e.g., pore size, strut thickness), and material composition of the metamaterial. This necessitates a robust quality-by-design approach, where the design space for the microstructure is rigorously defined and controlled. Standard ISO 10993 biocompatibility testing must be re-evaluated for metamaterials. The high surface-area-to-volume ratio and potential for novel degradation products arising from complex material combinations (e.g., polymer–ceramic–metal composites) pose unique risks. Assessments must go beyond cytotoxicity to evaluate long-term foreign body response, immunogenicity, and the fate of degradation byproducts from the architected matrix itself. The layer-by-layer additive manufacturing process introduces variability. Regulatory approval will hinge on validating that every

printed batch is equivalent. This requires the development of new in-process analytics and non-destructive testing methods (e.g., micro-computed tomography) to verify internal architecture and ensure the absence of critical defects that could compromise performance or safety.

The environmental footprint of advanced manufacturing cannot be ignored. A cradle-to-grave life cycle assessment is crucial for evaluating the true ecological cost of metamaterial-based DDSs. High-resolution 3D printing techniques (e.g., two-photon polymerization) and post-processing (e.g., SLS powder recycling) are energy-intensive. Comparisons with conventional manufacturing are needed. The environmental impact of sourcing synthetic polymers and metals must be weighed against the use of biodegradable alternatives derived from natural sources. Furthermore, support materials and failed prints contribute to plastic waste, necessitating the use of closed-loop recycling systems or water-soluble supports. The ideal scenario for single-use, implantable DDSs is complete, non-toxic biodegradation into metabolizable byproducts. Research must therefore prioritize green material strategies, including developing architectures from polymers such as PLGA and PCL with tunable degradation profiles, and utilizing chitosan, alginate, silk fibroin, and decellularized extracellular matrix to create metamaterials with inherent biocompatibility and reduced environmental impact.

The complexity of metamaterials demands a paradigm shift in quality control, moving from statistical sampling of final products to a comprehensive, data-driven assurance of every single unit. This can be achieved through the implementation of a digital twin framework. A digital twin is a virtual replica of the physical manufacturing process and the product itself. It begins with the computational design file and is fed by real-time data from printers (e.g., thermal cameras, laser power monitoring). This creates an unbroken “digital thread” linking design to production. Machine learning algorithms analyze the manufacturing data in real-time against the digital twin to predict critical quality attributes. For instance, a minor fluctuation in laser power during SLS could be flagged as potentially leading to a region of insufficient sintering that would alter drug release, allowing for the part to be rejected automatically.²¹² The digital twin, informed by the precise internal architecture from micro-computed tomography scans, can run finite element analysis and computational fluid dynamics simulations to predict *in vivo* performance.^{213,214} This includes forecasting drug release profiles,²¹⁵ predicting mechanical stability under load,²¹⁶ and estimating cell–scaffold interactions, providing a powerful tool for de-risking clinical translation and supporting regulatory submissions.

7. Conclusion

This review has outlined how the convergence of metamaterial science with additive manufacturing holds strong potential to reshape modern DDSs by enabling unprecedented precision in both therapeutic targeting and release regulation. Unlike conventional carriers, metamaterials with engineered microarchitectures can interact with biological tissues and electromagnetic fields in ways that confer higher levels of selectivity and functionality. These interactions open avenues for improving drug loading capacity and stability, increasing bioavailability, refining spatial and temporal release patterns, and thereby minimizing adverse reactions while enhancing overall therapeutic performance. By leveraging adjustable properties—such as pore structure, molecular transport capacity, and sensitivity to external stimuli including heat, acidity, and illumination—metamaterial-derived platforms provide a foundation for creating highly individualized therapeutic strategies. Their structural programmability also permits coupling with electromagnetic waves to direct or modulate drug transport, and carefully engineered configurations can be optimized to target specific cell populations or organ systems. Moreover, integrating responsive elements into these platforms enables finely tuned, externally triggered release profiles, thereby reducing systemic exposure and enhancing efficacy. Photoresponsive hydrogels, for example, maintain mechanical stability while undergoing light-induced volumetric changes, enabling controlled activation and long-term dosing. Importantly, biodegradable constructs circumvent the need for surgical removal and are preferable to non-degradable counterparts in clinical scenarios. Recent advances demonstrate that 3D-printed metamaterials, such as antibacterial wound patches, deliver tightly regulated drug release with minimal off-target effects, highlighting their advantages in safety and efficiency. The capacity to adapt to diverse stimuli further enhances therapeutic customization and supports precision medicine strategies. Taken together, these structural, mechanical, and electromagnetic characteristics highlight that bio- or 3D-printed architected metamaterials represent a compelling substitute for conventional DDSs, providing distinctive opportunities for tunable shape-memory functions and next-generation therapeutic release strategies.

Despite these encouraging developments, several critical challenges remain. First, the translation of complex laboratory-scale constructs into clinically viable products requires the establishment of reproducible, regulatory-compliant, and scalable manufacturing processes. Second, the biocompatibility, long-term safety,

and biodegradability of emerging metamaterial-based carriers must be rigorously assessed through systematic preclinical and clinical studies. Third, the integration of smart, stimuli-responsive functionalities with real-time sensing and theranostic capabilities is still in its early stages, necessitating the convergence of materials science, engineering, and biomedical research. Moreover, the field would benefit from the development of standardized evaluation metrics to compare different architectures and from computational modeling approaches that can more accurately predict drug transport and tissue responses.

Looking ahead, the future of 3D-printed metamaterials for drug delivery will likely be defined by three major directions. The first is personalized medicine, where patient-specific anatomical data and pharmacokinetic requirements can be directly translated into bespoke metamaterial-based devices. The second is the incorporation of multifunctional hybrid platforms, which combine structural programmability with biochemical cues, biosensing modules, and digital health interfaces for remote monitoring and control. The third is the establishment of manufacturing workflows that prioritize sustainability and compliance with regulatory standards will be crucial for translating laboratory breakthroughs into broad clinical implementation. The convergence of AI, bioresponsive design, and sustainable manufacturing is poised to redefine the trajectory of 3D-printed metamaterials in biomedical applications. The future will likely witness the emergence of intelligent metamaterials that self-learn from physiological feedback, adapt their microstructure autonomously, and coordinate with other therapeutic platforms in real time. To achieve this vision, interdisciplinary collaboration among material scientists, bioengineers, data scientists, and regulatory experts will be essential.

In conclusion, while metamaterial-inspired DDSs are still in their infancy, their potential to transform therapeutic strategies is evident. Continued interdisciplinary collaboration, coupled with advances in materials engineering and translational research, will be key to realizing their promise in personalized, efficient, and intelligent drug delivery.

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Conflict of interest

The authors declare that they have no conflict of interest.

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