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3D PRINTING TECHNOLOGY FOR ANTIBIOTIC-LOADED SCAFFOLDS IN THE TREATMENT OF POST-SURGICAL BONE REGENERATION: PRESENT STATUS, CHALLENGES, AND PROSPECTS

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ABSTRACT

Post-surgical bone infection is one of the most challenging complications in orthopaedic surgery due to the hypo vascularization of the affected tissue, bacterial biofilm formation, and inadequate antibiotic penetration to the infection site.[1,2] Currently available antibiotic-loaded systems, including polymethyl methacrylate (PMMA) bone cement, have a number of disadvantages, such as the need for surgical removal and low adaptability to heat-sensitive antibiotics.[3,4] Three-dimensional (3D) printing is a promising technology that allows the fabrication of patient-specific biodegradable scaffolds.[5–7] Such scaffolds can be loaded with antibiotics and possess both osteogenic and antibiotic elution properties.[5–7] The present review highlights recent advances in the development of antibiotic-loaded 3D-printed scaffolds for the treatment of post-surgical infections[8,9], including the description of various scaffolding technologies, materials suitable for 3D printing, methods for antibiotic incorporation, and the mechanism of their antibacterial and osteogenic activity.[5,6] Additionally, the

preclinical and clinical evaluation of antibiotic-loaded 3D-printed scaffolds, as well as the regulatory, safety, and translational aspects of their application in orthopaedics and future perspectives, including the use of stimuli-responsive scaffolds and artificial intelligence, are discussed.[10–12] Overall, antibiotic-loaded 3D-printed scaffolds represent a new generation of scaffolds with good prospects for future clinical applications in orthopaedics.[12,13]

KEYWORDS: Three-dimensional printing; Antibiotic-loaded scaffold; Bone tissue engineering; Osteomyelitis; Drug delivery; Bone regeneration; Additive manufacturing.

INTRODUCTION

Orthopaedic surgery is associated with a wide range of potential post-surgical complications, with surgical-site infections being among the most frequent and challenging ones to manage.[1,2] Orthopaedic surgical-site infections, such as osteomyelitis, often develop after open fractures, internal fixation surgeries, and joint arthroplasty and may lead to significant patient suffering as well as economic burden.[1,14] At the same time, the treatment of post-surgical bone infections is complex and often associated with recurrent surgical revisions since such infections lead to impaired bone healing, implant failure, and poor patient outcomes.[2,14] The key reasons for such a poor prognosis for orthopaedic surgical-site infections include the hypovascularization of the affected bone tissue and the frequent formation of bacterial biofilm by pathogens such as Staphylococcus aureus and Escherichia coli, which significantly hinder the treatment process.[2,14] Traditionally, infections were primarily treated either by aggressive surgical debridement with extensive removal of the affected tissue or by antibiotic therapy, often combined with the use of local antibiotic carriers to achieve effective local anti-inflammatory effects.[3,15] Such local carriers include PMMA bone cement, which allows for achieving high local concentrations of antibiotics.[3,15] However, the use of PMMA is associated with a number of significant limitations. First, since PMMA is a permanent implant, it usually has to be removed in a separate surgical procedure after the infection has been resolved.[3,4] Second, PMMA is thermally cured, which prevents the use of heat-labile antibiotics.[4,15] Finally, PMMA, as a traditional orthopaedic material, does not provide any osteogenic or regenerative properties to the affected bone tissue; rather, it is a temporary filler that has to be replaced by new bone.[3,5] Recently, additive manufacturing (AM), also known as 3D printing, has shown promise in the fabrication of patient-specific scaffolds with desired mechanical and biological properties.[6,7] Such scaffolds can serve as regenerative templates for the affected bone tissue and be

combined with antibiotics for the treatment of post-surgical infections.[7,10] On the one hand, such scaffolds allow for localized slow release of antibiotics to the infection site.[5,8] Moreover, they can also promote the regeneration of new bone tissue while biodegrading.[9,10] Biodegradable scaffolds eliminate the need for a second surgical site removal since they can entirely resorb in the patient's body.[5,7] The development of composite materials as well as the emergence of novel technologies for the fabrication of scaffolds with complex geometries and multifunctionality, including on-demand drug delivery, have greatly facilitated the design of new advanced orthopaedic scaffolds.[10,11]

The present review aims to highlight recent advances in 3D printed antibiotic-loaded scaffolds in orthopaedics. The rationale for localized antibiotic delivery and different 3D bioprinting technologies, as well as the properties of materials suitable for 3D printing, will be discussed.[5–7] Additionally, different methods for antibiotic incorporation into 3D-printed scaffolds and their antibacterialand osteogenic efficiency will be described.[5,6] Moreover, the preclinical and clinical data on the application of antibiotic-loaded 3D-printed scaffolds, as well as the regulatory, safety, and translational aspects, will be considered.[9–11] Finally, future perspectives including the use of stimuli-responsive scaffolds and artificial intelligence will be discussed.[10–12] Overall, 3D-printed antibiotic-loaded scaffolds represent a new class of biomedical devices with great potential for the treatment of post-surgical bone infections.[6,10]

RATIONALE FOR ANTIBIOTIC-LOADED 3D-PRINTED SCAFFOLDS

The treatment of post-surgical bone infections represents a major challenge in orthopaedics due to the complex nature of the disease.[1,2] The sites of implant placement, joint replacement, or bone reconstruction after tumour resection present with diminished vascularization and compromised circulation after the surgical procedures that increase the resistance to the healing process and reduce the concentration of antibiotics in the affected tissue.[1,14] Another challenge in managing post-surgical bone infections originates from the biofilm formation by pathogenic microorganisms on the host tissue and implant surfaces.[2,14] Biofilms represent a major threat in orthopaedic infections due to their complex structure that prevents the immune cells invasion and shields the bacteria from the systemic antibiotics pressure.[2] Thus, the development of antibiotic resistance and recalcitrant infection foci are more likely after biofilm-related injury.[1,2,14] Local antibiotic delivery was proposed as an alternative to systemically administered antimicrobials due to the opportunity to attain higher

concentrations of drugs in the targeted site and reduce toxicity.[3,15] One of the most established forms of local antibiotic delivery is the antibiotic-loaded polymethyl methacrylate (PMMA) bone cement, which has been clinically used for several decades.[3,15] PMMA bone cement is primarily used for filling the bony defect after surgical debridement; however, its application is limited by major disadvantages.[3,4] Due to the inert nature of PMMA, a second surgical intervention is typically required to remove the implant after the infection is resolved due to the absence of biodegradation.[3] More importantly, the antibiotic loaded into the PMMA matrix is subjected to high temperatures during the cement polymerization that inactivates the drug. Recent years have witnessed a growing interest in additive manufacturing as a potential tool for the fabrication of custom-designed antibiotic-loaded scaffolds that address the majority of the shortcomings associated with traditional implants. Additive manufacturing enables the production of implants that accommodate patient-specific anatomical needs identified from the MRI or computer tomography.[6,7] Scaffold architecture can be precisely designed and optimized in terms of pores size, shape, density, and geometry to create a structure that matches the biomechanics of the host bone and promotes vascularization and tissue ingrowth.[6,8] One of the main advantages of the 3D-printed antibiotic scaffolds is the possibility to locally deliver high concentrations of antimicrobials while simultaneously supporting the repair process.[7,9] The antibacterial agents can be incorporated in the polymer or ceramic structure or used as a coating on the surface of the scaffolds.[9,10] Local administration can prevent the systemic side effects of antibiotics and attain higher tissue concentration with lower overall doses.[9,10] During the healing period, the scaffolds can also serve as a biodegradable matrix for the cells colonization and assist in the bone regeneration.[8,9] The degradation rate can be engineered to match the repair process and resorb gradually over time instead of requiring a second surgery for implant removal.[5,7] Advanced concepts of multifunctional scaffolds include the possibility to incorporate additional biomolecules, such as growth factors, metallic nanoparticles, and other bioactive molecules as well as antibiotics.[10,11] Thus, the 3D-printed antibiotic scaffolds can serve as a next-generation platform for the treatment of post-surgical bone infections with superior healing outcomes.[10,13]

3D PRINTING TECHNOLOGIES USED FOR SCAFFOLD FABRICATION

3D printing or additive manufacturing is a process that enables the fabrication of complex anatomical structures from different materials.[5,6] The primary considerations in choosing a particular technology include material properties, geometrical complexity, mechanical

properties, resolution, working temperature, antimicrobial loading capability, and others.[6,8] There are several additive manufacturing technologies reported in the literature that can be used for scaffold fabrication; among them, fused deposition modelling (FDM), bioprinting through extrusion, stereolithography (SLA), digital light processing (DLP), selective laser sintering/selective laser melting (SLS/SLM), and powder-binder technologies are the most prevalent ones in the field.[5,6,8] Each of the 3D printing technologies offers different advantages and challenges and has specific indications in bone tissue engineering.[5,6,8]

Fused Deposition Modelling (FDM)

Fused deposition modelling is among the most commonly used additive manufacturing technologies for producing biodegradable and non-degradable polymer scaffolds.[6,15] In this technology, a thermoplastic polymer is melted at an elevated temperature and extruded through a fine nozzle to form filaments that are laid down layer-by-layer according to the designated pattern.[6] In bone tissue engineering, polycaprolactone (PCL) and polylactic acid (PLA) are frequently used due to their handling characteristics and biodegradability.[6, 15]

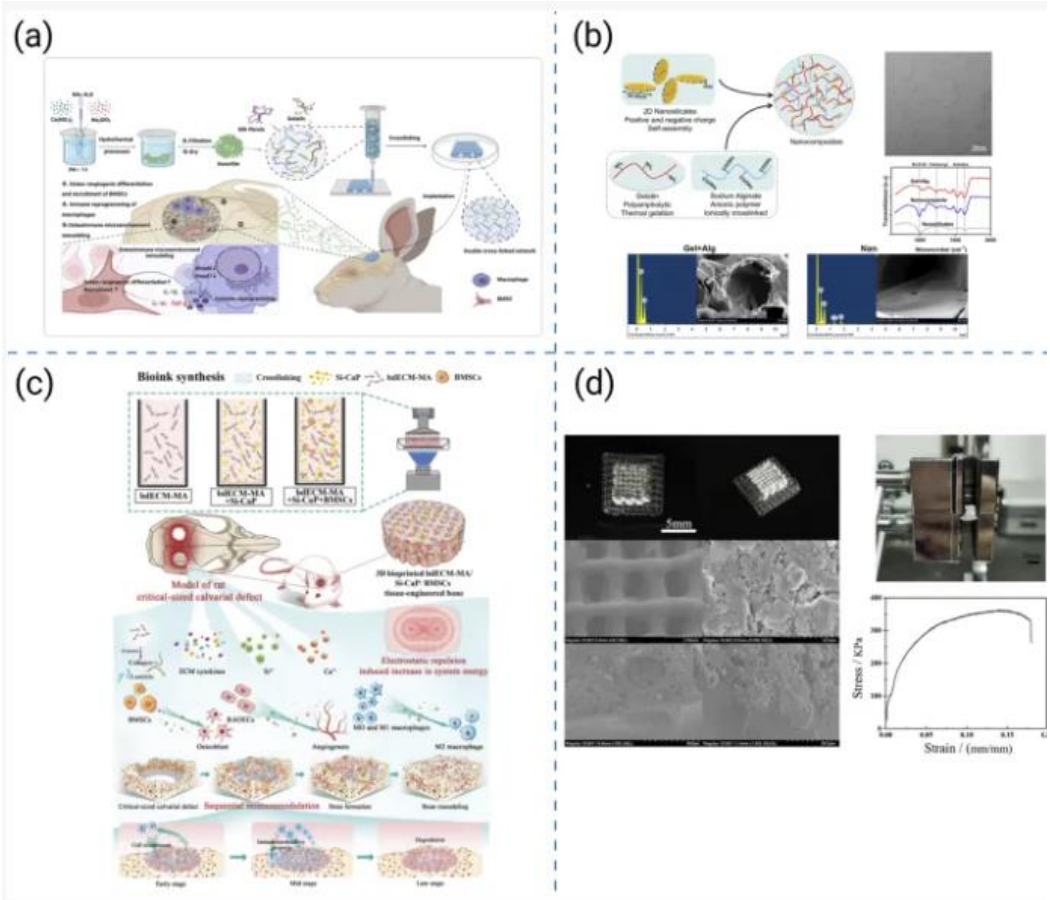
The primary advantage of FDM-printed scaffolds is the relatively low-cost technology that allows the production of patient-specific implants with consistent pore architectures.[6] Due to the lower processing temperatures, heat-labile antibiotics, such as rifampicin, can be incorporated with the polymer filaments without compromising their antibacterial activity.[15] Composite filaments have also been proposed to improve the osteoconductivity of the scaffolds.[16] FDM technology is limited by its relatively low resolution that typically prevents the fabrication of complex geometries.[6,8] Moreover, a significant amount of biodegradable polymers requires high-temperature processing, which could affect the stability of various antibiotics.[6,15]

Extrusion-Based Bioprinting and Direct Ink Writing

Extrusion-based bioprinting is a widely used additive manufacturing technology that utilizes biocompatible inks, hydrogels, and pastes, which are dispensed through a fine-tipped nozzle to form filaments with desired geometries.[5,6] Typically, the extrusion process is either driven by the pneumatic pressure or a screw system at room temperature.[5,6] Unlike FDM, 3D printing biocompatible inks at relatively low temperatures offer opportunities to incorporate heat-sensitive antibiotics and cells.[5,7]

Extrusion-based bioprinting is a promising technology for fabricating multifunctional

scaffolds due to the opportunity to incorporate different biomolecules and cells.[5,10] For instance, antibiotic-loaded poly(lactic-co-glycolic acid) microspheres could be incorporated into biodegradable scaffolds to enhance the antibacterial properties of the implant.[7] Additionally, there is an opportunity to load biocompatible inks with antimicrobial agents, such as silver nanoparticles, to improve the scaffold's antibacterial performance.[10] Overall, the extrusion bioprinting technology offers flexibility in terms of material selection and geometry; however, its resolution is lower than that of some other technologies, and the fabrication process is relatively slow.[5,6]



(a) 3D-printed hydrogel scaffolds reinforced with sepiolite nanofibers (Yang S. Y. et al., 2024). **(b)** Preparation and physical characterization of the nanocomposite hydrogels (Liu et al., 2020). **(c)** Construction and investigation schematic of the DLP 3D-bioprinted bdECM-MA/Si-CaP/BMSC tissue-engineered bone with exceptional mechanical strength (Liu et al., 2024). **(d)** Macrostructure and microstructure of the CDHA/PLGA bilayer scaffold in photographs and SEM images (Wu et al., 2021).

Figure 1: 3D printing Scaffolds construiction.

Stereolithography (SLA) and Digital Light Processing (DLP)

Stereolithography and digital light processing are two similar additive manufacturing technologies that utilize light-curing of UV- or visible-light sensitive resins.[6,8] Photopolymerization occurs in thin resin layers that are exposed to light from a light-emitting diode (LED) or another light source forming horizontal layers of the scaffolds.[6,8] The key advantage of SLA/DLP is that it is possible to fabricate scaffolds with very intricate geometries.[6,8] Nevertheless, biocompatible resins with adequate mechanical strength are still limited for orthopaedic applications.[6,12] The presence of toxic photoinitiators and the challenge of biodegradability also hinder the broader application of these materials.[6,12]
Selective Laser Sintering (SLS) and Selective Laser Melting (SLM).

With selective laser sintering and melting technologies, scaffold structures are formed from thermoplastic or metallic powder by subjecting the materials to high-intensity laser light.[6,8] Similar to SLA/DLP, laser technologies enable the fabrication of complex geometries with excellent resolution.[6,8] SLS/SLM are primarily used for metal scaffolds; however, biodegradable polymers could also be used.[6,8] The main limitation of laser-based fabrication is that laser light could affect the physical and chemical properties of many biodegradable polymers and antibiotics.[6,12] Therefore, laser technologies are predominantly used for metallic implants.[6,12]

Powder-Binder (3DP) Printing

3D powder printing technologies utilize liquid binder that is deposited on a powder bed in a predetermined pattern followed by the removal of the binder to form a scaffold with desired geometries.[6,17] Calcium phosphate and other biodegradable ceramics are particularly suitable for binder jetting technology since the manufacturing process takes place at relatively low temperatures thus preventing thermal degradation of antibiotics.[17] The advantages of the powder-binder printing include versatility in material selection, biocompatibility of scaffolds, and the ability to produce implants with appropriate mechanical properties.[6,17] The low processing temperatures also allow sustained loading of a wide range of antibiotics without compromising their antibacterial activity.[17] Scaffold mechanical properties could be optimized by selecting the appropriate composition of the binder solution.[6,17] On the other hand, the strength of 3DP scaffolds is typically lower than that of laser-printed or extruded implants, and additional post-processing steps might be needed to remove the binder solution.[6,12,17]

Table 1: Comparison of 3D Printing Technologies Used for Bone Scaffold Fabrication.[5, 6, 8, 12, 15, 17]

Technology DOCX	Description DOCX	Common Biomaterials DOCX	Advantages DOCX	Limitations DOCX	Application DOCX
FDM	Melt extrusion of thermoplastic filament	PCL, PLA	Low cost, simple, reproducible	Lower resolution, heat exposure	Bone scaffolds
Extrusion bioprinting	Extrusion of biocompatible inks	Hydrogels, PLGA, composites	Cell-friendly, multifunctional	Lower precision, moderate resolution	Tissue engineering
SLA/DLP	Photopolymerization of UV-light sensitive resins	Photocurable resins	Higher accuracy, smooth surface	Limited biomaterials	Complex scaffolds
SLS/SLM	Laser sintering of thermoplastic or metallic powders	Metals, polymers	High mechanical properties	High temperatures	Orthopaedic implants
3DP binder jetting technology	Deposition of liquid binder onto powder bed of bioceramics	Calcium phosphate, ceramics	Moderate mechanical properties	Lower resolution	Bone regeneration

Technology Description Common Biomaterials Advantages Limitations Application

FDM Melt extrusion of thermoplastic filament PCL, PLA Low cost, simple, reproducible Lower resolution, heat exposure Bone scaffolds

Extrusion bioprinting Extrusion of biocompatible inks Hydrogels, PLGA, composites Cell-friendly, multifunctional Lower precision, moderate resolution Tissue engineering

SLA/DLP Photopolymerization of UV-light sensitive resins Photocurable resins Higher accuracy, smooth surface Limited biomaterials Complex scaffolds

SLS/SLM Laser sintering of thermoplastic or metallic powders Metals, polymers High mechanical properties High temperatures Orthopaedic implants

3DP binder jetting technology Deposition of liquid binder onto powder bed of bioceramics Calcium phosphate, ceramics Moderate mechanical properties Lower resolution Bone regeneration

BIOMATERIALS USED AS ANTIBIOTIC CARRIERS

The properties of biomaterials used to fabricate antibiotic-loaded 3D-printed scaffolds play a critical role in determining the characteristics of the final construct, specifically mechanical properties, biodegradation rate, cell interactions, and antibiotic incorporation and release properties.[8,9] For bone tissue engineering applications, the material should exhibit excellent

biocompatibility and mechanical properties, be easily molded at different temperatures, and provide reliable antibacterial performance upon antibiotic incorporation.[8,9] Natural and synthetic polymers, biodegradable and non-biodegradable materials, as well as metallic implants, were considered for 3D-printed bone scaffolds.[8,9] Among these, biodegradable polymers and bioceramics are the most attractive options for the fabrication of antibiotic scaffolds for the management of post-surgical infections.[8,9]

Polycaprolactone (PCL)

Polycaprolactone is one of the most studied materials for 3D-printed bone scaffolds due to its relatively low melting temperature, excellent printing features, and mechanical and degradation properties.[6,15] Processing at a lower temperature is especially beneficial for incorporating heat labile antibiotics into the scaffolds.[15] PCL scaffolds have also been shown to exhibit excellent biocompatibility and mechanical stability in vitro and in vivo.[8,15] The slow rate of biodegradation of PCL is also a significant advantage, particularly when 3D-printed antibiotic scaffolds are used.[15] The combination of these properties allows the 3D-printed PCL scaffolds to maintain their mechanical integrity with continuous drug release over an extended period of time.[15] Several studies have shown that antibiotics, including rifampicin and vancomycin, could be incorporated into PCL scaffolds to improve their antibacterial properties.[10,15] Similar to many biodegradable polymers, PCL is hydrophobic and lacks significant osteogenic potential; therefore, it is often used in combination with other agents, such as bioactive ceramics or natural polymers, to improve cell adhesion, growth, mineralization, and overall healing.[8,10]

Polylactic acid (PLA)

Polylactic acid is another biodegradable polymer that has been used extensively for additive manufacturing due to its reasonably good mechanical properties, biocompatibility, and cost-effectiveness.[6,8] PLA is easily processed using various 3D printing technologies, including FDM, and has been used to fabricate patient specific implants.[6,16] While the mechanical properties of PLA are adequate for most orthopaedic applications, they could be further improved by combining this polymer with osteoconductive ceramics.[8,16] Similarly to PCL, PLA is not very hydrophilic and lacks biomineralization capacity, making it necessary to combine it with other bioactive molecules or materials.[8,16] Antibiotic-loaded PLA scaffolds have been fabricated using different 3D printing technologies.[8,16] For instance, vancomycin and minocycline-loaded implants exhibited excellent antibacterial properties and accelerated

bone regeneration.[10,16]

Poly(lactic-co-glycolic acid) (PLGA)

Poly(lactic-co-glycolic acid) is a biodegradable polymer with relatively good mechanical properties that has been used to fabricate a variety of implants using different manufacturing technologies.[8, 9] The major advantage of PLGA is that the degradation rate of this polymer could be precisely tuned by altering the ratio of glycolic and lactic acid chains in the polymer backbone.[9] The controlled degradation allows sustained release of the incorporated antibiotics, thereby providing excellent antibacterial performance.[9]

PLGA scaffolds have been extensively studied for their ability to incorporate various antibiotics, particularly vancomycin, rifampicin, moxifloxacin, and others.[7,9] In addition, this polymer could be used to form composite implants through mixing with other biodegradable polymers or hydrogels.[7,10] Despite the many opportunities offered by PLGA, the acidic byproducts of its degradation could affect the local tissue environment.[8,9] Therefore, careful optimization of the fabrication parameters is required to ensure that the degradation rate is adequate for the target application without compromising the tissue homeostasis.[8,9]

Calcium Phosphate and Bioceramic Systems

Calcium phosphate bioceramics have excellent osteoconductive and biomechanical properties and are biocompatible, which makes them ideal materials for orthopaedic implants.[8,17] These ceramics could be used to fabricate scaffolds with various pore sizes and architectures, depending on the target application. Low-temperature 3D printing technologies allow fabrication of such implants with minimal thermal degradation of antibiotics incorporated into the scaffolds.[17] One of the major advantages of using calcium phosphate scaffolds is that they could also provide mechanical stability while supporting tissue regeneration and vascularization.[8,17] Nevertheless, bioceramics are typically weak in tension; therefore, it is often recommended to combine them with other biodegradable materials, such as polymers.[8,12]

Composite and Functionalized Scaffolds

Composite materials offer a promising opportunity to enhance the performance of 3D-printed antibiotic scaffolds. These materials typically consist of biodegradable polymers, such as PCL or PLA, and bioactive ceramics, such as hydroxyapatite or β-tricalcium phosphate, to

improve the mechanical properties of standard implants.[8,10] Other additives, such as metallic nanoparticles or various bioactive molecules, could also be used to fabricate multifunctional scaffolds with enhanced antibacterial and osteoinductive properties.[10,11] Recent studies have demonstrated that such composite scaffolds exhibit reasonable biomechanical characteristics, adequate cell interactions, and excellent antimicrobial performance.[10,11] For instance, a gelatin/PCL/nano-hydroxyapatite composite has been reported to promote inflammation resolution and support bone regeneration.[11] Similarly, copper metal organic framework-coated hydroxyapatite/PCL scaffolds could be used for dual-purpose antibacterial and osteogenic treatments.[18] Composite scaffolds allow the incorporation of a wide range of bioactive molecules; for instance, silver nanoparticle-coated PLGA scaffolds have been shown to exhibit excellent antimicrobial properties while providing mechanical stability.[10] Surface functionalization of 3D-printed implants with different compounds, such as polydopamine and antibiotics-loaded microspheres, has also been reported as a useful strategy to enhance the antibacterial properties of the scaffolds.[7,10] Overall, composite materials appear to be a promising solution for developing next generation antibiotic scaffolds with enhanced biomechanical and osteogenic performance.[8,10] Further optimization of the fabrication process and material composition is likely to lead to the development of multifunctional implants that would provide better therapeutic outcomes when managing post-surgical bone infections.[12,13]

Table 2: Biomaterials Used in Antibiotic-Loaded 3D-Printed Bone Scaffolds.[7,8,10,15–18]

Biomaterial DOCX	Main Properties DOCX	Advantages DOCX	Limitations DOCX	Common Antibiotics DOCX
PCL	Biodegradable polyester	Lower melting temperature, good printability, sustained release	Hydrophobic, slower degradation	Rifampicin, Vancomycin
PLA	Biodegradable thermoplastic	Reasonably good mechanical properties, inexpensive	Brittle, low bioactivity	Minocycline
PLGA	Biodegradable copolymer	Controlled degradation, sustained release	Acidic degradation products	Rifampicin, Moxifloxacin, Vancomycin
Calcium Phosphate	Osteoconductive bioceramic	Good biocompatibility	Limited biodegradation	Various antibiotics
Composite scaffolds	Combination of materials	Improved properties	Multiple components needed	Various antibiotics

Biomaterial Main Properties Advantages Limitations Common Antibiotics

PCL Biodegradable polyester Lower melting temperature, good printability, sustained release Hydrophobic, slower degradation Rifampicin, Vancomycin. PLA Biodegradable thermoplastic Reasonably good mechanical properties, inexpensive Brittle, low bioactivity Minocyclin.PLGA Biodegradable copolymer Controlled degradation, sustained release Acidic degradation products Rifampicin, Moxifloxacin, Vancomycin. Calcium Phosphate Osteoconductive bioceramic Good biocompatibility Limited biodegradation Various antibiotics.. Composite scaffolds Combination of materials Improved properties Multiple components needed Various antibiotics

ANTIBIOTIC LOADING STRATEGIES AND DRUG RELEASE BEHAVIOUR

The properties of 3D-printed antibiotic scaffolds are mainly determined by the methods used to incorporate the antibacterial agents and the corresponding release profiles. Ideally, antibiotic scaffolds must exhibit rapid initial release of antibacterial compounds with a relatively high concentration to ensure immediate bactericidal effect followed by a slower release to maintain the therapeutic levels of antibiotics over a prolonged period of time. Thus, multiple approaches to incorporate antibiotics into the scaffolds have been described for optimal antimicrobial performance with minimum toxicity for the host tissues.[9,10] Engineering of appropriate drug release kinetics remains a challenging aspect of 3D-printed antibiotic scaffolds, and extensive research has been conducted to optimize the performance of such implants.[8,9] Multiple approaches to incorporate different antibacterial compounds, including vancomycin, moxifloxacin, rifampicin, and others, have been explored.[9,10]

Strategies for Antibiotic Incorporation

The methods for antibiotic loading typically depend on the characteristics of the target biomaterial, such as its thermal and mechanical stability, biodegradation rate, hydrophilicity, and other properties.[6,9] Direct incorporation into a biodegradable polymer is the simplest strategy to fabricate an antibiotic scaffold.[15] Antibiotics could either be mixed with molten thermoplastic filaments before printing scaffolds using fused deposition modelling (FDM) or dispersed into biocompatible hydrogels when using bioprinting technology.[6,9,10] Such methods usually allow relatively complete and consistent release of antibiotics due to the gradual biodegradation of the polymer scaffold,[9,15] Nevertheless, this approach might require high processing temperatures, which could damage heat-labile antibacterial agents, and the hydrophobicity of many biodegradable polymers could limit the extent of drug

release.[6,15] Another common strategy to incorporate antibiotics is to initially formulate them into biodegradable polymeric microspheres and then add them to the scaffolds.[7,9] This approach has been widely used in the fabrication of antibiotic scaffolds, such as those made of poly(lactic-co-glycolic acid) (PLGA).[7,9] Microspheres could either be mixed with biocompatible hydrogels or combined with biodegradable polymers using a variety of extrusion-based technologies.[6,7]

The simplest method to coat the scaffolds with antibiotics is to immerse them in an aqueous solution of antibacterial agents to allow their adsorption on the polymer surface.[9,10] This approach does not require high-processing temperatures; thus, it could potentially be used for temperature-sensitive compounds. Moreover, surface coating is a relatively straightforward procedure that allows additional functionalization of the scaffolds.[9,10] Nevertheless, such an approach usually results in uncontrolled and rapid release of antibiotics.[7,9] A variation of the coating method allows fabricating a thin film of biocompatible hydrogel on the surface of the scaffolds. The hydrogel layer could then be loaded with a variety of antibacterial agents, including rifampicin, vancomycin, and others.[7,9,10] The rate of drug release from such scaffolds could be precisely controlled by varying the mechanical properties, hydrophilicity, and thickness of the hydrogel layer.[7,9] Another method allowing controlled release of antibiotics from 3D-printed scaffolds is to combine them with various nanoparticles, such as chitosan or silica. Nanoparticles could be used both as a coating or incorporated into a biodegradable hydrogel layer to provide sustained drug delivery.[7,10]

Drug release from 3D-printed scaffolds is usually dependent on the physicochemical properties of the polymer and the characteristics of the incorporated antibiotics. In general, most polymers allow greater release of hydrophilic drugs than hydrophobic ones because of the differences in their solubility in water and the ability to be suspended in biodegradable hydrogels.[9,10] The rate of drug release is also affected by the mechanical properties of the scaffold, particularly its elasticity, as stiffer implants typically provide more consistent release of antibiotics.[9] For example, scaffolds made of poly(lactic-co-glycolic acid) (PLGA) exhibit faster drug release than those made of PCL.[10] Moreover, the release rate also depends on the molecular weight of the drug; smaller molecules tend to be released faster than large ones.[10]

Table 3: Common Strategies for Antibiotic Incorporation into 3D-Printed Scaffolds.[6,9,10]

Strategy DOCX	Description DOCX	Advantages DOCX	Limitations DOCX	Antibiotics DOCX
Direct incorporation	Mixing antibiotics with biodegradable polymer filaments or hydrogels before printing	Simpler fabrication process; complete release	Higher processing temperature needed; limited release from hydrophobic polymers	Rifampicin, Vancomycin
Microsphere loading	Encapsulation of antibiotics within polymeric microspheres followed by scaffold fabrication	Faster initial release of antibiotics	Limited variety of suitable polymers; additional step needed	Rifampicin, Moxifloxacin, Vancomycin
Surface coating	Antibiotic adsorption on the surface of 3D-printed scaffolds	Simpler fabrication process	Lower antibacterial performance; uncontrolled release of antibiotics	—
Hydrogel coating	Deposition of biocompatible hydrogel layer on the surface of scaffolds followed by antibiotic incorporation	Controlled rate of drug release	Additional processing step; rapid release if thin hydrogel layer is used	Rifampicin, Vancomycin

Strategy Description Advantages Limitations Antibiotics

Direct incorporation Mixing antibiotics with biodegradable polymer filaments or hydrogels before printing Simpler fabrication process; complete release Higher processing temperature needed; limited release from hydrophobic polymers Rifampicin, Vancomycin.Microsphere loading Encapsulation of antibiotics within polymeric microspheres followed by scaffold fabrication Faster initial release of antibiotics Limited variety of suitable polymers; additional step needed Rifampicin, Moxifloxacin, Vancomycin. Surface coating Antibiotic adsorption on the surface of 3D-printed scaffolds Simpler fabrication process Lower antibacterial performance Uncontrolled release of antibiotics.Hydrogel coating Deposition of biocompatible hydrogel layer on the surface of scaffolds followed by antibiotic incorporation Controlled rate of drug release Additional processing step; rapid release if thin hydrogel layer is used Rifampicin, Vancomycin.

CONCLUSIONS

While conventional methods of antibiotic delivery have been used extensively in the

management of post-surgical infections, a variety of challenges remain in designing ideal implants. Local administration of antibiotics has been shown to be a promising strategy for managing post-surgical orthopaedic infections; however, currently available solutions, such as antibiotic-loaded bone cement, have limited applications due to their inferior mechanical properties, lack of biodegradability, and difficulties in achieving optimal antibacterial properties. The application of 3D printing technologies offers a novel opportunity to address the majority of these limitations and incorporate multiple functionalities into a single implant. Additive manufacturing allows the design of personalized implants with precise geometrical parameters, mechanical properties, and biodegradability rate, which are critical for successful bone regeneration. The main focus of research into 3D-printed antibiotic scaffolds has been on optimizing the combination of biomaterials and methods for antibiotic incorporation to enhance antibacterial performance. The use of biodegradable polymers, such as PCL and PLA, allows complete degradation of the scaffold, thus eliminating the need for a second surgical intervention. Similarly, multifunctional scaffolds composed of biodegradable polymers and bioceramics have been reported to exhibit excellent antibacterial and osteogenic properties. Overall, the emerging field of antibiotic-loaded 3D-printed scaffolds holds great promise for the management of post-surgical orthopaedic infections with superior outcomes.

Local antibiotic delivery Administration of antibiotics in the targeted area following surgical procedures Higher tissue concentrations of antibiotics; reduced systemic effects Increased risk of biofilm formation and bacterial resistance.[1, 2, 14] Conventional antibiotic implants Use of antibiotic bone cements or spacers after surgical debridement of the infected site Lower cost; relative simplicity Inadequate performance; requires second surgery.[3 – 5] 3D printing of antibiotic scaffolds Scaffold fabrication using additive manufacturing technologies Individualized scaffolds; combined therapeutic functions Additional processing; higher cost.[5, 6, 8] Biodegradable polymers such as PCL, PLA Use of biodegradable materials for scaffold fabrication Elimination of second surgery Poor mechanical properties; inadequate bioactivity in certain polymers.[8, 9, 15] Composite scaffolds Combination of different materials to fabricate implants Enhanced biomechanical and biological properties Additional fabrication steps.[8, 11]

Nanoparticle-Mediated Drug Delivery

Recent advances have seen the incorporation of antimicrobial nanoparticles, including silver

nanoparticles into printable biomaterial based inks.[10] Nanoparticles offer not only bactericidal properties but also improve the mechanical properties and sustained drug release of the scaffolds they are incorporated into.[10] A high surface to volume ratio plus even dispersion of nanoparticles within a scaffold matrix can lead to increased antibacterial efficacy against a range of clinically relevant microorganisms commonly associated with bone infections.[10]

Factors Affecting The Release of Drugs And Antibiotics From The Scaffolds

The rate of drug release from biodegradable scaffolds can be tuned based on structural design parameters including scaffold porosity, pore size, wall thickness, infill, and polymer.[6,9] The release of embedded antibiotics can also be controlled by differences in polymer crystallinity, chain entanglement, polymer hydrolysis rates.[6,9] and drug spatial distribution within the scaffold.[6] An increase in scaffold porosity and pore size tends to favour faster fluid flow through the structure, while decreased scaffold wall thickness also facilitates quicker release rates.[6,9] Alternatively, increasing the amount of polymer within the scaffold design (i.e., increasing infill percentage) and reducing scaffold porosity, favours slower release rates.[6,9]

In addition to structural design, polymer selection also affects the rate of drug release.[8, 9] Polymers such as poly(caprolactone) (PCL) and poly(lactic-co-glycolic acid) (PLGA) have been shown to hydrolyze at predictable rates[9,15], while the use of computer aided design (CAD) softwares helps to engineer predictable geometries that help control drug dissemination rates.[6,9] Controlled/Responsive Release Of Drugs From The Scaffolds.A number of current innovations aim to achieve controlled release rates of embedded drugs from 3D printed scaffolds structures.[11,19] Some of these strategies have been shown to respond to changes in local physiopathological conditions such as changes in pH, enzyme activity and levels of other biomolecules to control rates of antibiotic release from biodegradable scaffolds.[11,19] Controlled release scaffolds can be leveraged to preferentially deliver antibiotics in response to the presence of microbial infections while reducing unnecessary systemic exposure and development of resistance.[11,19] More recent advances have been made in the use of AI, machine learning algorithms, and neural networks to design multifunctional scaffolds that can predict optimal combinations of polymer-drug interactions[8,12], while facilitating controlled release rates.[8,12] Overall, optimized antibiotic loading combined with controlled release rates help to increase therapeutic efficacy of 3D printed scaffolds while still promoting bone regeneration.[9,10]

Evidence of antibacterial and osteogenic efficacy

The overall goal of antibiotic-loaded scaffolds is to simultaneously eliminate microbial infections while promoting repair of damaged bone tissue.[9, 10] While traditional methods are typically focused on either combating infection or facilitating bone regeneration, multifunctional scaffolds have been shown to provide localised drug delivery of antibiotics while supporting osteogenesis and providing mechanical stability to the affected sites.[3,10] Several studies have shown promising results for antibiotic-loaded 3D printed scaffolds in terms of antibacterial efficacy[7,10,15,19] and osteogenic potential.[9,13,16]

Antibacterial Potential of The Antibiotic Loaded Scaffolds

A number of studies have demonstrated that antibiotic laden biodegradable scaffolds can be used to reduce bacterial load at the targeted infection site.[10,15] Rifampicin loaded PCL scaffolds demonstrated sustained antibacterial activity against S.aureus and E. coli while also maintaining cellular viability of osteoblasts.[15] Similarly, gelatin/PCL/nano-hydroxyapatite scaffolds loaded with diflunisal were able to reduce inflammatory response while protecting bone marrow stromal cells from bacterial endotoxins, while also promoting new bone formation in vivo.[11] Other studies have also demonstrated the ability of PLA/β-tricalcium phosphate scaffolds to promote early stage bone regeneration and improved mechanical properties over similar scaffolds made of PLA alone.[16] Overall, the addition of ceramics, polymers and antibiotics have enabled multifunctional scaffolds to provide combined bactericidal and osteogenic efficacy.[8,10]

Dual Antibacterial And Osteogenic Potential Of Antibiotic-loaded Scaffolds

One of the major advantages of antibiotic-loaded scaffolds is that they can serve more than one purpose.[10,13] Compared to antibiotic-containing implants such as PMMA (polymethylmethacrylate) bone cement, biodegradable scaffolds offer additional osteoinductive potential, sustained drug release, mechanical stability and controlled degradation rate.[3,10] This dual functionality helps to reduce bacterial load at the infection site while also supporting osteoblast proliferation, angiogenesis and overall accelerated bone regeneration.[9,10] In addition, since drug-loaded scaffolds are gradually degraded within the physiological environment, additional surgeries to remove implant materials are typically not required[5,7] Overall, a large body of experimental evidence demonstrates the ability of antibiotic-loaded 3D printed scaffolds to provide dual antibacterial and osteogenic potential, which makes them promising candidates for managing post-surgical infections.[10,13] While

most of the experimental evidence comes from in vitro and animal studies, several studies have also demonstrated antibacterial and osteogenic potential in vivo.[7,10,11,15]

Table 3: Summary of experimental evidence for antibiotic-loaded 3D printed scaffolds.[7,10,11,15,16]

Scaffold Composition DOCX	Antibiotic / Agent DOCX	Model DOCX	Major Findings DOCX
PCL	Rifampicin	In vitro	Effective antibacterial while maintaining good osteoblast compatibility
PCL + PLGA	Vancomycin	In vitro	Microsphere scaffolds showed sustained antibacterial activity against *S. aureus*
PLA	Minocycline	In vitro	Significant antibacterial zone demonstrated
Gelatin/PCL/nHA	Diflunisal	In vivo	Reduced inflammatory response and enhanced bone regeneration
PLLA/Pearl composite	Rifampicin + Moxifloxacin	Rabbit	Infection controlled and improved osteogenesis
PLA/β-TCP	—	Rat	Mechanical properties and early bone regeneration improved

Scaffold Antibiotic / Model Major Findings

Composition Agent

PCL Rifampicin In vitro Effective antibacterial while maintaining good osteoblast compatibility

PCL + PLGA Vancomycin In vitro Microsphere scaffolds showed sustained antibacterial activity against S. aureusPLA Minocycline In vitro Significant antibacterial zone demonstrated

Gelatin/PCL/nHA Diflunisal In vivo Reduced inflammatory response and enhanced bone regeneration

PLLA/Pearl composite Rifampicin + Moxifloxacin Rabbit Infection controlled and improved osteogenesis.PLA/β-TCP - Rat Mechanical properties and early bone regeneration improved

CLINICAL TRANSLATION: PROGRESS AND BARRIERS

While there have been a number of significant advances in the design and development of antibiotic-loaded 3D printed scaffolds, the clinical adoption of these multifunctional structures is still limited.[12,13] Majority of the studies conducted so far have shown promising results in vitro or in vivo, while only a few studies have demonstrated clinical efficacy.[12,13] For antibiotic-loaded 3D printed scaffolds to be successfully adopted in the clinical setting, a

number of scientific, regulatory, and manufacturing related barriers need to be overcome.[12,13]

Progress Toward Clinical Translation

The use of 3D printed scaffolds in orthopaedic, craniofacial and maxillofacial surgery has seen significant progress over the past decade.[12,20] Reports of patient-specific biodegradable scaffolds showing promising results in clinical settings have helped to demonstrate the efficacy of the approach.[12,20] However, such patient-specific scaffolds are typically associated with a number of challenges during fabrication including the need for segmentation of CT scans and fabrication of highly accurate models.[12] At the same time, the use of patient-specific scaffolds helps to improve post-surgical aesthetics by restoring facial symmetry and contour with greater precision than traditional methods.[20] Overall, the use of additive manufacturing has enabled the fabrication of customised implants with improved anatomical fit, biocompatibility and bone regeneration capacity.[20]

While antibiotic-loaded scaffolds have shown promising antibacterial and osteogenic potential in preclinical studies, the clinical evidence for most of these scaffolds is limited.[10,12] Most studies to date have been carried out in vivo or in vitro using various osteogenic cell lines.[10,12] As such, additional large-scale studies need to be carried out to determine the long-term safety profile, as well as the overall clinical efficacy of antibiotic-loaded scaffolds.[12,13]

Regulatory Hurdles

One of the major challenges in the clinical translation of antibiotic-loaded 3D printed scaffolds is the regulatory approval process.[12,13] Unlike traditional implants or drugs, multifunctional scaffolds require regulatory approval from both the drug and device regulatory agencies.[12,13] In addition to device specific guidelines related to clinical safety and performance, regulatory agencies such as the FDA may also require extensive clinical evidence regarding drug safety and pharmacokinetics.[12,13]

A number of antibiotic-loaded scaffolds are likely to require extensive clinical trials to demonstrate safety and efficacy before approval for commercial use.[12,13] In addition, due to the use of novel materials, multifunctional design capabilities and customisation options, most scaffolds will require extended regulatory reviews before approval.[12,13]

Manufacturing Considerations And Barriers

The successful clinical translation of antibiotic-loaded scaffolds also depends on a variety of manufacturing-related factors.[12,13] For example, the extrusion-based fabrication approaches typically used in additive manufacturing can have significant effects on cellular viability, mechanical properties, and overall structural integrity of the final scaffold.[6,12] Additional considerations include optimising printing parameters so that consistent structural integrity and homogenous cellular distribution can be achieved across multiple scaffolds.[12] Other manufacturing-related barriers include issues related to sterilisation, storage stability, preserving drug potency during scaffold fabrication and storage.[12,13] In general, heat-sensitive antibiotics are likely to be significantly impacted by variations in printing temperatures, necessitating additional manufacturing considerations to preserve drug integrity.[6,15]

Biological And Clinical Limitations Of Antibiotic-loaded Scaffolds.

A number of biological and clinical considerations also need to be taken into account when developing antibiotic-loaded scaffolds.[12,13] For example, while most biodegradable polymers gradually degrade in vivo over time, the overall degradation profile can vary depending on the specific polymer used.[8,12] Similarly, prolonged sub-therapeutic exposure to antibiotics may increase the likelihood of developing antimicrobial resistance.[9,12]

A lack of long term clinical studies has also limited confidence in the overall safety and efficacy of antibiotic-loaded scaffolds in different clinical settings.[12,13] The use of scaffolds varies depending on the type and severity of the bone defect.[1,14] In addition, patient-related factors such as age, obesity, smoking, diabetes, osteoporosis, and immune status can also affect patient outcome following scaffold implantation.[1,14]

Future Requirements for Clinical Implementation

To ensure clinical translation, future research should prioritize standardized scaffold fabrication processes, advanced manufacturing techniques, optimized sterilization protocols, and large-scale multicenter clinical trials.[12,13] Increased collaboration between biomaterials scientists, pharmaceutical researchers, biomedical engineers, orthopedic surgeons, microbiologists, and regulatory agencies is needed to accelerate the clinical development of antibiotic-loaded 3D-printed scaffolds.[12,13] Overall, while significant progress has been made in the field, additional multidisciplinary studies are needed to fully realize the therapeutic

potential of these advanced systems.[12,13]

Table 4: Major Challenges Limiting Clinical Translation of Antibiotic-Loaded 3D-Printed Scaffolds.[6,8,9,12,13]

Challenge DOCX	Impact on Clinical Translation DOCX	Possible Future Solution DOCX
Regulatory approval	Complex evaluation of drug-device combination products	Harmonized regulatory guidelines and standardized testing
Manufacturing reproducibility	Batch-to-batch variability	Advanced quality control and process validation
Sterilization	Potential degradation of antibiotics	Development of low-temperature sterilization techniques
Mechanical stability	Low mechanical strength	Composite biomaterials and scaffold design optimization
Long-term biodegradation	Degradation products and tissue response	Long-term in vivo and clinical studies
Antibiotic resistance	Risk of prolonged subtherapeutic drug release	Intelligent and stimuli-responsive drug delivery systems
Limited clinical evidence	Lack of human data	Large-scale multicenter randomized clinical trials

Challenge Impact on Clinical Translation Possible Future Solution.Regulatory approval Complex evaluation of drug-device combination products Harmonized regulatory guidelines and standardized testing. Manufacturing reproducibility Batch-to-batch variability Advanced quality control and process validation.Sterilization Potential degradation of antibiotics Development of low-temperature sterilization techniques. Mechanical stability Low mechanical strength Composite biomaterials and scaffold design optimization.Long-term biodegradation Degradation products and tissue response Long-term in vivo and clinical studies.Antibiotic resistance Risk of prolonged subtherapeutic drug release Intelligent and stimuli-responsive drug delivery systems.Limited clinical evidence Lack of human data Large-scale multicenter randomized clinical trials.

FUTURE DIRECTIONS

Recent advances in biomaterials, additive manufacturing and drug delivery technologies have opened up new opportunities for improving the clinical performance of antibiotic-loaded 3D-printed scaffolds.[8,11] Future research should be focused on the development of multifunctional scaffolds able to control infection and support bone regeneration.[10,11] The design of stimuli-responsive systems for the controlled release of antibiotics in response to

local infection cues represents a promising direction, with potential to minimize bacterial resistance while maximizing therapeutic efficacy.[11,19] Another emerging area is the development of multi-drug scaffolds incorporating various antibiotics, as well as osteogenic and immunomodulatory molecules, that would allow simultaneous control of infection, reduction of inflammation and promotion of bone healing.[10,11] The use of nanotechnology to enhance the antibacterial properties of scaffolds is also a promising approach, with silver nanoparticles and metal-organic frameworks showing particular potential in this regard.[10,18] The use of computational approaches such as artificial intelligence and machine learning to design and optimize scaffolds is another exciting frontier in this field that has the potential to lead to the development of next-generation antibiotic-loaded 3D-printed scaffolds that exceed the performance of currently available options.[8,12] Nevertheless, additional preclinical and clinical studies will be needed to fully elucidate the long-term safety and efficacy profile of these innovative devices before they can be adopted in clinical practice.[12,13]

CONCLUSION

Antibiotic-loaded three-dimensional (3D) printed scaffolds offer a promising approach for the treatment of post-surgical infections by combining the properties of antimicrobial agents and biomaterials.[7,10] Compared to conventional antibiotic delivery systems, these scaffolds possess several key advantages, including patient-specific design, localized drug delivery, long-term release, controlled biodegradation and osteogenic potential, and reduced systemic toxicity.[3,6,9] Recent advances in biomaterials science, additive manufacturing and drug delivery technologies have contributed to the development of multifunctional scaffolds with enhanced antibacterial and osteogenic properties.[6,10] Preclinical studies have demonstrated that such scaffolds can effectively prevent and control bacterial infections while promoting bone regeneration, thus offering a potential solution to the challenging clinical problem of post-surgical bone infections.[7,10,15]

Despite these promising results, further research is needed to address the key challenges related to regulatory approval, manufacturing standardization and clinical validation before these innovative medical devices can be widely adopted in orthopaedic practice[12,13]

Antibiotic-loaded 3D-printed scaffolds represent a potential next-generation therapeutic option for the management of post-surgical bone defects[10,13], and future studies will be critical in advancing our understanding of this innovative technology and its clinical applications.

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Conflict of interest

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