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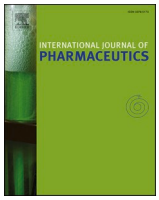

Review

Research progress on biodegradable polymeric platforms for targeting antibiotics to the bone

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ABSTRACT

The treatment of bone infections still involves systemic or local antibiotic therapy in high doses for prolonged periods. Current research focuses on the application of different drug delivery systems to the bone, aiming at a targeted local administration that will decrease the number of drugs used and their toxicity, compared to the systemic route. The gold standard in clinical practice is currently poly(methyl methacrylate) (PMMA) cement. The main drawback of PMMA, however, is that it is non-biodegradable, requiring a second follow-up surgery to remove the implant. Biodegradable delivery systems, on the other hand, are easily resorbable within the organism, and less invasive alternative with better patient compliance. Among biodegradable materials, natural and synthetic polymers are being studied as local drug delivery systems due to their excellent biocompatibility, sustained effect, and antibiotic release with high penetrability to infected bone and soft tissue. In this review, we focus on biodegradable polymeric platforms, such as micro- and nanoparticles, scaffolds, and hydrogels, as well as multi-delivery systems for targeting antibiotics to the bone. Additionally, we discuss the reported drug release profiles that provide important information about the systems' functionality.

1. Introduction

Antibiotic therapy continues to play a vital role in the clinical treatment of infections associated with bone (e.g. orthopedic implants, osteomyelitis) usually involving systemic or local antibiotic therapy at high doses over a prolonged period (Nie et al., 2022).

For local bone delivery, particularly, a broad application of different drug delivery systems is being tested in research and used in clinics, aiming at the delivery of high amounts of the drug at the target site and the decrease in toxicity in comparison to the systemic route (Nandi et al., 2016). However, the current antibiotic therapy is still far from satisfactory due to multiple factors, including reduced bone penetration related to the local ischemic condition, low efficacy associated with bacterial resistance, and poor anti-biofilm activity (Gatti et al., 2022; Nandi et al., 2016; Zilberman and Elsner, 2008). Therefore, there is an urgent need to propose novel therapeutic approaches to enhance antibiotic efficacy and, in particular, when administered locally associated with a carrier.

Drug delivery systems can be classified into non-biodegradable and biodegradable, depending on the materials used and their properties. Poly(methylmethacrylate) (PMMA) cement is a non-biodegradable material, considered for over 40 years as the gold standard biomaterial for local antibiotic delivery for both prophylaxis (Buchholz and Engelbrecht, 1970) and treatment of bone infection (Klemm, 1979). The acrylic bone cement beads are widely used for the local delivery of high antibiotic concentrations and to fill up dead space caused by debridement surgery (Masuda et al., 2017; Webb and Spencer, 2007). However, there is a limitation in the drugs that can be loaded in the PMMA bone cement. The antibiotics must be stable at very high temperatures, as the polymerization of the PMMA occurs along with the drug and it is a heat-generating exothermic process. Because of that, the preferentially used antibiotics to load in the bone cement are aminoglycosides such as streptomycin, gentamicin, amikacin, and tobramycin or cephalosporins (Smith et al., 2022). The elution profile of the drugs is mostly bimodal. In the first 24 h, around 5 % of the drug is rapidly released followed by a slower sustained release over the next 4–6 weeks. However, it has been

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reported that PMMA cement displays an incomplete drug release, most likely due to the polymer's hydrophobic nature (Bettencourt and Almeida, 2012).

Recently research has focused on developing drug delivery systems using biodegradable materials, because of their many advantages over non-biodegradable ones. The main reason is the lack of additional surgical procedures to remove the implant, as it is easily resorbable within the organism, which is less costly and creates better patient compliance. After its degradation, the biomaterial is replaced by the host's new tissues (Smith et al., 2022). Furthermore, biodegradable materials show better biocompatibility and greater bone restoration properties by having an osteogenic potential and flexibility that helps in osteogenesis (Nandi et al., 2016).

Among biodegradable materials, we can distinguish metals, ceramics, and polymers (Modrák et al., 2023; Shekhawat et al., 2021), whose main advantages and disadvantages are displayed in Fig. 1. Metals have been used in the bone repair field for a long time. Biodegradable metals are gathering attention lately, supported by their excellent degradability and biocompatibility (Wei et al., 2020). Ceramics are also well-researched and their use is described in the production of drug delivery systems, due to their excellent biocompatibility and osteoconductive potential. Recently, ceramic materials have been more often replaced by polymers due to their multiple advantages that overcome ceramics' and other materials' limitations (Inzana et al., 2016). Ceramics are stiffer than bone while polymers are more flexible. Polymers significantly reduce the stress shielding within implants during their degradation by transferring the load to the healing bone (Mulchandani et al., 2019).

Polymers can be further divided into natural and synthetic polymers based on their origin. Natural polymers such as collagen, fibrin, chitosan, and alginates offer better biocompatibility (Nayak et al., 2019). The most researched one is collagen, which is an important extracellular matrix protein and has a positive effect on tissue regeneration. Chitosan is also generally explored because of its antimicrobial properties against a wide spectrum of pathogens. However, natural polymers display antigenicity and are variable in properties (Smith et al., 2022). Synthetic polymers are produced using multiple pathways which enables them to be made with specific required properties. They also display less batch-to-batch variation as it is easier to produce them in a reproducible manner (Smola-Dmochowska et al., 2023). Due to their sustained effect and antibiotic release with high penetrability to infected bone and soft tissue, synthetic polymers have gained a lot of popularity as local drug delivery systems (Nandi et al., 2016). Furthermore, in contrast to non-biodegradable PMMA cement, these polymers are highly compatible with a wide range of different antibiotics such as ampicillin, gentamicin, and polymyxin-B (Nandi et al., 2016). The use of copolymers was also reported to increase the compatibility with antibiotics like tobramycin, clindamycin, and vancomycin (Billon et al., 2008). According to a systematic review of biomaterials performed by Inzana et al., the most common polymer used for local antibiotic delivery in recent years is poly (lactic-co-glycolic acid) (PLGA) (Inzana et al., 2016). Other commonly used synthetic polymers include polyesters such as poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL) and poly(glycolic acid) (PGA), polyurethanes and polyanhydrides (Smith et al., 2022). These materials show a very slow degradation rate during a long period so they can provide a lasting release of antibiotics. Also, by changing the physical, biochemical, and molecular structural properties of these polymers, the antibiotic release profile can be modulated as required (Nandi et al., 2016).

All the above-mentioned polymers can be used to compose drug delivery platforms for the treatment of bone infection. These drug delivery systems include macro-platforms like scaffolds and hydrogels, and

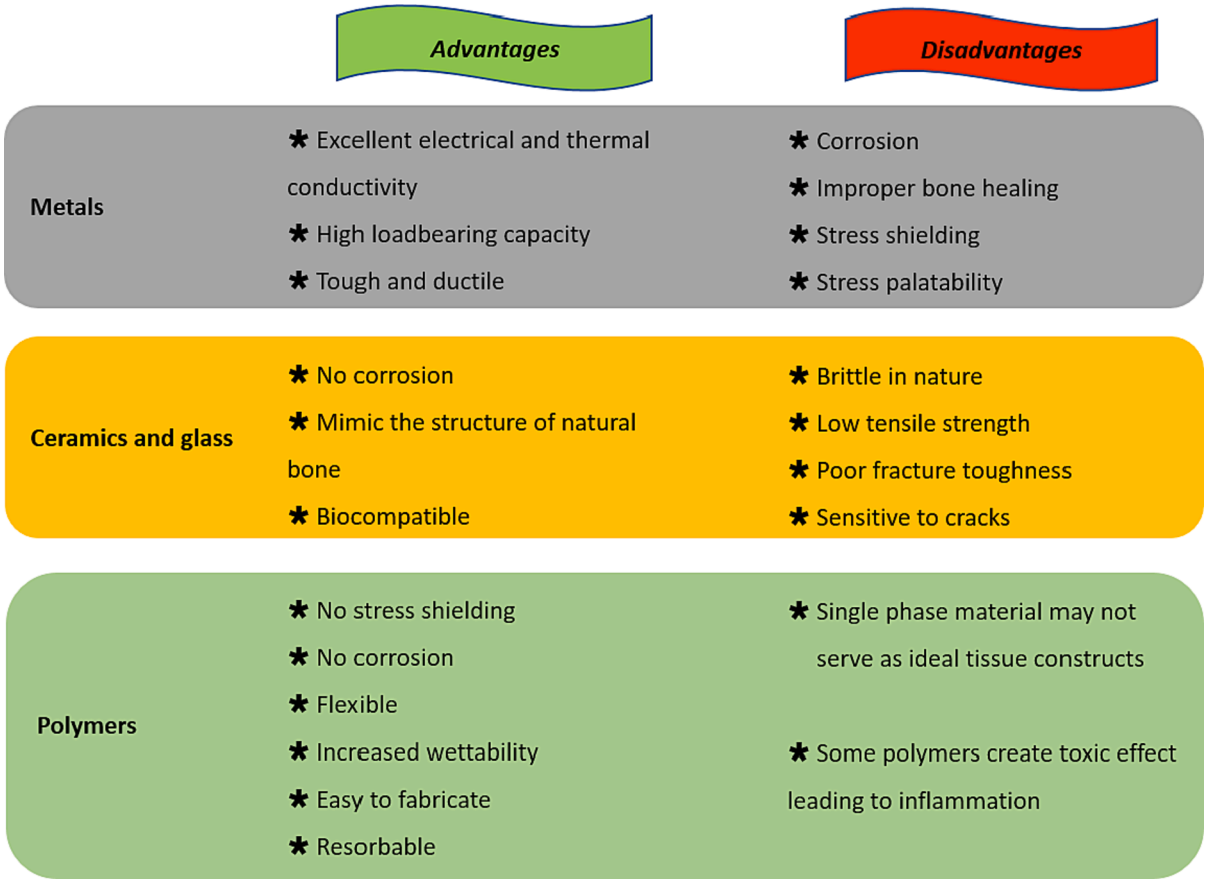

Fig. 1. Summary of advantages and disadvantages of biodegradable materials.

systems in the micro- and nanoscale, particularly microspheres and nanoparticles. Recently, they have been investigated to develop multi-systems, combining two or more delivery systems in one, as they can combine advantages and overcome limitations of currently available solutions (Gopi et al., 2018; Zweben, 2015).

In this review, we will further focus on the most recent research related to biodegradable natural and synthetic polymeric and multi-delivery systems for targeting antibiotics to the bone. In addition, we will discuss the release profiles of the mentioned drug delivery systems, as they provide important information about the functioning of the systems.

2. Micro- and nanoscale drug delivery systems

Nanotechnology has been described as effective in both the treatment and diagnosis of bone infection (Zeng et al., 2023), and its potential is still being extensively researched. Innovative proposals to manage bone infection may result in a reduction of recurrent infection rates and the improvement of patient outcomes. (Zapata et al., 2022).

2.1. PLA

Among these micro-and nanoscale strategies (Table 1), Wang and colleagues (Wang et al., 2020) proposed rifapentine PLA sustained-release microspheres (mean particle size of 27.67 ± 2.05 μm), fabricated through the double emulsion solvent evaporation technique and directed to the management of osteoarticular tuberculosis. The microspheres were integrated into hydroxyapatite/β-tricalcium phosphate scaffolds or allogeneic bone. The evaluated scaffold presented a long-term inhibitory effect on *Mycobacterium tuberculosis* growth, good stability, biocompatibility, osteoconductivity, and osteoinductivity. On the other hand, it displayed a biphasic release profile, with a burst release phase in the first 6 days, followed by a smooth decreased release rate for approximately 80 days. When compared to the platform prepared with allogeneic bone, the scaffolded drug delivery system had a longer duration of sustained release and was more stable. Beyond serving as drug-directed sustained release, the scaffolded system may serve a purpose in the replacement of bone defects (Wang et al., 2020).

2.2. PCL

Another proposal by Inês Ferreira research team (Ferreira et al., 2015) is based on daptomycin-loaded PCL microparticles (with volume mean diameter of 1.37 ± 0.12 μm), notably aimed against mature staphylococcal biofilms. Formulations containing vancomycin were also assessed for comparison purposes. All the microparticles were prepared by a modified method based on double-emulsion w/o/w-solvent evaporation (Bettencourt et al., 2010; Florindo et al., 2008). To characterize the systems, in vitro release behavior is one important predictor of antibacterial activity, often controlled drug release leads to high antibacterial efficacy (Pourseif et al., 2023). That was the case observed in this study in which daptomycin-loaded microparticles presented a controlled release that could be observed within 72 h in comparison to vancomycin-loaded microspheres. Daptomycin microspheres were more effective against planktonic *S. epidermidis* and methicillin-resistant *Staphylococcus aureus* (MRSA) when compared to vancomycin-loaded microparticles. Remarkably, it displayed superior activity even against MRSA biofilms, though against *S. epidermidis* biofilms no significant mass decrease was observed (Ferreira et al., 2015).

2.3. PLGA

Mahmoud and colleagues (Mahmoud et al., 2019) developed a novel therapeutic approach based on PLGA nanoparticles, surface-modified with a peptide (BAR) derived from *Streptococcus gordonii*, to target bone infection associated with periodontitis. In this context, BAR may serve as a different treatment to periodontitis control, since it inhibits the adherence of *Porphyromonas gingivalis* to commensal *Streptococcus gordonii*, reducing the virulence of this last pathogen. BAR surface-modified PLGA nanoparticles (NPs) (with average hydrated diameters of 333.8 ± 17.8 nm) were synthesized using a single emulsion technique (Martin et al., 2014; Sims et al., 2016). In this investigation, authors assessed the *in vivo* efficacy of this drug delivery system in a murine model of periodontitis. The release profile was not evaluated. These NPs reduced bone loss and the interleukin-17 (a pro-inflammatory cytokine) expression in infected mice, suggesting them as a novel proposal for drug delivery in the oral cavity (Mahmoud et al., 2019).

Another research group established gentamicin-loaded magnetic gelatin NPs directed for osteomyelitis treatment (Ak et al., 2021). Gelatin NPs were prepared by a method described elsewhere (Hamarat Sanlıer et al., 2015) and interestingly, the formation of these NPs needed to use a bifunctional cross-linker as genipin, once crosslinking is described as an important step for NPs fabrication, affecting both drug release and biodegradability (Niknejad and Mahmoudzadeh, 2015). *In vitro* drug release was assessed using a 10 mM phosphate buffer (pH 7.4) into dialysis membrane tubing. Gentamicin-loaded magnetic gelatin NPs (size of 253.7 ± 11.8 nm) showed a controlled drug release profile since gentamicin was released slower at the first few hours when compared with the free drug displayed burst-type. Furthermore, all the antibiotics were released only after 41 h. Regarding the release kinetics from the NPs, only the zero-order kinetic model was fitted with a high degree of linearity, evidencing that burst release was disfavored while antibiotics' release rate was essentially constant over time (Ak et al., 2021).

Table 1
Innovative micro or nanoscale drug delivery systems proposed for the treatment of bone infection, where polymers play an important role. **Abbreviations:** PLA, polylactic acid; PCL, polycaprolactone; PLGA, poly(lactic acid-co-glycolic acid); BAR, a peptide derived from *Streptococcus gordonii*.

Micro- or Nanoscale system	Polymer	Additive	Antibiotic	Release profile	Kinetic model	Reference
Microspheres	PLA	–	Rifapentine	Biphasic release profile. Burst release phase: 6 days. Smooth decreased release: 80 days.	Not specified	Wang et al., 2020
Microparticles	PCL	–	Daptomycin	Sustained release: 72 h.	Not specified	Ferreira et al., 2015
Nanoparticles	PLGA	–	Peptide (BAR)	No data available	Not specified	Mahmoud et al., 2019
Nanoparticles	Gelatin	Genipin and magnetite	Gentamicin	Slower release at the first few hours and 100 % released in 41 h	Zero-order	Ak et al., 2021
Nanoparticles	Gelatin	Colistin	Rifampicin, Moxifloxacin	Coating reduced premature drug release for 24 h	First-order	Aguilera-Correa et al., 2022
Nanospheres	Gelatin	–	Vancomycin	No data available	Not specified	Zhang et al., 2018

2.4. Gelatin

An interesting approach based on mesoporous silica nanoparticles (MSNs) was suggested recently (Aguilera-Correa et al., 2022), where the nanocarriers were engineered with a functional coating composed of gelatin and colistin (an antibiotic with biofilm-disaggregating features), to slow down the release of loaded antibiotics, namely moxifloxacin, and rifampicin. Enzymatically degradable gelatin and colistin coating is one of the main features of the proposed platform, to minimize premature drug release, besides the use of aspartic acid hexapeptide to prevent NPs quick clearance from the bone area. Gelatin coating was prepared by the modification of methods described previously (Martínez-Carmona et al., 2016; Zou et al., 2013). Briefly, the NPs were suspended in a gelatin solution and after the reaction, phosphate-buffered saline (PBS) was added. Glutaraldehyde (1 %) was also used as the crosslinking agent to prevent gelatin premature dissolution in aqueous media. The antibiotic release was studied for 24 h with phosphate buffer saline solution (PBS), one of the most used solutions to evaluate release from nanomaterials. The researchers concluded that the coating could reduce the drug release by 40 % (moxifloxacin) and 60 % (rifampicin) when compared to pristine NPs. In both studied cases, the release displayed a biphasic behavior, with an initial phase where a large amount of antibiotic was quickly released and a second moment where a sustained release was observed. In this research, the experimental data fitted a first-order kinetic model. The use of both moxifloxacin- and rifampicin-loaded MSNs led to synergistic effects that may be an important help in addressing bone infections by methicillin-resistant staphylococci and the worldwide problem of antimicrobial resistance (Aguilera-Correa et al., 2022).

Bone infection is regularly connected to the intracellular survival of bacteria, as it has been described to *Staphylococcus aureus*. Since most antibiotics present low intracellular efficacy, Zhang et al. proposed gelatin nanospheres (size of 329 ± 5 nm) loaded with vancomycin to improve results directed to overcome this limitation. The research focused on the assessment of drug local delivery into macrophages of zebrafish larvae *in vivo* (Zhang et al., 2018). Gelatin nanospheres were fabricated via a two-step coacervation method (Song, 2016; Song et al., 2015). The drug release profile was not evaluated by researchers, but the injected nanospheres' biodistribution and the macrophage response were analyzed. When compared to administration by intravenous injection, intramuscularly injected gelatin nanospheres were kept in the muscle tissue alongside the injection area and were internalized by macrophages. This study proposes that gelatin nanospheres might be an important alternative as carriers directed to local delivery of antibiotics, especially when infection is related to intracellular bacteria. Besides, another possibility is to incorporate these nanocarriers within coatings on medical devices and implants (Zhang et al., 2018).

Since NPs can provide significant control over the properties of scaffolds, such as providing controlled release of bioactive agents and tuning their mechanical strength (Fathi-Achachelouei et al., 2019), research has been focused on incorporating NPs into biomaterial scaffolds as the ones described in the next chapter, to achieve effective effects on cell proliferation, viability, migration, and adhesion (Habibzadeh et al., 2022).

3. Polymeric scaffolds

The bone scaffold can be defined as a three-dimensional (3D) matrix that allows and stimulates the proliferation and attachment of osteoinducible cells on its surfaces (Ghassemi et al., 2018). The use of biodegradable scaffolds provides a framework for tissue repair as well as a substrate for the inclusion of antimicrobial properties. Scaffolds present a straightforward approach for the prophylaxis and localized treatment of bone infection, targeting mainly bacteria (especially *S. aureus*, commonly associated with these infections) but also fungi (Zegre et al., 2022), with sustained antimicrobial release in the bone matrix, good biocompatibility and low ability to develop inflammatory response (Mostafa et al., 2017; Zhou et al., 2018). Some of the most innovative and inspiring scaffold-based drug delivery systems for the treatment of bone infection are presented in Table 2.

3.1. PDLLA

Amongst novel strategies based on scaffolds to target bone infection, our research group (Zegre et al., 2022) proposed poly(DL-lactic acid) (PDLLA) platforms functionalized with collagen and loaded with an antibacterial (minocycline) and an antifungal (voriconazole), directed to a polymicrobial biofilm model (Fig. 2). A dual-functional (anti-microbial action and osteogenesis promotion) scaffold like this can provide single-stage treatment that avoids multiple surgeries, simplifies the therapy and minimizes the time required for treatment, when compared with conventional methods (Cui et al., 2022). Biofilms can be considered a severe menace in modern medicine since their development is common in implants and medical devices (van de Belt et al., 2001; Veerachamy et al., 2014). Single-species biofilms have been broadly researched, however, in the last years, several studies have emphasized that the majority of infections are originated from polymicrobial biofilms, responsible for higher mortality rates when compared with single-species biofilms. Infections evolving from mixed fungal-bacterial biofilms are considered a primary public health problem in clinics (Ma et al., 2020). The scaffolds were prepared by solvent casting/particulate leaching method (Martin et al., 2019a), responsible for a well-structured porous network, presenting macropores interconnected with micropores, that may support cell proliferation and nutrition. Release studies were accomplished with HEPES buffer 10 mM (pH = 7.4) at 37 °C, throughout 120 h (5 days). A higher initial drug delivery was observed (burst phase) for all analyzed groups of scaffolds, which may have a positive impact on the prevention of antibiotic resistance. On the other hand, a significant amount of the drugs was released during the first 24 h and on the first day after scaffolds' implantation which can favor infection control. Additionally, this innovative drug delivery system displayed cytocompatibility and functional activity when tested in human MG-63 osteosarcoma cells. Finally, the dual-delivery scaffolds proved to have activity against *S. aureus* – *C. albicans* mixed biofilms (Fig. 2) (Zegre et al., 2022).

3.2. Polyurethane

A different approach is presented by Kuang et al., who developed a composite scaffold where polyurethane (PU) plays a key role (Kuang et al., 2021). Polyurethanes are a class of biodegradable and biocompatible block copolymers, whose application as carriers for drug delivery and scaffolds for tissue engineering has been described (Chiono et al., 2017). Additionally, the composite structure also involves nano-hydroxyapatite (n-HA), taking advantage of its comparable architecture to normal bone, and levofloxacin-loaded mesoporous silica microspheres (MSNs). The n-HA/PU scaffolds were fabricated using the *in situ* foaming method (Li et al., 2015). The authors did not present drug release profile results, though a controlled release from the MSNs-based system is described. Furthermore, the material induced osteogenic differentiation of bone marrow mesenchymal stem cells in vitro and inhibited bacterial growth, viability, and microbial adhesion of *S. aureus* and *Escherichia coli*. This dual function of osteogenesis and anti-infection proposes this system for clinical application in the future (Kuang et al., 2021).

3.3. PLC

Another research group designed a distinctive composite scaffold, based on a recently introduced copolymer of PLA and PCL called poly-lactide-co-ε-caprolactone (PLC), combined with calcium phosphate (bioceramic). Moxifloxacin was the selected model drug, once it was proposed as a solid choice for antimicrobial treatment of bone infection,

Table 2
Novel scaffold-based drug delivery systems for the treatment of bone infection. Abbreviations: PDLLA, poly(DL-lactic acid); PLC, poly-lactide-co-Ɛ-caprolactone; PLA, polylactic acid; PLGA, poly(lactic acid-co-glycolic acid).

Drug delivery system	Polymer carrier	Additional materials	Antimicrobial	Release profile	Reference
Scaffold	PDLLA	Collagen	Minocycline Voriconazole	Initial burst release. Significant drug release within the first 24 h.	Zegre et al., 2022
Composite scaffold	Polyurethane	Nano-hydroxyapatite	Levofloxacin	Controlled release.	Kuang et al., 2021
Composite scaffold	PLC	Calcium phosphate	Moxifloxacin	Initial burst release after 24 h. Slower rate of drug release for 42 days.	Radwan et al., 2021
3D-printed scaffold	PLA	Nano-hydroxyapatite Collagen Iron oxide NPs	Minocycline	Most available drug released within 24 h. Burst over 40 % observed in the first 15 min.	Saraiva et al., 2021
3D-printed scaffold	PLA	Hydroxyapatite NPs Collagen	Minocycline	Burst release within the first hour. Progressive release from 4 to 24 h.	Martin et al., 2019b
Composite scaffold	PLGA	Mesoporous bioactive glass	Vancomycin	Quick release within the first 72 h Release performance over 58 days.	Cheng et al., 2018

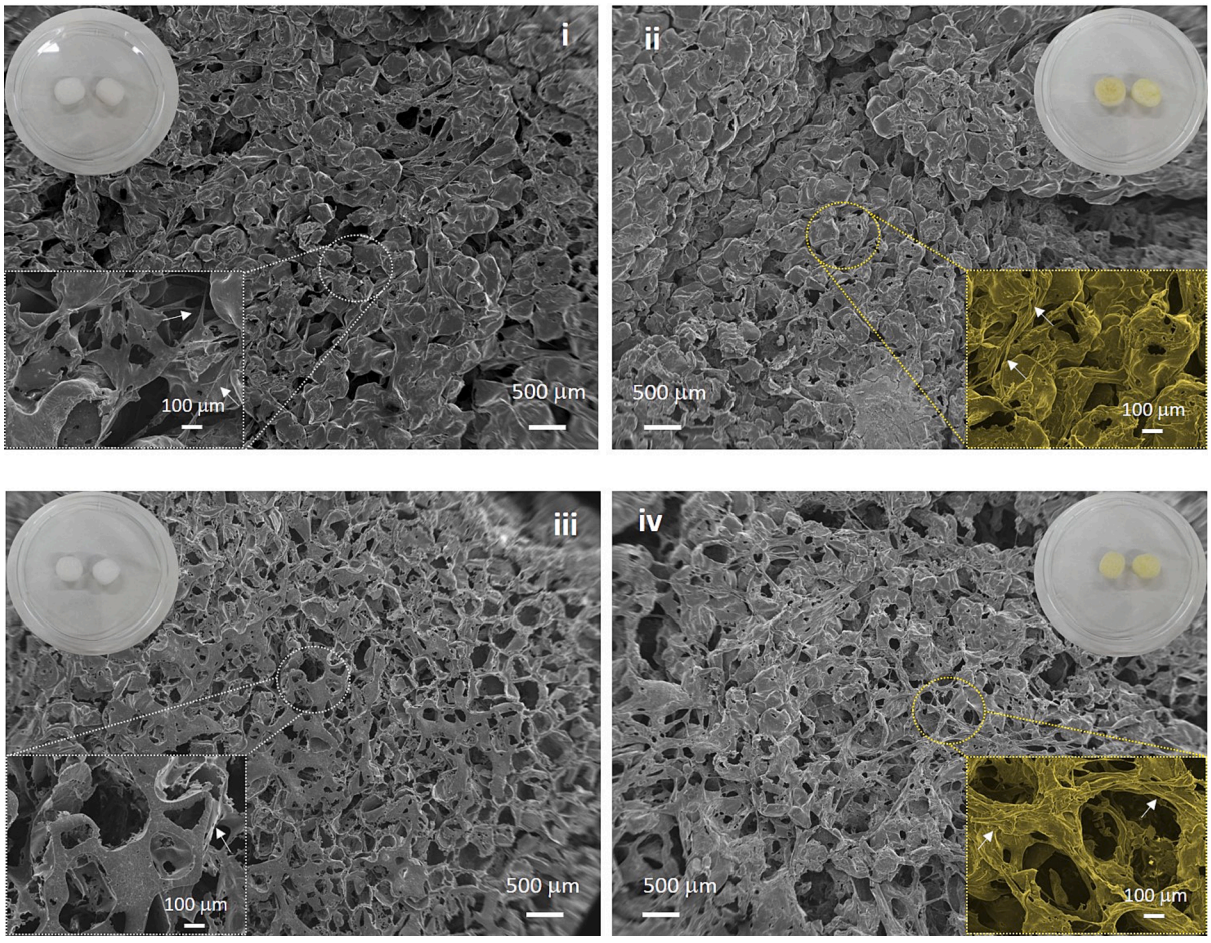

Fig. 2. Representative optical images and SEM micrographs (A) of the PDLLA scaffolds (i) with different compositions (PDLLA-Min (ii); PDLLA-Vor (iii) and PDLLA-Min-Vor (iv)) showing in detail the morphological and structural features of the scaffolds (inset images). Adapted with permission from (Zegre et al., 2022). Copyright © 2022 Elsevier. Abbreviations: PDLLA, poly(DL-lactic acid).

with relevant bone and plasma concentrations (Malincarne et al., 2006). *In vitro* release of the antibiotic was appraised with PBS (pH = 7.4) as the selected media, at 37 ± 0.5 °C. All studied scaffolds presented an initial burst release after 24 h, which helps to instantaneously increase the antibiotic concentration to eliminate most of the pathogens locally present. After this first period, globally, it was observed a slower rate of drug release for 42 days, although the results show oscillations dependent on PLC matrices of different grades (70/30 and 85/15) and the scaffolds' synthetic pathways applied (in the case of sodium methoxide is present as an intermediate step, or not). From different scaffolds analyzed, the moxifloxacin-loaded *in-situ* scaffold with a PLC matrix of 85/15 grade displayed the smallest initial burst release, with a gradual rate of antibiotic release for 42 days. This selected scaffold also improved the differentiation and the proliferation of MG-63 osteoblasts cell line, while significantly reducing the count of *S. aureus* after incubation (when compared to free moxifloxacin) (Radwan et al., 2021).

3.4. PLA

Since bone infection is described as a destructive condition caused by microbial infection of the bone, innovative treatments such as antibiotic-impregnated 3D-printed scaffolds represent encouraging strategies for

the prevention and management of this devastating disease (Masters et al., 2019). Porous scaffolds created by 3D printing technology have gained attention as an emergent trend, considering that in terms of microstructure and appearance, they are considered similar to human bone and their fabrication can be more reproducible compared, for example, with solvent casting/particulate leaching techniques (Feng et al., 2021). Martin et al. (Martin et al., 2019b) emerged with a singular strategy to enhance bone tissue regeneration and simultaneously control bacterial biofilm. The proposed minocycline loaded 3D-printed scaffolds were fabricated through a fused deposition modeling process, by the extrusion of a PLA filament with 1.75 mm of diameter. To improve surface hydrophilicity and roughness aiming for superior cell adhesion, the scaffolds were submitted to alkali hydrolysis treatment. Collagen and nanosized hydroxyapatite were also added to the platforms. Moreover, in another work the scaffolds were also loaded with iron oxide NPs (IONPs) (Saraiva et al., 2021). Interestingly, the IONPs preparation method was based on a facile chemical co-precipitation method, in an aqueous medium at room temperature. Additionally, these 3D constructs presented exceptional bioactivity, osteogenic outcomes on immortalized and primary bone cells, cytocompatibility (Fig. 3), and activity against *S. aureus* (Saraiva et al., 2021). Moreover, Martin and colleagues showed that the fabricated 3D-printed platforms demonstrated exceptional compressive strength, adequate wettability, and uniform macroporous structure close to natural bone architecture. Minocycline release profile (Fig. 4) was determined for 24 hours with HEPES buffer 10 mM (pH = 7.4) at 37ºC, while antibiotic quantities were evaluated by spectrophotometry (λ = 350 nm). The analyzed scaffolds presented a burst release within the first hour, followed by progressive release from 4 to 24 h time-points. The proposed drug delivery 3D-printed polymeric system, resulted in a platform with a suitable combination of osteogenic and antibacterial/antibiofilm properties, exhibiting further mechanical and morphological characteristics that mimic trabecular bone, opening up excellent prospects for the use of this polymer in clinical context (Martin et al., 2019b).

3.5. PLGA

To produce a bone tissue-engineered composite scaffold, combining it with an antibiotic delivery system, Cheng et al. prepared an innovative platform by freeze-drying fabrication. Vancomycin was the selected antibiotic to integrate in mesoporous bioactive glass (MBG), a carrier that subsequently was incorporated in a stable sol of PLGA. The antibiotic release profile was assessed in PBS (pH = 7.4) at 37 °C, and vancomycin quantities were determined for more than eight weeks using UV/Vis spectrophotometry (λ = 280 nm). The antibiotic was quickly released from the composite scaffold studied within the first 72 h, and then a gradual release followed, with a smooth slope. Scaffolds with PLGA and vancomycin-loaded MBG incorporated, maintained a significant release performance over 58 days, with cumulative releases of almost 53 %, which contrasted with values of 23 % found in individual PLGA scaffolds (loaded with the drug but without the MBG carrier) after more than eight weeks. This platform also displayed controlled degradability, osteoblastic differentiation properties, suitable cytocompatibility (when compared to pure PLGA scaffold), antibacterial activity against *S. aureus* (the most common bacteria found in infected bone tissues), and even inhibited biofilm formation (Cheng et al., 2018).

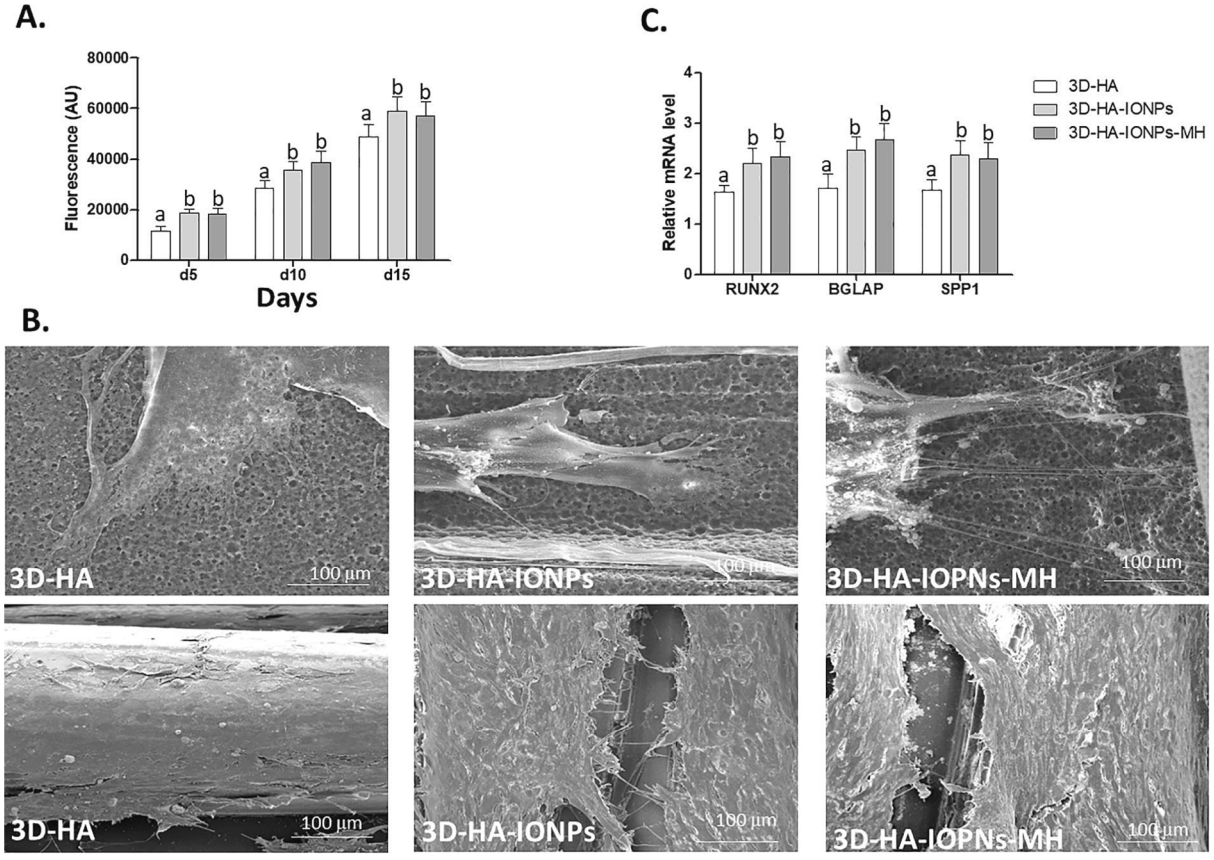

Fig. 3. Cytocompatibility assays with hBMSCs. A. Metabolic activity by resazurin assay, established for up to 15 days on the 3D platforms. B. Representative SEM images of the cultures established for 5 (top row) and 15 (bottom row) days on the surface of PLA 3D platforms. C. Relative expression of the osteogenesis-related genes RUNX2, BGLAP, and SPP1. Note: different lowercase letters (a and b) indicate significant differences between the groups, with $p \leq 0.05$. Adapted with permission from (Saraiva et al., 2021). Copyright © 2021 Elsevier. Abbreviations: IONPs, iron oxide nanoparticles; hBMSCs, human bone marrow-derived mesenchymal stromal cells; HA, hydroxyapatite; MH, minocycline; PLA, poly(lactic acid).

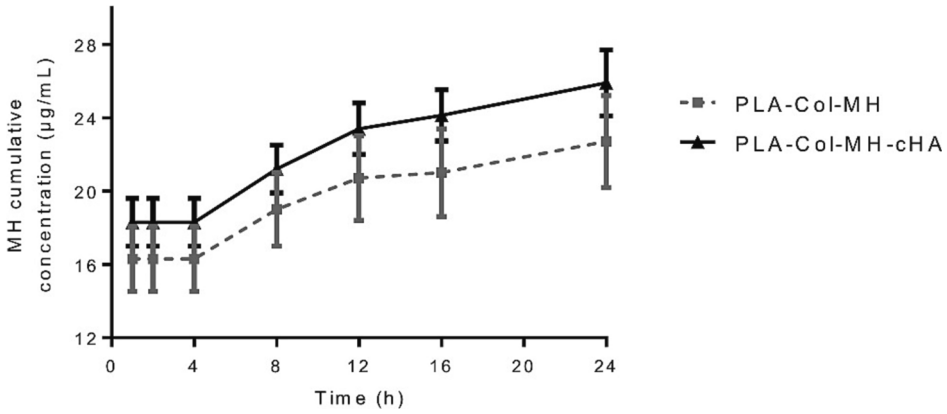

Fig. 4. Cumulative minocycline (µg/mL) release profile (24 h). Adapted with permission from (Martin et al., 2019b). Copyright © 2019 Elsevier. **Abbreviations:** Col, collagen; cHA, hydroxyapatite nanoparticles; MH, minocycline; PLA, poly(lactic acid).

This research promotes once again, polymeric-based scaffolds as an innovative and promising strategy for infection containment and bone infection management.

4. Hydrogels

Hydrogels are water-based porous 3D networks with flexible structure made of natural or synthetic hydrophilic interlinked polymer chains. (Lavanya et al., 2020). In the context of bone targeting, natural polymers such as alginate, gelatin, and chitosan have been favored in the production of hydrogels due to their excellent biocompatibility as they can mimic the natural extracellular matrix of the bone, creating a promising template for bone regeneration and local drug delivery.

In general, there are two basic methods for hydrogel formulation, i.e., physical and chemical crosslinking. In the chemical method, the covalent bonds are being produced between the polymer chains. Those methods can use free radical polymerization, addition and condensation polymerization, enzyme-induced crosslinks, high energy irradiation, and chemical reaction of complementary groups (Hennink and van Nostrum, 2012). Chemical methods provide mechanically stable hydrogels with permanent bonds between polymers, however, there is a disadvantage of the potential absence of residual chemical crosslinking agents, which may cause some cytotoxic adverse effects (Lavanya et al., 2020). Contrarily, the physical methods form non-covalent bond interactions between polymer chains using subsidiary forces such as hydrophobic interactions, crystallization, ionic and charge interactions, physical mixtures and hydrogen bonding interactions, and stereocomplexation (Parhi, 2017). Hydrogels prepared using these methods are reversible and not permanent or stable, which may cause natural dissolution (Lavanya et al., 2020).

Drugs can be loaded into hydrogel porous structures and be released while the polymer degrades or due to hydrogel swelling caused by water ingress. Hydrogels are easily resorbable and can be cleared from the body within 2 to 6 weeks, however, the degradation rate can also be tailored by changing the composition or amount of crosslinked polymers (Smith et al., 2022). At the same time, it also modifies the release profile, which typically is reported as an initial burst of the drug followed by slower, low-dose sustained antibiotic elution (Cobb et al., 2020). Table 3 describes novel hydrogel systems for antibiotic delivery and specifies their release profiles.

As the release of drugs is exceptionally important to maintain sustained local antibiotic concentration for a long period and above MIC to successfully cure bone infection, researchers are developing new ways to improve and extend it. One of them is using composite materials for producing hydrogels, which can overcome the limitations of each polymer when used separately (Xin et al., 2022). To extend the release of gentamicin and vancomycin the HA-PNIPAM hydrogel was developed. It's a composite from two different natural polymers – hyaluronic acid (HA) and poly(N-isopropyl acrylamide) (PNIPAM), combined by functionalizing the carboxy groups of HA with amino-terminated PNIPAM via amide formation (D'Este et al., 2012). The antibiotics from this hydrogel were released for more than 2 weeks in vitro (Boot et al., 2021) and 3 weeks in vivo (Foster et al., 2021). The other proposition for vancomycin delayed elution was PEG-based hydrogel mixed with crosslinked starch (CSt), which inhibited hydrogel swelling therefore slowing down the drug release. The release profile of this synthetic polymers' hydrogel showed a sustained antibiotic elution for 3 weeks in vitro and for over 4 weeks in vivo with no initial burst release (Li et al., 2017). It was reported that this system displayed a Ritger-Peppas kinetic model, which was specifically developed for the drug molecule release from a polymeric matrix such as hydrogel (Bruschi, 2015). The other hydrogel made of the combination of alginate and HA, prepared by mixing simple solutions containing mentioned polymers, was reported to release vancomycin and BMP-2 continuously for 6 weeks (Jung et al., 2019).

Another way of improving the release profile is adding transglutaminase (TGase), which is widely used in biotechnology to produce protein conjugates derivatized at the level of Gln and/or Lys residues

Table 3
Hydrogel systems for antibiotic delivery. **Abbreviations:** BMP-2, bone morphogenic protein 2; PEG, polyethylene glycol; TGase, transglutaminase.

Material	Additive	Antibiotic	Release profile	Release kinetics	Reference
PEG and crosslinked starch	–	Vancomycin	Sustained release for 3 weeks in vitro and over 4 weeks in vivo with no initial burst	Ritger–Peppas model	D. Li et al., 2017
Alginate and hyaluronic acid	BMP-2	Vancomycin	Continuous release for 6 weeks	Not specified	Jung et al., 2019
Chitosan, β-glycerophosphate, and hyaluronic acid	–	Vancomycin	Release controlled by the hyaluronidase concentration	Not specified	Y. Li et al., 2020
Gelatin and alginate	Tgase	Vancomycin or gentamicin	Release for more than 120 h with 1 % of Tgase	Not specified	Sun et al., 2021
Hyaluronic acid and poly(N-isopropyl acrylamide)	–	Vancomycin and gentamicin	Antibiotics released for more than 2 weeks in vitro and 3 weeks in vivo	Not specified	Boot et al., 2021

(Duarte et al., 2020). Sun et al. developed a novel TGase cross-linked gelatin-alginate hydrogel encapsulating vancomycin or gentamicin as an antibiotic slow-release system, obtaining 90 % of crosslink. The release time of both antibiotics extended with a higher degree of TGase used for crosslinking from 20 min with no TGase to more than 120 h for 1 % TGase. However, in studies using rats as animal model, only the hydrogel with vancomycin reduced the inflammation and biofilm formation on site and showed significant regeneration of the bone. Gentamicin-loaded crosslinked hydrogel did not show the same in vivo results (Sun et al., 2021).

As the technology progressed, different methods were researched for creating "smart implants". The idea behind it is to develop an implant that would release the drug according to the presence of bacteria or its metabolites, avoiding unnecessary waste of the released drug. It can be especially useful for the prevention of bone infection post-surgery, as the drug will be released only when the bacteria will accumulate. Such smart delivery systems will be specifically designed to respond to a specific stimulus like pH gradients, temperature, or enzymes, causing a change in its physical properties and provoking drug release (Lavrador et al., 2018).

One of the examples is using hyaluronic acid as a trigger for antibiotic release on demand. *S. aureus*, which is one of the main pathogens causing bone infection, produces an enzyme hyaluronidase. Its concentration increases with the amount of bacteria spread. In that research, Li et al. developed a hyaluronic acid chitosan/β-glycerophosphate system loaded with vancomycin hydrochloride (VH-HA-CS/β-GP), in which the speed of drug release can be controlled by the hyaluronidase concentration on site. At 25 days the released drug concentration was much higher than MIC in in vitro studies, and in vivo the drug concentration could increase up to 30 days when the drug is exhausted, but that was reported to be sufficient to prevent surgical site bone infection. Moreover, the aforementioned hydrogel can be instantly constructed on top of TCP scaffolds during surgery or possibly also onto other implants with porous structure (Li et al., 2020).

For most of the hydrogels, the viscosity of the material might limit the efficacy of this delivery system application into the infected site. One of the solutions that overcome this issue was developed by Yu and Ding, a thermo-responsive implant that would solubilize only after reaching its destination (Yu and Ding, 2008). For that purpose, researchers used PNIPAM, which was able to change its properties with temperature. In this case, the parameter of lower critical solution temperature (LCST) of composite material is essential (Jeong et al., 2002). A hydrogel created with a mixture of HA with PNIPAM was designed to have low modulus at room temperature, but when it comes in contact with tissue and body fluid it changes to a gel state due to temperature higher than its LCST (ter Boo et al., 2016). Loading the hydrogel with gentamicin sulfate lowered LCST from 28 °C to 25 °C, however, it was reported that it did not impact its delivery or applicability as it was still successfully solidifying in body temperature after injecting (Boot et al., 2021). The PNIPAM and HA hydrogel was also successfully incorporated with different drugs namely rifampicin and antiseptic chlorhexidine with low influence on its gelation (Pérez-Köhler et al., 2020), suggesting that this hydrogel is likely to be loaded with a wide range of antimicrobial agents (Boot et al., 2021).

5. Multi-delivery systems

To overcome the limitation of one single drug delivery system, recent studies focused on developing multi-systems combining a couple of platforms enhancing their abilities and properties when working together. Table 4 gathers information about novel multi-systems with hydrogel as the main platform.

The thermosensitive hydrogel was used in a multi-system embedding nanoparticles inside, to amend the injectability, which is the main limitation of nanoscale systems (Tao et al., 2020). Hydrogels also can be tailored to achieve specific geometry for application in the form of injection, without using extensive surgery (Bai et al., 2018). Using this feature there was proposed an injectable hybrid system of PLGA nanoparticles embedded in a gellan gum hydrogel, with both platforms loaded with gentamicin. This combination increased the amount of

Table 4
Multi-systems composed of hydrogel and additional platforms for antibiotic delivery. Abbreviations: NPs, nanoparticles; PCL, polycaprolactone; PLGA, poly(lactic-co-glycolic acid); PEG, polyethylene glycol.

Multi-system	Platforms	Material	Antibiotic	Release profile	Release kinetics	Reference
NPs in hydrogel	NPs Hydrogel	Gellan gum PLGA	Gentamicin	Burst release within first 12 h followed by a sustained release within 90 days	Not specified	Posadowska et al., 2016
Liposome in hydrogel	Hydrogel Liposome	PLGA PEG Phospholipid	– Isoniazid	Decreased burst release from 60 % to 40 % followed by an extended release up to 120 h	Korsmeyer-Peppas model	Liu et al., 2019
NPs embedded in hydrogel	Hydrogel NPs	Chitosan Chitosan	– Vancomycin	Sustained release over 26 days	Not specified	Tao et al., 2020
Scaffold encapsulated by hydrogel	Scaffold Hydrogel	PCL Alginate	Cefazolin Rifampicin	Burst release within first 8 h Sustained release for up to 7 days	Not specified	Lee et al., 2022
Hydrogel scaffold loaded with NPs	Hydrogel NPs	Silk fibroin Sodium alginate Silk fibroin	Teicoplanin	Sustained pH-dependent drug release for over 35 days with decreased burst release	Ritger-Peppas model	Motasadizadeh et al., 2022
NPs embedded in hydrogel	NPs Hydrogel	PLGA Gelatin methacrylate	Rifampicin Vancomycin	Biphasic release: initial burst release followed by sustained drug release	Not specified	Martínez-Pérez et al., 2023
Hydrogel based on NPs	NPs Hydrogel	Hydroxyapatite Chitosan	Quercetin Vancomycin	Release pattern of both drugs was pH sensitive Cumulative release percentage increases at pH of 5.7	Not specified	Akhlaghi and Najafpour-Darzi, 2023
Hydrogel with scaffold incorporated with NPs	Hydrogel Scaffold NPs	Chitosan Hyaluronic acid PCL MSNs	Vancomycin	Quick release at initial stage followed by a sustained release	Not specified	Zhang et al., 2023
Polymeric system containing NPs	Polymeric system NPs	PLGA Chitosan	Vancomycin	Burst release reduced by 44 % after adding NPs to the system	Not specified	Aghazadeh et al., 2023
Hydrogel loaded with liposomes	Hydrogel Liposomes	PLGA PEG Phosphatidilcholine Cholesterol	Vancomycin	Vancomycin displayed a sustained release up to 14 days DNase I presented burst release within 72 h	Not specified	Li et al., 2023

antibiotic rapidly released in the first 12 h compared to the release from NPs alone and lowered the amount of drug in the follow-up sustained elution, however, extended this phase from 35 days for NPs alone to 90 days (Posadowska et al., 2016).

Another feature of NPs-Hydrogel systems that put a lot of attention towards them lately, is the ability to reduce the initial burst release and achieve only a sustained continuous drug elution for a long period (Ma et al., 2019). Proposed vancomycin-loaded NPs embedded into chitosan hydrogel showed a controlled gradual release over 26 days resulting in 65 % of total drug release. The mechanism of release from this multi-system is thought to be a mix of diffusion and erosion of the hydrogel, sustaining the elution (Tao et al., 2020). Liu et al. developed a thermoresponsive hydrogel encapsulating liposomes containing isoniazid to treat bone tuberculosis, which showed a slowed-down release in comparison to isoniazid in hydrogel only. It decreased the amount of drug released in an initial burst from 60 % to 40 % and extended the sustained residual isoniazid elution to more than 120 h. It was reported that the drug release from this multi-system fitted the Korsmeyer-Peppas model suggesting Fick's diffusion mechanism (Liu et al., 2019). This information points out that the drug release rate was determined by its diffusion from the hydrogel, which depends on the liposome-drug hydrophobic interactions and the hydrogel's mesh size (Barzegar-Jalali et al., 2008). Additionally, this proposed multi-system shows not only thermoresponsiveness, enabling easier application to the infected site, but it is also reported that this PLGA-PEG-PLGA copolymer hydrogel has self-healing properties after damage, decreasing the injection frequency and protecting the rapid leaking of drug out of the hydrogel (Liu et al., 2019).

The multi-systems with a hydrogel as the main platform can also be modified to create an intelligent implant. Motasadizadeh et al. developed a multi-system reacting to a particular stimulus which is a change in pH. Adding polymeric material alginate to the delivery system made of silk fibroin (SF), composed of nanoparticles embedded into the hydrogel, was reported to quicken the release of teicoplanin and phenamil in alkaline pH, because of the conversion of alginate's COOH groups to COO^-, which increases the repulsion between negatively charged polymers and therefore the swelling of the hydrogel increases. The proposed multi-system achieved a sustained pH-dependent drug release for over 35 days with decreased burst release in comparison to the hydrogel alone. The drug release was fitted into the Ritger-Peppas model and showed that the transport mechanism of teicoplanin from all pH values was anomalous (non-Fickian), suggesting swelling-controlled release and transport mechanism of phenamil was super case II (Fickian-controlled diffusion) (Motasadizadeh et al., 2022).

As mentioned earlier, some hydrogels can be easily adapted on top of another platform for example scaffolds (Li et al., 2020). This method can serve either as an application of the original system during the surgery or it can serve as a dual-drug delivery. For the latter purpose, Lee et al. developed a system composed of a 3D-printed PCL scaffold containing cefazolin, which was encapsulated by a second platform – alginate hydrogel loaded with rifampicin. It was reported that rifampicin inhibits biofilm formation, while the internal drug cefazolin acted synergistically and increased antibacterial activity. The rifampicin was abruptly released in the first 8 h, while the cefazolin was gradually slowly eluting for up to 7 days. This was the first report to note the low-temperature processing of creating a platform that enabled encapsulation and maintained the antibacterial activity of heat-sensitive cefazolin, previously also successfully loading rifampicin into the scaffold (Lee et al., 2020).

The development of 3D-printed dual rifampicin- and vancomycin-loaded PLGA NPs, embedded into hydrogels made of gelatin methacrylate, was the approach selected by Martínez-Peréz et al. to target implant-related infections. While NPs loaded with rifampicin were prepared following the single emulsion and evaporation process, NPs loaded with vancomycin were produced by the double emulsion and evaporation process. Antibiotics' release from PLGA NPs was studied for 21 days in PBS. PLGAs with three different molecular weights were used initially. The cumulative drug release showed a strong dependency on the molecular weight of PLGA and the NPs composed with the Lower Molecular Weight PLGA exhibited the quickest drug release in the first 3 weeks. A biphasic release was recognized, with an initial burst release followed by a sustained drug release over time, making these NPs the selected candidate to be incorporated into the 3D-printed gelatin methacrylate hydrogels. Two resistant strains of *S. aureus* were tested with the Kirby-Bauer agar diffusion assay, and both were targeted with this double antibiotic-releasing hydrogel, showing that this system can be used to treat or prevent implant-associated infections (Martínez-Pérez et al., 2023).

The treatment of orthopedic implant-associated infections was also the concern that led Akhlaghi and Najafpour-Darzi to develop thermosensitive injectable chitosan-based hydrogel, associated with hydroxyapatite NPs, containing vancomycin and quercetin (drug with antioxidant properties) loaded in pluronic F127 micelles. (Akhlaghi and Najafpour-Darzi, 2023) Hydroxyapatite NPs were synthesized according to a method previously introduced by Zhao and Ma, with some modifications (Zhao and Ma, 2005), while hydrogel nanocomposites were prepared using ionic crosslinking. The release of both drugs from hydrogels was investigated at two different pH values of 7.4 and 5.7 for 10 days. The release pattern of vancomycin and quercetin from hydrogel was pH sensitive since the cumulative release percentage increased at an acidic pH value of 5.7 when compared to neutral pH. Antibacterial performance assessment revealed that drug release efficiently occurred and that the anti-biofilm properties of the dual drug-loaded hydrogel were enhanced by the combination of pluronic F127 micelles. The presented thermosensitive injectable hydrogel may emerge as an innovative antioxidant, anti-biofilm, and antibacterial coating design, directed to local delivery in bone infection (Akhlaghi and Najafpour-Darzi, 2023).

In the study of Zhang et al., a dual drug delivery PCL scaffold system was developed by the combination of vancomycin-loaded hydrogel (prepared with aldehyde hyaluronic acid and carboxymethyl chitosan) with 3D printed scaffold, incorporated with biodegradable MSNs loaded with fingolimod (promotor of osteogenesis, angiogenesis and provider of structural support). Results assessed in vitro demonstrated that the fingolimod-loaded composite scaffold exhibited excellent vascularization, osteogenic ability, and biocompatibility. The hydrogel composite scaffold displayed antimicrobial properties that were vancomycin concentration-dependent. Concerning drug release, the vancomycin-loaded hydrogel presented an initially quick release at the initial stage, followed by a sustained release profile. These results may provide infection control initially and an extended antibacterial effect. As in vitro outcomes demonstrated that the dual drug delivery scaffold displays osteogenic and antibacterial activity, besides good compatibility, this seems a promising candidate for infected bone defects management (Zhang et al., 2023).

In situ forming systems are currently being investigated as osteomyelitis treatment possibilities. Aghazadeh et al. propose the long-term release of vancomycin through a PLGA system loaded with drug-containing chitosan NPs, prepared using the ionic gelation method. Release profiles were analyzed and revealed that adding NPs to the system reduces burst release by 44 %, then increasing release time. The system tested is biocompatible and non-toxic, which means it can be used for loading an assortment of released drugs and loaded drugs in NPs to treat an infectious disease, such as chronic osteomyelitis (Aghazadeh et al., 2023).

The eradication of *methicillin-resistant S. aureus* (*MRSA*) infection in vivo, was addressed by Li et al. through the development of DNase I and vancomycin hydrogel delivery vehicle. The antibacterial drug was encapsulated in liposomes and then these structures and the enzyme were loaded in novel thermosensitive PLGA-PEG-PLGA hydrogel. Vancomycin and DNase I in vitro release profile was determined at 37 °C with PBS and 0.2 % tween-20. While vancomycin displayed a sustained

release (82.6 %) up to day 14, DNase I presented a burst release (77.2 %) within 72 h. *In vivo* efficacy was also evaluated and, in the co-delivery system group analyzed, the bacteria on bone and implant were eradicated. These findings display promising clinical translational value (Li et al., 2023).

6. Future perspectives

Local drug delivery systems made of biodegradable polymers seem to be an attractive approach quickly gaining popularity in the treatment of bone infection. Furthermore, with the development of technology, the future of drug delivery systems seems to be evolving rapidly. There are already many propositions for 3D printed scaffolds targeting osteomyelitis (Bai et al., 2020; Lee et al., 2022; ; Sadaba et al., 2020; Saraiva et al., 2021), which have great potential to become more popular as of many advantages of this technology. It would enable the customization of the size and shape of the platform, personalization of an active drug load amount, and modification of the drug release profile and kinetics. It also increases the precision and complexity of formulations with an excellent reproducibility not comparable to manual techniques (Cui et al., 2021).

As the process of 3D printing is time-consuming, needing to choose the appropriate printable material, design the platform, and optimize the process, recently came into view the proposition of applying artificial intelligence (AI) to accelerate the 3D printing of pharmaceutical products. With the use of machine learning the optimization parameters can be easily and accurately predicted (Elbadawi et al., 2021). Already in 2020, researchers developed a web-based pharmaceutical software M3DISEEN to accelerate 3D printing by fused deposition modeling (FDM). This predictive tool was designed by training models based on an extensive dataset of 614 drug-loaded formulations to predict key fabrication parameters such as printability, filament characteristics, and FDM processing temperatures (Elbadawi et al., 2021). Not soon after the software expanded when the developers integrated a combined dataset of 1594 formulations of hot melt excretion (HME) or FDM 3D printed formulations to increase the accuracy of prediction (Ong et al., 2022).

Among polymers, we can distinguish some that can be named shape memory materials (SMMs), which can be programmed to have a specific shape, however later triggered by some stimuli like contact with water or temperature and pH change, they come back to their original shape. Based on that the new attractive approach for developing local drug delivery systems is 4D printing combining printing three-dimensional structure with shape change over time, which possibly can also alter the performance and functionality of the platform (Melocchi et al., 2021, 2019). This idea might be especially useful for bone implants, allowing them to change their structure to fit the remaining treating space. Little yet is known about this technology in the pharmaceutical field, where every formulation must strictly comply with quality and safety requirements, however, it is expected that 4D printing and AI will largely expand in the next years, as we still learn about its full potential (Melocchi et al., 2021).

We are aware that there are problems with using antibiotics as there is still growing antibiotic resistance. In research, there are many new approaches to avoid the usage of antibiotics, such as the use of polymers with antibacterial properties, for example, polystyrene (Suga et al., 2022). The other methods include the use of different antimicrobial agents instead of antibiotics like antimicrobial peptides, enzymes, quorum sensing inhibitors, and bacteriophages (Cobb et al., 2020). However, despite all those new approaches, the most common and established in the clinic to treat and prevent bacterial infections are still antibiotics (Johnson and García, 2015).

7. Conclusions

Extensive research is targeting alternative biodegradable polymers to replace non-biodegradable ones such as PMMA in bone infection applications. Examples of the newest strategies were reviewed in this article. These include micro and nanoplatforms as well as macro (scaffolds and hydrogels) and multi-delivery systems. Examples are mostly related to a proof-of-concept phase and the methods of characterization including drug release profiles are heterogeneous. Even though many drug delivery systems exhibit an initial burst release, positive to minimize antimicrobial resistance, researchers aim to more or less complex structures that allow a sustained release over time.

Selected antimicrobials and even their class remains a topic of discussion, although vancomycin is still one of the most researched drugs, probably due to a remarkable efficiency over all staphylococcal strains, both methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* (MRSA). Concerning polymers, the multiplicity of options is noteworthy, albeit PLGA is confirmed as one of the most explored biomaterials, along with gelatin, alginate, or chitosan. As local delivery is well-identified by researchers, biodegradable natural and synthetic polymers are the trend nowadays. Besides, innovative approaches such as 3D-printing allied with AI tools will certainly add advances in the field and allow polymers to establish as an effective alternative to target bone infection.

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CRediT authorship contribution statement

M. Zegre: Conceptualization, Methodology. **E. Poljańska:** Conceptualization, Methodology. **L.A. Caetano:** Supervision. **L. Gonçalves:** Supervision. **A. Bettencourt:** Conceptualization, Supervision.

Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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