

B30: “Are There Any Technological Advances in Creating Smart Antibiotic Carriers in the Fight Against Biofilms?”

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Response/Recommendation: Yes, significant technological advances have been made in smart antibiotic carriers for combating biofilms. Extensive preclinical evidence supports innovations that enhance antibiotic delivery, biofilm penetration, and overall anti-biofilm efficacy. While strong preclinical data support this conclusion, clinical validation remains necessary. Phase I and II trials will be essential to establish safety and efficacy in patients.

Level of Evidence: STRONG

Delegate Vote: Agree: [% vote], Disagree: [%], Abstain: [%]

Rationale: Bacterial biofilms contribute to orthopedic implant failures and chronic musculoskeletal infections¹. These microbial communities, encased in an extracellular polymeric substance (EPS), form protective barriers that hinder antibiotic penetration and immune responses^{2;3}. Biofilm-related infections, including periprosthetic joint infection, osteomyelitis, and fracture-related infections, are challenging to treat and often require surgery combined with prolonged antibiotic therapy¹. Innovative drug delivery systems can enhance antibiotic penetration and achieve localized drug release at bacterial biofilms.

Smart materials, also known as intelligent or environmentally responsive materials, can serve as advanced antibiotic carriers, enhancing antibiotic efficacy against biofilms by leveraging their specialized physicochemical properties. These smart antibiotic carriers improve antibiotic efficacy through various mechanisms, including (1) enhancing antibiotic penetration and retention within bacterial biofilms, (2) facilitating targeted antibiotic accumulation at infection sites, and/or (3) enabling precise, stimulus-responsive antibiotic release for optimal antimicrobial effect. These features are critical considering the unique microenvironment in biofilms and the metabolic adaptation of biofilm-residing bacteria.

Biofilms significantly hinder antibiotic efficacy through multiple defense mechanisms, complicating infection treatment^{4;5}. The EPS matrix serves as a physical barrier, restricting antibiotic penetration⁶. Additionally, dormant bacteria within the biofilm exhibit antibiotic tolerance, while efflux pumps actively expel antimicrobial agents, further diminishing their effectiveness^{7;8}. Furthermore, biofilm-associated bacterial enzymes, including β -lactamases, aminoglycoside-modifying enzymes, and macrolide esterases, degrade antibiotics before they reach their cellular targets, which can render treatments ineffective^{9;10}. Due to these defense mechanisms, bacteria residing in biofilms can be up to ~1000-fold more resistant to antibiotics as compared to their planktonic (free-floating) counterparts^{5;11}.

To answer the question if there are any technological advances in creating smart antibiotic carriers in the fight against biofilms, a systematic literature search was performed in PubMed using the terms ("Antibiotic") AND ("Biofilms"[MeSH] OR "Microbial Biofilms" OR "Bacterial Biofilms" OR "Biofilm-associated infections") AND ("Smart" OR "Smart Materials" OR "Carrier") NOT ("Review"[Publication Type]). Inclusion criteria included (1) studies reporting novel antibiotic carriers with smart features for biofilm-targeting, (2) studies published within the last five years, and (3) studies presenting in vitro and/or in vivo data. Exclusion

criteria included studies unrelated to biofilm-targeting smart antibiotic carriers. Of the 66 retrieved articles, 30 were included for review based on relevance, while 36 were excluded.

Technological Advances in Smart Antibiotic Carriers

- **pH-Responsive Antibiotic Carriers:** These carriers leverage the acidic biofilm microenvironment (pH ~5.5–6.5) to enhance drug efficacy through charge reversal, enhancing antibiotic retention in the biofilm, and/or controlled release of antibiotics¹². Deiss-Yehiely et al. (2023) developed layer-by-layer nanoparticles with pH-triggered charge reversal, achieving 3.2-fold greater bacterial reduction with tobramycin in *Pseudomonas aeruginosa* (*P. aeruginosa*) biofilms¹³. Cui et al. (2022) designed pH-responsive vesicles that switched charge and released >90% apramycin at pH 5.5, improving biofilm penetration and eradication¹⁴. Hu et al. (2024) developed a zwitterionic antibacterial coating for titanium implants that repelled bacteria initially and released gentamicin upon acid-triggered hydrolysis, reducing bacterial adhesion by 90% and effectively eradicating biofilms in rat models¹⁵.
- **Enzyme-Responsive Antibiotic Carriers:** These carriers use bacterial enzymes to trigger targeted drug release, enhancing biofilm disruption. Sun et al. (2019) developed hyaluronidase-responsive hollow carbon nitride spheres capped with hyaluronic acid¹⁶. In methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms, bacterial hyaluronidase degraded hyaluronic acid, triggering the sequential release of quorum sensing inhibitors (QSIs) and ampicillin. QS inhibition weakened biofilm defenses and enhanced the anti-biofilm efficacy of ampicillin¹⁶.
- **Reactive Oxygen Species Responsive Antibiotic Carriers:** These carriers exploit the oxidative stress of infections to trigger antibiotic release, enhance biofilm penetration, and disrupt bacterial defenses, ensuring localized drug delivery. Stavrakis et al. (2016) developed a ROS-responsive poly(ethylene glycol)-poly(propylene sulfide) (PEG-PPS) polymer implant coating that provides a passive and oxidative-triggered antibiotic release¹⁷. In a mouse model of post-arthroplasty infection, PEG-PPS-tigecycline-coated implants completely prevented bacterial colonization, and the biodegradable polymer coating degraded within 14 days, avoiding long-term foreign material retention¹⁷.
- **Light-Responsive Antibiotic Carriers:** These carriers use light to enable targeted drug release, biofilm disruption, and enhanced antibiotic delivery through heat or ROS generation¹⁸. Alenezi et al. (2019) developed a photon-induced drug delivery coating using gold nanorod-incorporated poly(N-isopropylacrylamide) polymer films¹⁹. Near-infrared light irradiation triggered polymer phase transition, releasing vancomycin on demand and inhibiting *Staphylococcus epidermidis* (*S. epidermidis*) biofilms, while non-irradiated samples retained the drug¹⁹.
- **Heat-Responsive Antibiotic Carriers:** These carriers, including hydrogels, nanoparticles, and polymer coatings, enable targeted, on-demand drug release. Hydrogels undergo phase transitions, nanoparticles degrade, and polymer coatings release drugs under induction heating²⁰. Kwan et al. (2023) developed heat-triggered polymer coatings on titanium implants for controlled rifampicin release. The poly(ester amide) coating allowed slow rifampicin release over 100+ days without heat but accelerated release (26% in 1 hour) with induction heating (50°C)²¹. This heat-drug synergy achieved >99.9% bacterial reduction in *Staphylococcus aureus* (*S. aureus*) biofilms while minimizing tissue damage²¹.
- **Ultrasound-Responsive Antibiotic Carriers:** These carriers can enhance drug release and biofilm disruption. Xiu et al. (2023) developed ultrasound-triggered catalytic microbubbles

(MB-Pip) with a Fe₃O₄ nanoparticle shell encapsulating piperacillin. Ultrasound (400–900 kHz) induced rapid piperacillin release (~83.2%), physically disrupted biofilms, and enhanced piperacillin biofilm penetration (6.3-fold increase)²². Fe₃O₄ nanoparticles generated ROS, degrading biofilms and killing bacteria, while also activating macrophages to boost immune clearance. In a mouse lung infection model, MB-Pip with ultrasound significantly reduced biofilm burden²².

- Magnetically Guided Antibiotic Carriers: These carriers use magnetic nanoparticles (MNPs) to enhance drug delivery, biofilm penetration, and bacterial clearance under an external magnetic field. Quan et al. (2019) developed gentamicin-conjugated MNPs, which achieved uniform biofilm distribution after 5 minutes of magnetic-field exposure. This homogeneity was confirmed using confocal laser scanning microscopy and resulted in superior bacterial killing compared to free gentamicin²³. Bhuyan et al. (2020) introduced T-Budbots, tea bud-derived micromotors coated with MNPs to mechanically disrupt biofilms and release ciprofloxacin in acidic environments²⁴.
- Antibiotic carriers that Enhance Biofilm Penetration: Lee et al. (2022) demonstrated that vancomycin-loaded lipid-coated hybrid nanoparticles (LCHNPs) with a poly(lactic-co-glycolic acid) (PLGA) core and cationic dioleoyl-3-trimethylammonium propane (DOTAP) shell enhance antibiotic penetration of *S. aureus* biofilms via electrostatic interactions, achieving 99.99% bacterial clearance²⁵. Ferreira et al. (2021) showed that negatively charged rifabutin-loaded liposomes exhibited enhanced biofilm penetration and bacterial clearance in *S. epidermidis* biofilms, significantly outperforming free antibiotics²⁶. For osteomyelitis treatment, Kadry et al. (2004) encapsulated ciprofloxacin and vancomycin in liposomal formulations, achieving 100% bone sterilization in a rabbit model of chronic *S. aureus* osteomyelitis with intravenous (IV) liposomal therapy. In contrast, IV vancomycin and IV ciprofloxacin combined failed to achieve complete bone sterilization²⁷.
- Antibiotic Carriers that Bind to Tissue with Biofilms: Affinity-based antibiotic drug carriers enhance targeted drug delivery to specific tissues, ensuring localized antibiotic release. Ren et al. (2023) developed hydroxybisphosphonate-conjugated sitafloxacin (HBCS) for bone-targeted antibiotic delivery in MRSA osteomyelitis²⁸. In a murine femoral plate infection model, IV HBCS + vancomycin significantly reduced bacterial burden, prevented catastrophic fractures, and improved bone healing and implant osseointegration²⁸. In a transtibial implant model with MRSA infection, IV HBCS outperformed both IV vancomycin and IV sitafloxacin monotherapy, demonstrating superior biofilm reduction and bone infection targeting²⁸.
- Antibiotic Carriers that Bind to Biofilms: Biofilm-binding antibiotic carriers, such as aptamer-functionalized liposomes, enhance localized drug accumulation, ensuring higher antibiotic concentrations at biofilm sites. Ommen et al. (2022) developed aptamer-functionalized liposomes targeting *S. aureus* biofilms in vitro²⁹. Aptamer SA31 was identified as a high-affinity binder to *S. aureus* biofilm, facilitating deep penetration and liposome retention. Confocal microscopy confirmed widespread liposome distribution throughout the biofilm. When loaded with vancomycin and rifampicin, the aptamer-liposomes achieved enhanced biofilm eradication in vitro, significantly outperforming non-targeted liposomes²⁹.

Smart Antibiotic Carriers: Road to Clinical Application: Despite preclinical success, smart antibiotic carriers for bacterial biofilm face biocompatibility, regulatory, and scalability challenges, delaying clinical translation³⁰. These systems require rigorous validation of controlled drug release, long-term safety, and manufacturability while overcoming

pharmacokinetic hurdles such as immune clearance and toxicity³⁰. Liposomes stand out as clinically validated antibiotic carriers. Arikayce® (liposomal amikacin) became the first FDA-approved liposomal antibiotic in 2018 for non-tuberculous mycobacterial lung infections and is being tested in patients with chronic *P. aeruginosa* infections with cystic fibrosis³¹. However, smart antibiotic carriers will require Phase I and II trials to establish safety and efficacy, particularly for orthopedic infections. Furthermore, clinical investigations are needed to confirm the role of these smart carriers specifically for anti-biofilm efficacy. Developing a gold-standard, minimally invasive biomarker for biofilm burden in clinical settings, such as advanced imaging or molecular diagnostics, would enhance the longitudinal evaluation of biofilm-targeting therapeutic efficacy^{32; 33}.

Conclusion: Technological advances have been realized in the development of smart antibiotic carriers aimed at combating bacterial biofilms, a major cause of orthopedic implant failures and persistent musculoskeletal infections. Preclinical research demonstrates that these innovative carriers enhance antibiotic penetration, targeted delivery, and biofilm eradication. These advancements represent a meaningful step forward, providing strategies to overcome the robust defensive mechanisms employed by biofilms. However, while strong preclinical evidence underscores the potential of these smart carriers, clinical validation through rigorous Phase I and II trials remains imperative to establish their safety, efficacy, and clinical utility.

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