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Perspective: Nanoparticles for oral biofilm treatments

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Abstract

Pathogenic oral biofilms are universal, chronic, and costly. Despite advances in understanding the mechanisms of biofilm formation and persistence, novel and effective treatment options remain scarce. Nanoparticle-mediated eradication of the biofilm matrix and resident bacteria holds great potential. Particularly, nanoparticles that target specific microbial and biofilm features utilizing non-toxic materials are well-suited for clinical translation. However, much work remains to characterize the local and systemic effects of therapeutic agents topically applied to chronic biofilms, such as those that cause dental caries. This perspective summarizes the pathogenesis of oral biofilms, describes current and future nanoparticle-mediated treatment approaches, and highlights outstanding questions that are paramount to answer to effectively target and treat oral biofilms.

Introduction

Nanoparticles are a highly promising treatment modality for biofilms. Many nanoparticle strategies have aimed to inhibit biofilms within the oral cavity. Oral biofilms also serve as excellent models for other healthcare-associated and industrial biofilms that may benefit from nanoparticle approaches. Nanoparticles can be directly bactericidal or designed to enhance drug aqueous solubility, and through precise adjustments of chemical compositions, size, surface charge, and other properties, can provide unparalleled flexibility to carry, retain, and release drugs exactly when and where needed most. Additionally, nanoparticle drug delivery systems can both protect conventional drugs from pH and/or enzymatic degradation

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in the harsh biofilm niche, while also exploiting these unique microenvironments for stimuli-responsive drug release. While outstanding progress has been made investigating nanoparticles as anti-biofilm treatments, comprehensive evaluation of chronic exposure limits, especially for oral biofilm treatments, must be investigated to ensure safe and biocompatible delivery approaches are pursued. Alternative strategies that leverage biomimetics may also be advantageous for the prevention of chronic infections, such as caries.

This perspective provides a succinct overview of nanoparticle treatment strategies for oral biofilms with a focus on Naha et al., who reports on the robust anti-oral biofilm efficacy of iron oxide-based nanoparticles in this issue. Furthermore, we will offer perspectives on critical areas in this field that require major focus for realization of clinical translation of these therapeutic approaches. For recent, more comprehensive overviews of nanoparticle strategies to treat biofilms, the following reviews are suggested for the interested reader:[1–10].

Significance of Biofilms

The majority of persistent infectious diseases in humans are caused by virulent biofilms, including those within the mouth[11–12]. The annual cost of treatment of oral biofilm-related infectious diseases, such as dental caries, exceeds $81 billion in the US[12–13], motivating the development of new, more effective treatment modalities. Due to its ease of access and high bacterial species diversity, the oral cavity is an opportune setting to study new approaches for biofilm treatments, which can then be translated to other biofilm-associated conditions affecting human health or for use in industrial settings. The assembly of tooth-decay causing (cariogenic) biofilms is a prime example of how bacteria accumulate on surfaces and form structured communities within an extracellular matrix comprised of polymeric substances such as exopolysaccharide (EPS)[11,14]. Advantageously, oral biofilms can be treated topically, obviating systemic delivery hurdles of other healthcare-associated biofilms. Similar to other biofilms, the EPS-rich matrix of cariogenic biofilms creates spatial and microenvironmental heterogeneities, which modulate growth and provide protection for pathogens against intrinsic and applied antimicrobials[11,14]. Within the oral microbiome, *Streptococcus mutans* (*S. mutans*) adheres to the tooth pellicle then rapidly orchestrates the formation of cariogenic biofilms on teeth in the presence of dietary sucrose (Figure 1). *S. mutans*-released exoenzymes (e.g., glucosyltransferases) produce glucans-rich EPS from sucrose, thus promoting local colonization and accumulation of microbes as well as formation of the protective multifunctional scaffold and diffusion-limiting matrix[15–17]. In parallel, sugars are fermented by bacteria within this matrix, creating a highly acidic microenvironments (pH 4.5–5.5)[18–19]. The low pH niches induce further EPS synthesis while cariogenic (acid-tolerant and acidogenic) flora prosper[17]. Consequently, local acidity ensures continuous biofilm build up and demineralization of adjacent tooth enamel, leading to the onset of dental caries. The continually evolving knowledge of this intricate pathogenic process provides new opportunities for unique and effective treatment strategies (Figure 1).

Current oral biofilm treatment options

Preventing or treating pathogenic oral biofilms is challenging. Topically applied drugs suffer from rapid salivary clearance, poor penetration of the EPS matrix, and a lack of substantivity (i.e., retention on tooth surfaces) to address continual biofilm formation. The presence of EPS with its altered microenvironment reduces drug access and triggers bacterial tolerance to antibiotics[10–11,14], making bacteria difficult to treat without disturbing normal flora. Furthermore, the acidic pH indicative of oral biofilms reduces efficacy of many antibiotics[20–21]. Importantly, the ubiquitous and chronic nature of oral biofilms requires that any therapeutic be tolerated for continual use over an extended time period with minimal toxicity and off-target effects.

Current agents for controlling oral biofilms are restricted to broad-spectrum antimicrobial drugs, such as chlorhexidine, which is limited by adverse effects (calculus formation and tooth staining) and therefore, is not suitable for daily, long-term use. Alternative anti-biofilm agents include naturally occurring drugs such as terpenoids, essential oils, and flavonoids that disrupt assembly of cariogenic biofilms and/or reduce EPS synthesis[22–28]. These drugs impact *S. mutans* viability, acid production, acid tolerance, and EPS synthesis at acidic pH[24,29]. However, their anti-biofilm efficacy is still hampered by poor drug solubility, EPS diffusion, and substantivity[22–24].

Nanoparticle-based oral biofilm treatments

Nanoparticles hold significant promise for addressing the challenges of oral biofilm drug delivery. The chemical flexibility and relative ease of nanoparticle preparation allow for the development of unique biofilm treatments[30]. Nanoparticles can be directly bactericidal or designed to enhance drug aqueous solubility and transport into bacterial cells. Anti-biofilm nanoparticles can be developed from metals or metal oxides, synthetic or natural polymers, or hybrids therein. Furthermore, through precise adjustments of chemical compositions, size, surface charge and other properties, nanoparticles provide unparalleled flexibility to ensure robust biofilm targeting and retention through biofilm matrix interactions, thereby enhancing substantivity and anti-biofilm efficacy. Nanoparticles' high surface area to volume ratios enable robust drug or drug combination loading that may result in synergistic anti-biofilm efficacy. Furthermore, the resulting highly complex antimicrobial mechanism of action may overcome common bacterial resistance mechanisms, including permeability regulation, multidrug efflux pumps, and target binding affinity site mutations[5,30–31]. Data suggest nanoparticles can also lower the potential for bacterial resistance and protect conventional drugs from pH and/or enzymatic degradation in the harsh biofilm microenvironments[5,30]. Critically, nanoparticle design can be tuned to become activated in response to unique biofilm pathologic microenvironmental triggers, such as pH or hypoxia.

Nanoparticle design properties for anti-biofilm treatments

Chemistry and material architecture (solid nanoparticles, such as silica or metals, liposomes, micelles, dendrimers, etc.) define overall nanoparticle properties including size, shape, surface functionalization, and core properties that impact anti-biofilm efficacy, as recently

reviewed[5,8] and depicted in Figure 2. Nanoparticle size impacts diffusion into the EPS biofilm matrix after topical delivery, with diameters up to 130 nm showing robust biofilm penetration[8,32]. The effect of surface charge on biofilm penetration shows that positively charged nanoparticles possess excellent biofilm penetration versus anionic or uncharged counterparts, potentially due to a catch-and-release phenomenon within the anionic EPS matrix[33]. Additionally, hydrophobic cationic nanoparticles are taken up by bacteria while hydrophilic cationic particles remain bound to the EPS[33]. Nanoparticle core properties (e.g., solid or hydrophobic/hydrophilic depots) can enable loading of a variety of anti-biofilm drugs or sensitization agents for delivery. For example, cationic and hydrophobic core-shell nanoparticles capable of loading antibacterial oils showed robust anti-biofilm efficacy and selective cytotoxicity to bacteria versus fibroblast cells[25]. Thus, size and charge as well as nanoparticle core properties can be exploited to ensure appropriate nanoparticle localization to maximize anti-oral biofilm efficacy. The interplay between nanoparticle size and shape can also be harnessed to increase the efficacy of biofilm targeting nanoparticles[34], though it has yet to be established as a critical design parameter for oral biofilm treatments.

Selectivity of therapeutics is critical when designing nanoparticle drug delivery systems, especially for the complex microenvironment of the oral cavity. In particular, *S. mutans* biofilm pH has been exploited to stimulate selective anti-biofilm efficacy using nanoparticles that exhibit inherent pH-responsive anti-biofilm activities or release anti-biofilm drugs via pH changes[26–28,35]. pH-responsive functionalities include imidazoles, amines, amides, amino acids or acid-sensitive degradable linkages, such as esters, ketals, acetals, and anhydrides. For example, we have pioneered the use of multi-surface binding and pH-responsive nanoparticles for anti-biofilm applications[26–28]. These polymeric diblock co-polymer nanoparticles have high affinity to tooth, pellicle, and glucose-coated biofilm surfaces due to tertiary cationic surface residues and may distribute uniformly throughout the biofilm matrix when used with saturated drug solutions[27]. Drug is retained within nanoparticles bound to biofilms until the pH becomes acidic. Then, the nanoparticles exhibit drug release via protonation-mediated destabilization, resulting in substantial enhancement of drug efficacy (≥ 3 log CFU) *in situ* and *in vivo*[26]. Importantly, due to flexibility and ease of preparation, polymeric nanoparticles can entrap other topical anti-biofilm drugs that otherwise suffer similar solubility and retention issues[26–28,36–38].

Catalytic nanoparticles that target oral biofilms

In the publication by Naha et al., the acidic pH of the biofilm matrix was exploited to activate catalytic iron oxide nanoparticles, termed CAT-NP, mediating anti-biofilm activity[39]. Metal and metal oxide-based nanoparticles have longstanding use for their native antibacterial properties, with copper, titanium, gold, silver, and iron oxide-based nanoparticles having shown bactericidal effects[40–42]. Metal or metal-oxide-based nanoparticles exert antibacterial effects in a variety of ways. Mechanisms can include direct interaction with the bacterial cell wall, inhibition of biofilm formation by affecting glucans production or quorum sensing, recruiting innate and/or adaptive host immune cells, generation of reactive oxygen species (ROS), or via deleterious interactions with bacterial DNA and/or proteins[41–48]. All of these mechanisms align with excellent bactericidal

activity, even against persister cells that are dormant and thereby resistant to traditional antibiotics[49].

Earlier studies by Gao et al. demonstrated initial anti-biofilm efficacy of CAT-NP[50]. When treated in combination with hydrogen peroxide, these nanoparticles produced reactive oxygen species (Figure 3). ROS-mediated oxidative stress typically leads to oxidation of biomolecules and cell components resulting in severe cellular damage[1,51–52]. In this case, ROS directly contributed to biofilm exopolysaccharide matrix degradation and killing of *S. mutans*. The iron oxide particles, in particular, exhibited robust peroxidase-like activity only at an acidic pH characteristic of those produced by *S. mutans*. Importantly, and owing to the pH-responsive behavior of the nanoparticles, which limited free radical production at physiological conditions, normal tissues were protected from off-target effects. Though topical treatment once daily of a rat biofilm model was effective in reducing tooth decay, the iron oxide particles suffered from poor colloidal stability and indiscriminate tissue binding, limiting overall clinical translation[50]. Thus, dextran coatings were developed for CAT-NP, referred to as Dex-NZM in this issue, that maintained underlying iron oxide catalytic behaviors and enhanced the selectivity of nanoparticle binding to biofilm versus gingival tissue. Similar to bare iron oxide particles, treatments *in vivo* reduced the occurrence and severity of caries[39].

Naha et al. developed their anti-biofilm treatments strategy using a platform with long-standing clinical use, suggesting excellent systemic biocompatibility[39]. Feridex is a systemically delivered iron oxide-based magnetic resonance imaging (MRI) contrast agent which was approved by the Food and Drug Administration (FDA) more than 20 years ago. Oral mucosa is protected, as the iron oxide particles exhibit little enzymatic activity at physiological pH. Additionally, the native microbiota composition and diversity was largely intact post-treatment, indicating that even in close proximity, ROS-mediated damage was limited to the cariogenic *S. mutans*. No systemic toxicity-related adverse side effects were observed in this study (e.g., no rat weight reduction), when the iron oxide/H_2O_2 treatment was applied in a once daily regimen for 21 days.

The iron oxide particle-based system has many inherent advantages over other nanoparticle-based systems. It is a drug-free approach, thus overcoming limitations of drug dosing, requirement of drug loading compatibilities, and risks associated with drug resistance. However, there are still outstanding questions regarding the clinical translation of the approach including aesthetics associated with black tooth staining from nanoparticles during treatment and potential off-target effects within the oral cavity and systemically for the CAP-NP/Dex-NZM system and other nanoparticle approaches. To routinely manage oral biofilms, which are pervasive and have genetic and dietary underpinnings, chronic treatment extending for months or years will likely be necessary. Thus, the local and systemic effects of chronic exposure, whereby ingestion is the likely path, remain critical to characterize.

Perspectives and Future Outlook

Ensuring safety of nanoparticle anti-biofilm treatments

Non-specific off-target effects of oral anti-biofilm treatments can occur both immediately to local tissues and after clearance of nanoparticles. The predominant clearance route of topical treatments in the mouth is via ingestion, which may result in systemic circulation and tissue distribution. Therefore, it is critical to evaluate potential off-target biodistribution and effects prior to translation of new anti-biofilm nanotechnologies. This point is especially true for anti-oral biofilm therapies. Caries affects all ages and treatment is a persistent challenge. Thus, chronic off-target accumulation of nanoparticles may result in long-lasting effects. Metal or metal oxide-based nanoparticles can be absorbed within the gastrointestinal tract. Though bioavailability may be low (e.g., <5% of ingested dose), off-target systemic effects of nanoparticles have been reported[3]. Metal nanoparticles with larger doses have resulted in weight loss and increases in oxidative stress in blood and liver, brain, kidney, and spleen[53] with long-term residence in brain[54]. Additionally, tissue fibrosis[55–56] and DNA damage have been reported[57]. Though it is unclear if iron oxide particles will have similar toxicity profiles, their likely transport through the acidic stomach milieu, which will itself result in robust radical production, motivates careful evaluation of systemic effects of this powerful anti-oral biofilm treatment strategy as well as other nanoparticle-based approaches.

Alternative approaches should be considered that abrogate systemic exposure. For example, nanoparticle systems that dissociate into non-toxic and easily cleared components, such as those formed via self-assembly[25–28] or using degradable biomaterials, should be considered. Highly ubiquitous, degradable poly(lactide-co-glycolide)-based nanoparticles with cationic functionalities have been exploited to enhance the bactericidal activity of vancomycin[58]. Additionally, polymers have been developed that release nitric oxide free radicals that may enable similar proton-catalyzed anti-biofilm effects seen with CAT-NPs[59–63]. Such NO-releasing systems can be combined with degradable polymers from polyesters[64] or polyphosphazenes, which are designed to degrade as a result of nitric oxide release[65], to prevent chronic nanoparticle exposure.

Potential to augment efficacy of nanoparticle delivery

Ensuring the optimal efficacy of developed nanoparticle strategies is paramount to limit potential chronic effects due to repeated treatments. While Naha et al. showed significant anti-biofilm efficacy with minimal off-target effects in short duration treatments, two approaches should be considered to further improve this and related strategies. First, introduction of targeting groups may increase selectivity towards virulent versus commensal bacteria. For example, immunoliposomes conjugated with anti-*Streptococcus oralis* strongly adsorb to *S. oralis* biofilms while showing decreased affinity to other oral bacteria biofilms[66]. Moreover, these immunoliposomes successfully encapsulated bactericidal agents and inhibited *S. oralis* growth more than that of other bacteria tested[67]. For *S. mutans*, lectins, including concanavalin-A (Con A) and wheat germ agglutinin (WGA), have been used[68]. A potential drawback to matrix-targeting therapies is that enhanced binding to superficial regions of the biofilm may also retard biofilm penetration, resulting in poor distribution to interior biofilm regions. As the deeper regions of biofilms harbor resistant cell

types (e.g., persisters), this hurdle is significant[69]. Alternatively, co-delivery of agents that synergistically disrupt biofilms or activate typically dormant and highly resistant persister cells together with bactericidal agents may further increase nanoparticle therapeutic efficacy. Persister cells can be activated by introducing sugar and glycolysis intermediates, such as mannitol, glucose, fructose, and pyruvate[70], DNA crosslinkers (e.g., cisplatin[71]), or *cis*-2-decenoic acid, which results in upregulation of protein synthesis[72].

While improvements to nanoparticle-based treatment strategies will augment current anti-biofilm efficacy, it is unclear if the cost-benefit ratio will overcome standard treatment regimens of mechanical clearance (e.g., tooth brushing), antiseptic use (e.g., essential oils, cetylpyridinium chloride, chlorhexidine), and/or topical fluoride applications (e.g., toothpaste, varnish). Furthermore, the paucity of comparisons in the literature to these gold standard treatments during in vivo testing is striking. Regardless, nanoparticle-based anti-biofilm designs developed for treating dental caries will undoubtedly translate to improved treatment strategies for other healthcare-associated biofilms, such as those known to cause orthopaedic and catheter-associated infections.

Alternative biomimetic approaches

The oral microbiome is highly regulated and balanced to ensure homeostasis. The key host factor that modulates the oral microbiome is saliva, which contains a variety of mucin molecules. In particular, the mucin MUC5B plays a critical role in preventing *S. mutans* surface attachment and biofilm formation by maintaining planktonic growth[73]. Importantly MUC5B protects by reducing microbial virulence through disrupted quorum sensing rather than binding directly to the microbes[73–75]. These findings suggest that MUC5B biomimetics may enable balancing of the oral microbiome thereby preventing *S. mutans* virulence, obviating the need for chronic nanoparticle-based treatments. However, mucin structures are complex and poorly-understood, presenting challenges in the development of engineered mimetics. Alternatively, modulating salivary gland mucous acinar cell synthesis of MUC5B may also be a promising strategy for caries prevention.

Conclusions

Altogether, nanoparticle strategies have promise for anti-oral biofilm treatments, but they have yet to overcome translational hurdles for successful clinical adoption. Naha et al. present compelling data in this issue to support further translational efforts in this field. However, off-target, chronic effects due to routine therapeutic treatment regimens, opportunities for improved efficacy, and novel biomimetic strategies should be carefully considered to ensure continued forward progress for oral and other healthcare-associated biofilm nanoparticle therapeutic technologies.

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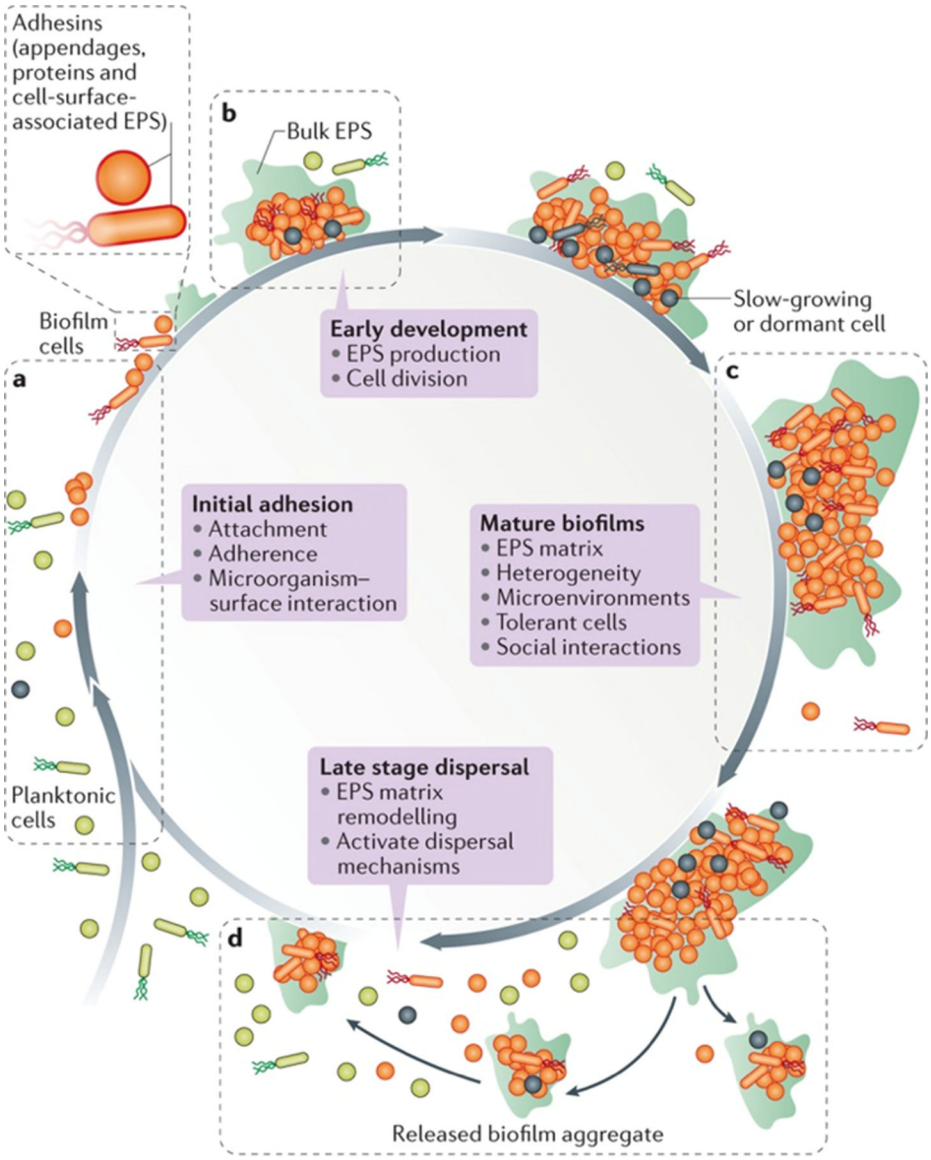

Figure 1.

Bacterial biofilm developmental stages highlighting various opportunities for therapeutic interventions (reproduced with permission from[6]). EPS-exopolysaccharide.

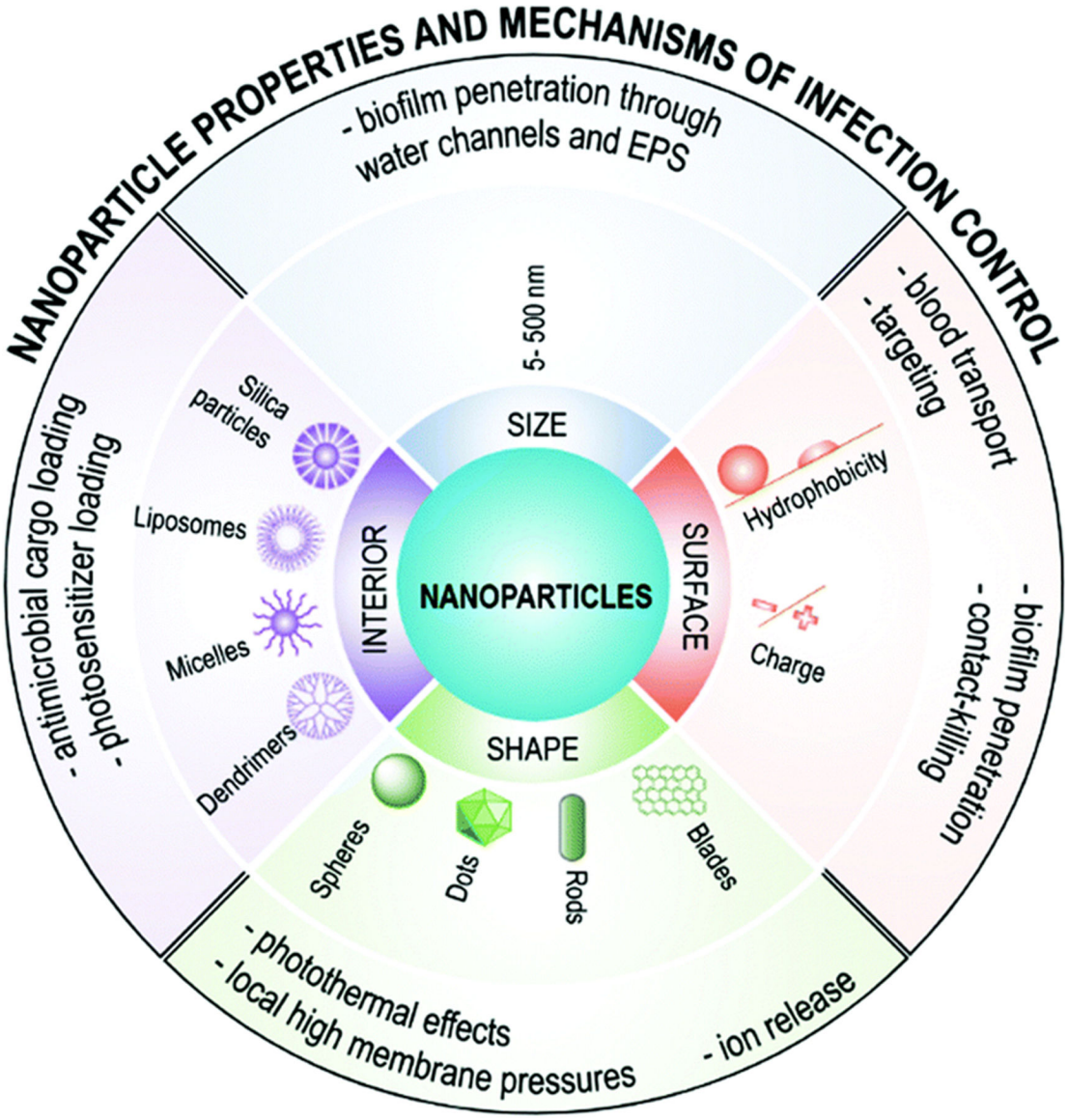

Figure 2.

Nanoparticle properties are important for their use in anti-biofilm strategies (reproduced with permission from[8])

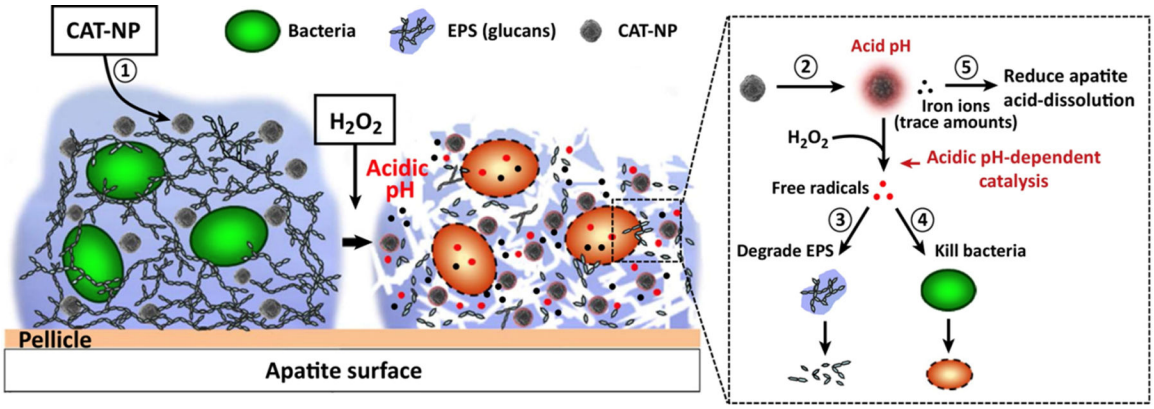

Figure 3.

Catalytic nanoparticles (CAT-NP), comprised of iron oxide nanoparticles coated with dextran, known in this issue as Dex-NZM, result in biofilm disruption via local pH-dependent free radical production, resulting in degraded EPS and bacteria cell killing (reproduced with permission from[4]).