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Lipid and polymer nanoparticles for drug delivery to bacterial biofilms

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ABSTRACT

Biofilms are matrix-enclosed communities of bacteria that show increased antibiotic resistance and the capability to evade the immune system. They can cause recalcitrant infections which cannot be cured with classical antibiotic therapy. Drug delivery by lipid or polymer nanoparticles is considered a promising strategy for overcoming biofilm resistance. These particles are able to improve the delivery of antibiotics to the bacterial cells, thereby increasing the efficacy of the treatment. In this review we give an overview of the types of polymer and lipid nanoparticles that have been developed for this purpose. The antimicrobial activity of nanoparticle encapsulated antibiotics compared to the activity of the free antibiotic is discussed in detail. In addition, targeting and triggered drug release strategies to further improve the antimicrobial activity are reviewed. Finally, ample attention is given to advanced microscopy methods that shed light on the behavior of nanoparticles inside biofilms, allowing further optimization of the nanoformulations. Lipid and polymer nanoparticles were found to increase the antimicrobial efficacy in many cases. Strategies such as the use of fusogenic liposomes, targeting of the nanoparticles and triggered release of the antimicrobial agent ensured the delivery of the antimicrobial agent in close proximity of the bacterial cells, maximizing the exposure of the biofilm to the antimicrobial agent. The majority of the discussed papers still present data on the *in vitro* anti-biofilm activity of nanoformulations, indicating that there is an urgent need for more *in vivo* studies in this field.

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1. Introduction

In the late 1970's, the biofilm mode of growth was recognized as the predominant form in which bacteria are present in many different environments [1]. Although seemingly trivial at that time, this discovery has had a profound impact on our understanding of the pathogenesis and treatment of bacterial infections [2–5]. Today, treating biofilm infections is one of the major challenges the medical community is facing and is expected to remain so for many years to come.

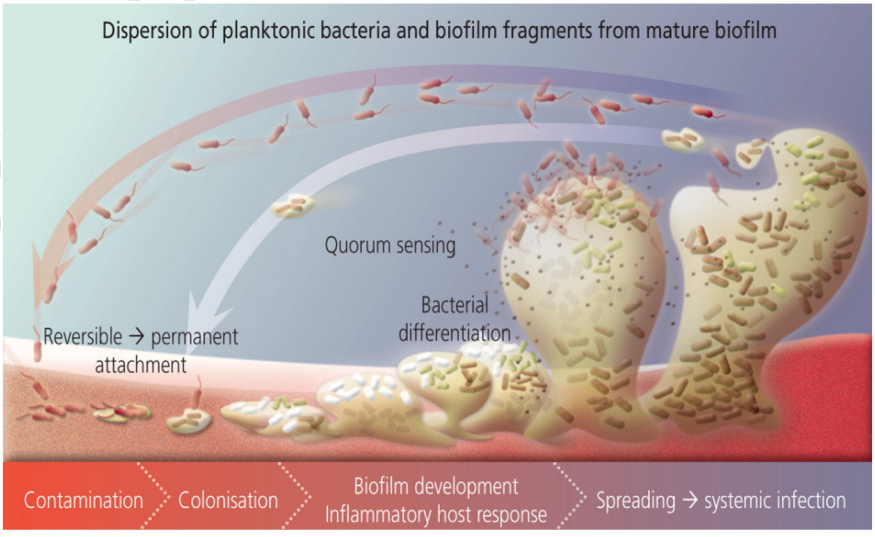
By definition, biofilms are matrix-enclosed, complex and differentiated communities of bacteria that are adherent to inert or biological surfaces [6]. Upon adhesion, the bacterial cells start producing extracellular matrix and group together in densely packed bacterial clusters. From the mature biofilm, individual cells or biofilm fragments are released and can colonize new surfaces (Fig. 1) [7]. It was observed that biofilm associated bacteria, termed sessile cells, display a profoundly different phenotype compared to their free swimming, planktonic counterparts [7]. The biofilm bacteria are able to communicate and alter each other's phenotype by a process called quorum sensing [8–10]. This allows the biofilm to respond cooperatively to environmental changes and threats. Thus, the biofilm mode of growth is an adaptation which allows the bacteria to survive and thrive in otherwise hostile environments.

Besides their presence in natural and industrial settings, biofilms can also form in the human body, causing recalcitrant infections [12]. Parsek and Singh have proposed a set of criteria to determine if biofilm formation is involved in an infection [5]. Firstly, the bacteria must be surface associated. Secondly, the bacteria must be present in clusters or microcolonies embedded in an extracellular matrix. Thirdly, the infection should be confined to a particular location and finally, the infection cannot be eradicated by using classic antibiotic therapy. The reason why these infections are hard to eradicate is twofold. On the one hand, the biofilm bacteria display increased antimicrobial resistance and tolerance compared to planktonic bacteria [13–15]. On the other hand, the biofilm mode of growth enables the bacteria to evade the immune system of the host [16,17]. As a consequence, biofilms can cause devastating chronic infections and are associated with an increased morbidity and mortality. It is now estimated that over 60% of bacterial infections in humans involve biofilm formation [17]. As a consequence, the economic burden due to biofilm infections is substantial. For example, catheter related sepsis costs an additional $ 28,000 per case. Nosocomial urinary tract infections, which are a subset of these catheter related infections, account for approximately 900,000 admissions annually in the US [18].

The biggest challenge in treating biofilm infections is overcoming the resistance and tolerance against antimicrobial agents. Several mechanisms of antimicrobial resistance and tolerance have been suggested such as limited diffusion of antimicrobial agents in the biofilm matrix, deactivation of the antimicrobial agent in the outer layers of the biofilm *via* binding to matrix components or enzymatic modification and the occurrence of niches in the biofilm with less sensitive cells, including starved cells and persister cells [15,17,19–21]. There is an urgent need for innovative strategies that are able to overcome these mechanisms of resistance. One possible approach which is gaining considerable interest is the use of nanoparticles for antimicrobial drug delivery.

The number of publications involving the use of nanomedicines in the prevention of biofilm formation and the eradication of existing biofilms has been growing steadily over the past decade, with special attention going to lipid and polymer nanoparticles. The attractive properties of these particles are their biocompatibility, the versatility of materials and surface modifications, the possibility for targeting and triggered release, their ability to incorporate lipophilic as well as hydrophilic drugs and a reduction of unwanted side effects of the drug [22,23]. In the context of treating biofilm infections, the use of nanoparticles to encapsulate antimicrobial agents might have several benefits. The nanoparticles can protect the antimicrobial agent from binding to matrix material and enzymatic inactivation. Lipid nanoparticles can fuse with the bacterial outer membrane, delivering the antimicrobial agent directly to the bacterial cells. Furthermore, by targeting of the nanoparticles to the biofilm, a high dose of antimicrobial agents can be delivered in the direct proximity of the bacterial cells, thereby maximizing therapeutic benefit while reducing unwanted side effects.

In this review, an overview of lipid and polymer nanoparticles for drug delivery to bacterial biofilms is provided. First, the delivery of antimicrobial agents to bacterial biofilms is discussed. A distinction is made



Q6 **Fig. 1.** Biofilm formation and dispersal. Reprinted with permission from [11].

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