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Antibiofilm Applications of Nanotechnology

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Biofilms are high degree organization communities where microorganisms form a structured, coordinated and functional thin layer [1]. The biofilm production is a successful strategy for microbial survival and infection establishment. The host defense mechanisms and the antimicrobial responses are very impaired against the microorganisms inhabiting the biofilm [2]. This resistance may be related to the antimicrobial penetration difficulty by the cell wall composed (extracellular polymeric substances such as EPS). Such factor enables unlimited dissemination and expression of resistance genes with phenotypic changes of microorganisms in the biofilm [1]. In addition, microorganisms in the biofilm are mostly in their stationary phase, hindering the action of beta- lactam drugs.

Biofilms are responsible for up to 80% of microbial infections and cause about 100,000 deaths per year in the United States [3]. The treatment of these infections is conducted with high doses of antibiotics and by long-term therapy. In this context the toxicity and drug interactions in the treatment is often ineffective. Faced with this resistance to conventional antibiotics there is a great need to new antimicrobial drugs develop or new pharmaceutical forms and therefore new methods to reduce bacterial activity and combat associated infections [4].

Aiming to eradicate the biofilm, several alternatives including the prevention of microbial adhesion surfaces, complementary approaches (electrical therapy, ultrasound, photodynamic therapy), and nanomaterials (liposomes, nanospheres, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, polymeric micelles) are used [5]. Considering this context, nanotechnology is a promising strategy that has been studied to overcome the biofilm. Since nanoparticles have completely different mechanisms of antibacterial activity than traditional antimicrobials, offering an attractive option. Research has shown that certain nanostructures controlled and sustained release, improving stability and reducing drugs toxicity [6].

Recently, Haghighi et al. [7] produced TiO_2 and EDTA nanoparticles and assessed their effect on biofilms formed by several strains of *Candida albicans*. The results show that the TiO_2 nanoparticles can be considered as a new alternative for prevention of fungal biofilm therefore prevent adhesion of microorganisms. The authors propose that TiO_2 can be used to coat medical devices.

Biodegradable hydrogels have also been successfully used as antimicrobial agents. Lee et al. [8] produced Vitamin E incorporated with cationic functionalized polycarbonates made from nanostructures such as 'ABA type triblock copolymer (MTC-VE) 1.25- PEG (20K) - (MTCVE) 1.25. As a result, the authors showed strong antimicrobial activity against both Gram positive and negative, and antifungal activity (more than 99.9% efficiency). Furthermore, these hydrogels are able to eradicate the biomass and significantly reduce the viability of *Staphylococcus aureus*, *Escherichia coli,* and *C. albicans* biofilms. Polycarbonates in combination with antifungal agents (inserted in hydrogel) provide a high level of activity, showing a synergistic antifungal effect. The authors suggest that these polycarbonate hydrogels nanoparticles can be used to remove both planktonic and sessile (biofilm) forms, representing a promising approach in the prevention and treatment of biofilm infections.

The catheter-related urinary tract infections are also quite common. The arrangement in biofilms decreases the susceptibility of microorganisms to treatment, resulting in antimicrobial resistance. He et al. [9], used nanotechnology associated with a new antimicrobial spray (silicon compound and organic quaternary ammonium salt). The authors produced nanoparticles with different electric charge surfaces, which through physical attraction, bind to microorganisms, eliminating them. These nanoparticles were effective against bacteria, fungi, and viruses. In biofilms of *E. coli*, these nanoparticles were extremely effective in both prevention and eradicating biofilms.

Hetrick et al. [10] developed in 2009 silica nanoparticles containing nitric oxide. There was action against biofilms of *S. aureus*, *S. epidermidis*, *Pseudomonas aeruginosa*, *E. coli,* and *C. albicans*. Besides the elimination of biofilm, the addition of nanoparticles in catheters prevented colonization of the surface of these medical supplies. Similar results were obtained *in vitro* by Rai et al. [11]. In this study, the authors used silver nanoparticles in the inhibition of biofilm of *S. aureus*, *Enterococcus* sp., *E. coli*, *P. aeruginosa* and *C. albicans*.

Some parameters are decisive for the selection of the ideal characteristics which should be taken when selecting a nanoparticle [12]:

1. Particle diameter: with the smaller diameter, the greater antimicrobial effect. The nanoparticles seem to be able to penetrate the bacterial cell membrane causing interference and loss of cell viability;

2. Charge surfaces: the more positive Zeta potential, the greater attraction surfaces of the negative bacterial cell wall and thus more easily occur the membrane disruption, resulting in a high antimicrobial effect.

The chemistry surface including Nano scale topography is another interesting point. This aspect has been extensively studied in relation to eukaryotic cells, but little is understood regarding bacterial cells. The small number of studies to date shows a very promising path. The production of surfaces with nano-roughness aims to prevent the adherence of microorganisms and consequently biofilm formation. Although the potential clinical use of nanoparticles is fantastic, it is important to study the surface characteristics which could be alternative strategies for the control of biofilm formation [13]. In a study endotracheal tubes with nano-roughness were developed [14].

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The modification of the material of the tubes showed a significant decrease in the dynamic formation of biofilms, showing the potential use of nanotechnology in the field of infectious processes.

Faced with the increasing rates of resistant microorganisms to traditional antimicrobials and the ability to form biofilms, it is vitally important to develop alternative therapies. Recent publications presented here, clearly show the great potential of nanotechnology to overcome such resistance through alternatives for both the prevention of biofilm formation as well as for its treatment.

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