

## Review Article

# Advances in Nanotechnology as an Alternative against Superbugs

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## Abstract

Since 1940 when the first resistant strain was described, antibiotic resistance has increased alarmingly to the point where we are again on the cusp of an era without antibiotics. In this review we will explore developments in nanoparticle technologies and how they bring new hope to the fight against infections.

Nanocoating and shuttle systems have shown great promise *in vitro* and animal models, amplifying drug efficiency, preventing nosocomial infections and ultimately leading to a reduction in health care costs. Further studies and clinical trials are required for more conclusive results, but initial seem to suggest that novel nanoparticle solutions could be an integral part of keeping infection rates under control.

## Keywords

- Nanotechnology
- Shuttle delivery system
- Coating
- Medical devices
- Drug resistance

## ABBREVIATIONS

EDTA: Ethylene Diamine Tetra Acetic acid; MIC: Minimal Inhibitory Concentration

## INTRODUCTION

The era of antibiotics started in 1940 with the introduction of penicillin [1]. The infections that used to cause millions of deaths started to seem a minor problem that could be fought with this new tool. But abuse and lack of control of antibiotic usage, together with the ability of bacteria to rapidly adapt and evolve is threatening humanity with the possibility of re-entering an era of non-treatable infections: the era of resistant superbugs. Soon, many infections that would once be easily treated will no longer be curable with current antimicrobials used in regular doses. Super-resistant bacteria are not just nosocomially acquired [2,3], they can also be found in the community [4], this exposes several classes of individuals to a high risk; children, elderly, patients with chronic diseases and those with immune disorders. The origins of increasing antibiotic resistance are diverse, self-medication, poor adherence to treatment programme, increased usage of antibiotics in livestock as a growth promoter, to name but a few [4,5]. In the report of, Ears-Net 2013, the “European antibiotic resistance surveillance network” [6], established that antibiotic resistance and other infectious disease treatments, are the cause of substantial problems in health, not just in developing countries, but also developed countries, due to the increases of expense in patient care, failure of treatment and in the worst case scenario, the death of the patient.

The increase in the usage of broad spectrum antibiotic has several consequences; for example, in a hospital in the U.S.A. [7] there was a large outbreak of infections caused by ESBL-producing pathogens in the early 1990s, cephalosporin usage was reduced 80% throughout the hospital, accompanied by a 71% reduction in ceftazidime resistant *Klebsiella spp.* in the ICU. Still the damage was that overuse of carbapenems resulted in a 69% increase in imipenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [8].

Nowadays the controversy between the *in vitro* laboratory results and what to report for treatment are important as CLSI and EUCAST trying to control the problem of increasing antibiotic resistance, suggest in their formative reporting Extended Spectrum Beta-Lactamases (ESBLs) producers ‘as found’ rather than resistant to all cephalosporins. This can bring terrible consequences as the treatment failure rate might increase and the number of ESBLs producers can increase due to the lack of using the right treatment [9].

There are variants that arise by spontaneous mutation in inducible strains, and the likelihood of their selection during therapy, with consequent treatment failure, is as high as 20-30% when third-generation cephalosporin are used to treat an *Enterobacter spp.* bacteraemia; the mortality rate is 50% and a substantial increase in cost is incurred attempting successful treatment and patient survive. Some studies have shown that the *Escherichia coli* living in the gut are ESBLs producers in 40% of total tested isolated, increasing the chance of a serious infection and dramatic cost increase. Finally the number of patients that

are infected by strains producing carbapenemases is dramatically increasing, of which the mortality rate is higher than 50% [10].

### Evolving mechanisms of resistance in Superbugs

**Beta-lactamases:** Beta-lactamases are enzymes that can hydrolyse the antibiotic. They are classified into four different groups according to Bush, Jacoby and Medeiros' classification [11].

Class A: Most of these enzymes hydrolyse oxyimino-cephalosporins. They have serine in the active site; they are inhibited by clavulanic acid, and other similar inhibitors. In this group are the Extended Spectrum Beta-Lactamases, known as ESBLs. ESBLs are one of the most frequent mechanisms of resistance in enterobacteriaceae bacteria and they are classified into several groups according to their amino-acid sequence homology. TEM-1 was described in the early 1960s [12], today the prevalence of this type of resistance and the quantity of variants is alarmingly high. Concern over the frequency of isolates with ESBL enzymes has naturally been on the increased, but now isolates are not just resistant to third generation cephalosporins but as well carbapenems.

Class B: These are metallo-enzymes that harbour a Zn<sup>2+</sup> in the active site, these enzymes hydrolyses most of the beta-lactams including carbapenems and they are not inhibited by classical inhibitors (like clavulanic acid) but they are by Ethylene diamine tetra acetic acid (EDTA).

Class C: They have a serine in the active site and they are known as cephalosporinases. They have some resistance to classical inhibitors and they are found in the chromosome of most enterobacteriaceae.

Class D: They have a serine in the active centre. High ability to hydrolyze oxacillin, cloxacillin and methicillin and they are not inhibited by clavulanic acid.

Today, over 890 unique β-lactamases have been identified in naturally occurring bacterial isolates [8]

**Efflux pumps:** This system is an active system of expulsion of the antibiotic. It uses transmembrane proteins that eject the antibiotic outside the cell, regardless of the concentration gradient [13,14]. Efflux pumps are important mechanisms not just for resistance; they play a crucial role in bacterial communication (known as quorum sensing) among other biological processes.

**Porins:** Porins are nonspecific diffusion channels [15,16]. Resistance comes in form of diminution in the expression or in most cases a loss of a porin, as well but less common mutation can change porin structure [15-17].

**Modification of the target:** This mechanism of resistance is one of the most common mechanisms found in different bacteria against different families of antibiotics. Modification of the target occurs through mutations in the DNA that makes targets unrecognizable to the antibiotic or causes a loss of affinity in the binding process [18].

Table 1 and 2 show the mechanisms of action of different families of antibiotics and the mechanisms of resistance more frequent for each family.

**Table 1:** Mechanisms of action of the most frequently used family of antibiotics.

Antibiotic target	Antibiotic family
Cellular Wall	Beta-lactams and vancomycin
Synthesis DNA/RNA	Fluoroquinolones, Rifamicin
Synthesis folato	Trimetropin, Sulfonamides
Cellular membrane	Daptomicin, Polimixin
Protein synthesis	Linezolid, Tetracyclins, Macrolides, Aminoglicosides

**Table 2:** Mechanisms of resistance of the different antibiotic families.

Mechanism of resistance	Antibiotic family
Efflux pumps	Fluoroquinolones, Aminoglicosides, Tetracyclin, Beta-lactams, Macrolides
Immunity and Bypass	Tetracyclines, Trimetropin, Sulfonamides
Modification of the target	Fluoroquinolones, Rifamicin, Vancomycin, Penicilin, Macrolides, Aminoglicosides
Inactivation of the antibiotic by enzymes	Beta-lactams, aminoglicosides, Macrolides, Rifamicin

### Biofilms

A biofilm is a matrix of an enclosed bacterial population, where the matrix is attached to a surface; surfaces can be comprised of nearly anything. Biofilm bacteria behave differently to planktonic cells; they are more resistant against antibiotics, cleaning and eradication than planktonic cells. Public reports state that 60 to 85% of all microbial infections involve biofilms [19] and the number of infections associated to biofilm formation in medical devices is more than 25% [20]. Microbial infections are responsible for greater mortality and morbidity rates in patients with indwelling or implanted devices, significantly increasing costs associated with long term treatment, repeated surgical interventions and hospitalization of these individuals. It is estimated that hospitalization expenditure increases from \$296 million USD to \$2.3 billion USD annually for patients with infected implanted devices [20]. In most cases the treatment for patients with infected prosthetic devices is a surgical treatment, where the removal of the infected device is needed. Antibiotic resistance and the ability to produce biofilms, has made some bacteria almost impossible to eradicate. Hospital acquired infections such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, are no longer the only infections on a clinicians check list, new species are being added at an alarming rate.

### Nanoshuttles and coating systems for infection control

Trying to look for new solution, nanotechnology is developing different tools, new therapies to control and combat infections. With reference to bacterial resistance, nanotechnology offers a solution in form of nanoshuttles that can deliver antibiotics to a precise location and release them progressively at a controlled rate. These systems are showing real promise and preliminary results show how the concentration of the drug needed to kill the microorganisms is lower than in the normal conditions. An additional advantage is that the risk of inadvertently creating resistance in other present strains is diminished.

Nanotechnology is also making great progress in combatting biofilms on medical devices; many have been successfully coated with nanoparticles that inhibit biofilm formation. Most studies have been focused on pathogens that are frequently associated with nosocomial infections. In this review we will explore the advances in nanotechnology, novel treatment systems and new coating systems that can prevent bacterial infections and colonisations.

### Coating systems

With nanotechnology we are able to explore new tools for the prevention of biofilm formation on medical devices. Hip and teeth implants have already proven to be highly successful [20], while preliminary results in other medical devices have shown great promise, many are ready for further study.

In 2011 Saviuc et al [21] reported a new hybrid core/shell/coated-shell nanosystem created using a modified Massart method, for the stabilization of essential oils and for the further improvement of their antifungal properties. The nanosystem coating strongly inhibited fungal adherence for over 24 hours of incubation. However, the degree of biofilm development on uncoated cover slips proved to be dependent on the tested strain and time. They demonstrate that the dynamic of fungal biofilms development on the glass cover slips and respectively on essential oil based nanosystem is much more reduced and exhibits a simplified architecture. All these results demonstrate that core/shell/adsorption-shell magnetite nanosystems could be used as successful coating agents for obtaining antibiofilm pellicles on different medical devices, opening a new perspective for obtaining new antimicrobial and antibiofilm surfaces, based on hybrid functionalized nanostructured biomaterials.

Limban et al. in 2012 described an efficient procedure for the synthesis of 2-((4-ethylphenoxy) methyl)-N-(substituted-phenylcarbamothioyl)-benzamide. All the results demonstrate the efficiency of the core/shell/adsorption-shell nanosystem based on magnetite nanoparticles/lauric acid/new benzamides. This structure optimized materials resistant to microbial colonization, useful for the further development of functionalized anti-biofilm surfaces with medical applications in the field of catheter-associated infections [22].

Anghel et al. [23] recently reported a successful antimicrobial system that has proven to be effective in a range of medical implementations, from prosthetic devices to bandages. Coatings of a hybrid nanofluid based on magnetite and natural vegetal compounds (eugenol and limonene). The functionalized textile coated dressing accumulate the anti-adherent properties of magnetite and microbicidal activity of eugenol and limonene, exhibiting significant anti-adherence and anti-biofilm properties against bacterial pathogens. Because they are natural compounds the side effects are low or non-existent.

The properties of *Rosmarinus officinalis* where published recently, its essential oil coated nanoparticles strongly inhibited the adherence ability and biofilm development of *Candida albicans* and *C. tropicalis* on the surface of catheters [24].

Grumezescu et al. demonstrated that micro-biocoated titanium samples impaired biofilm development and adhesion

to the surface in *S. aureus*. Furthermore, the fabricated micro-coating does not alter titanium slides biocompatibility, being appropriate for cultured human cells development. Another important advantage of this system is that micro-biocoated titanium samples have proven to maintain coating concentrations within acceptable therapeutic limits. Grumezescu also shows that by replacing some synthetic anti-biofilm compounds for natural compounds can lower therapeutic doses, reducing dose-related side effects and provide prolonged biological activity [25].

### Shuttle system

Nanoparticles can be efficiently used as delivery shuttles and controlled released systems for several antibiotics and natural products; nanoparticles are free to move uninhibited in to cells where the antibiotics are then released. As antibiotics can be released inside the micro-organism this leads to an increase in the therapeutic index and reduction in overall serum concentration and deleterious side effects to other organs [26].

Devanand et al. in 2011 [26], reported successful use of hydroxyl apatite nanoparticles, ciprofloxacin-loaded hydroxyapatite nanoparticles and zinc-doped hydroxyapatite nanoparticles as a carrier for ciprofloxacin drug delivery system due to the strong antimicrobial activity of these compounds against *P.aeruginosa* and *S.aureus*. Presence of zinc increases the drug release percentage and controls the manner in which it is released. Hydroxyapatite has a low solubility in physiological condition, meaning that it performs well as a carrier for the local delivery of drugs both by surgical placement and injection. By using local delivery systems there is substantial decrease of toxicity in other organs and the concentration of antibiotics in the blood. Zinc participates in the activity of enzymes and is an antioxidant. The authors observed that as the concentration of zinc increases agglomeration of the nanoparticles increases too, that the release of the antibiotic is in a slow and controlled manner and that antimicrobial efficiency intensifies with increases in zinc and drug concentration.

In 2011, Breitbach and co-workers developed a surface-mediated release method of a synthetic AHL for modulating bacterial QS. They demonstrated that the synthetic AHL was released gradually from thin films of poly (lactide-co-glycolide) (PLG) and efficiently activated QS, in model using *Vibrio fischeri*, at levels that exceed those promoted by direct solution-based administration. This strategy based on active surfaces with controlled release of an appropriate QS modulator may be a great tool in developing prosthetic devices with modified surfaces, adequate for preventing bacterial infections by gradually modulating their QS and virulence.

Mihaescu et al. [27], reported a novel nanosystem based on  $Fe_3O_4$ ,  $SiO_2$  and antibiotics, deposited as a thin film on different surfaces. This magnetite silica films is a promising candidate for the development of novel materials designed for the inhibition of medical biofilms formed by different pathogenic agents on common substrates, frequently implicated in the etiology of chronic and problematic infections. Studies revealed that the nanosystem inhibits the development of mono-specific biofilms formed by *S. aureus* or *P. aeruginosa*. The differences within the dynamics of bacteria biofilms on the tested substrates may be

explained by different growth rates, as well by interfering with microbial adhesion.

Anghel and Limban [28] have designed a nanofluid of  $\text{Fe}_3\text{O}_4/\text{C}_{12}$  nanoparticles with 2-((4-ethylphenoxy) methyl)-N-(subtitled-phenylcarbamothioyl)-benzamides, that have proved to be non-cytotoxic and that does not affect the physiological processes in eukaryotic cells. They show gradual decrease of the microbial colonization from the uncoated catheter to the catheter pelliculized with nanofluids. The coating system represented by nanoparticles proved to be efficient in preventing both the initial formation as well the development of mature microbial biofilms formed by *S. aureus* and *P. aeruginosa*, demonstrating the efficiency of the nanoparticle coating in the delivery of the chemical compound in active forms for a long period of time. The long-lasting efficacy of the active compounds loaded on the nanoparticles could be considered as a future solution to provide persistent, broad-spectrum antibacterial effects with minimal side effects.

A paper published recently by Grumezescu on a new drug delivery system reported successful fabrication of a biocompatible  $\text{Fe}_3\text{O}_4@$ AMO nanosystem, with great antimicrobial activity. This bio-active nano-sized material proved to enhance the efficacy of low doses of amoxicillin against both the Gram negative pathogen *E. coli* and the Gram positive *S. aureus*. Furthermore, the obtained functionalized magnetite was proved to be well circulated through the mammalian body, offering the perspective of being used as an efficient drug delivery and controlled release nanosystem for active drugs in different localized infections. [29]

It was reported in 2012, that an increased concentration of ceftriaxone leads to a decrease of the bacterial encapsulation efficiency and enhancement of loading capacity. Greater release of the antibiotic is higher in higher concentrations of antibiotic, at 1 mg/ml ceftriaxone loading, 23% of the drug was released within the first hour followed by a slow and gradual release with 73% drug release in 96 h. These particles show haemolysis of 15%, which is substantially reduced for colloid dispersion of chitosan and they show no cytotoxic effect and cell compatibility at 12 mg/ml. In the cellular up take assay ceftriaxone-Chitosan nanoparticles were rapidly and efficiently taken up and internalized in Caco-2 and in J774.2 cells, the cellular uptake was more significant at 37°C and highly decreases at 4°C, this could be explain because endocytic uptake is energy dependent. The antibacterial effect was proved showing how this shuttle system increases the absorption of ceftriaxone [30].

In 2013 Harsha et al. [31] published work on a new shuttle system to deliver drugs against infections produced by *Helicobacter pylori*. The authors study the properties of a new technology to deliver amoxicillin nanoparticles, the Büchi Nano Spray Dryer B-90. This is an important area of research as the treatment for *H. pylori* is amoxicillin but the concentrations that are reached in the stomach mean long periods of high dose treatments is needed for reliable success. Several other systems have proved successful before, but this one has shown to be more effective in animal models. The nanoparticles used in this study enabled sustained release of amoxicillin over an extended period of time, up to 12 hours, and were stable for 12 months under accelerated storage conditions of 25°C.

A work published by Anghel and Grumezescu [19] recently reported the fabrication of a 5 nm core/shell nanostructure combined with *Menthapiperita* essential oil to obtain a unique surface coating with improved resistance to staphylococcal adherence and further development of biofilms. The number of biofilm embedded viable cells after 24, 48, and 72 hours incubation was significantly decreased on the modified surfaces in a time dependent manner. It seems that the anti biofilm effect of the obtained coating is remnant, probably due to the gradual release of the essential oil compounds from the coating, as stated by the authors. The results prove that these modified surfaces manifest a dual benefit due to their anti-adherence and microbicidal properties. The microbicidal effect may be explained by the stabilization, decrease of volatility, and controlled release of the essential oil.

In a work published in 2013 [32], the authors studied the use of solid lipid nanoparticles with amikacin for their use in the cystic fibrosis. The results show that administration in aerosol form of the antibiotic increases the concentration in lung (higher than with I.V. administration) and the concentration in kidneys is lower. These results are promising for enhancing the effects of this drug in cystic fibrosis and reduce the side effects.

Zhao et al [33], studied biocompatible ciprofloxacin-loaded carboxymethyl chitosan nanoparticles. About 9%–27% of total drug was released rapidly in the first 30 minutes and more than 95% released in 24hours. There is low cell toxicity and the results proved that these nanoparticles increase the efficiency of ciprofloxacin. Antibacterial activity of ciprofloxacin loaded in nanoparticles was increased by a factor of two. The carrier material had good biocompatibility, and no significant cytotoxicity was observed after incubating ciprofloxacin-free nanoparticles with liver carcinoma cells. Furthermore, these nanoparticles showed obvious cellular uptake, thereby improving the antimicrobial drug permeability.

Farnesol has proved to be an effective compound against *Staphylococcus spp.* infections and biofilm formation, being of great potential use in patients with indwelling devices. In some conditions, this compound has proved to be more effective against Staphylococcal development than several antibiotics [34].

## CONCLUSIONS

In the XXI century nanotechnology brings new hope in the fight against infections. Shuttle drug delivery systems and coated medical devices are giving highly promising preliminary results. The evolution of this technology is occurring fast and is a new hope for keeping us in the race against antibiotic resistance. Hopefully soon we will be able to implement these systems in health care services and they will help to reduce not just the amount of infections but as well the number of people that die due to acquisition of multidrug resistance bacteria. This will also slow the increase in antibiotic resistance, the number of nosocomial acquire infections and potentially save millions of dollars a year.

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