

## Antimicrobial properties of silica modified nanoparticles

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The ability of certain strains of bacteria to withstand the effects of common antibiotics has led to find novel strategies for the treatment of infections associated to antimicrobial resistance and biofilm development in affected patients. The use of nanoparticles containing antibiotics has demonstrated numerous advantages. As the antibiotic is held into the nanoparticle, chemical composition and modifications on the NP's surface enable to prolong, localize, target and have a protected drug interaction with the diseased tissue. In this way, higher antibiotic concentrations are attained in the targeted cells, managing to reduce the frequency of the dosages taken, reducing the drug side effects and fluctuation in circulating levels, improving the overall pharmacokinetics. A large variety of nanomaterials for efficient antibiotic drug delivery have been developed and their efficacy has been demonstrated. Due to high thermal and chemical stability, high surface area and good biocompatibility, silica nanoparticles are a good option to deliver drugs such as antibiotics. In this chapter, we will give an overview about the use of nanosized silica particles and silica modified nanoparticles loaded with antimicrobial agents for infection prevention and treatment.

**Keywords** antimicrobial materials; silica nanoparticles; drug delivery; bio-functionalization

### 1. Introduction

Nowadays, antibiotics resistance is one of the most important worldwide healthcare problems. Different causes are associated to this phenomenon, such as overuse of broad-spectrum antibiotics, including second- and third-generation cephalosporins, leading, as a result, to the development of Methicillin-resistant *Staphylococcus aureus* (MRSA). Other factors contributing to the resistance include incorrect diagnosis, unnecessary prescriptions, improper use of antibiotics by patients and unfinished antibiotic prescription. As a result, multiple drug resistance has appeared, mainly connected to hospital-associated infections and biofilm formation.

The ability of certain strains of bacteria to withstand the effects of common antibiotics has led to find novel strategies for the treatment of infections associated to antimicrobial resistance and biofilm development in affected patients. The use of nanoparticles containing antibiotics has demonstrated numerous advantages [1, 2]. As the antibiotic is held into the nanoparticle, chemical composition and modifications on the NP's surface enable to prolong, localize, target and have a protected drug interaction with the diseased tissue. In this way, higher antibiotic concentrations are attained in the targeted cells, managing to reduce the frequency of the dosages taken, reducing the drug side effects and fluctuation in circulating levels, thus improving the overall pharmacokinetics. Other benefits of this type of drug delivery systems applied to antibiotic therapy are the reduction of the antimicrobial resistance, the enhancement of the solubility of some antibiotics and the widener therapeutic index.

On the one hand, the applications of inorganic nanoparticles and their surface modifications, to achieve good antimicrobial activity is growing fast [3]. On the other hand, since this is a brand-new field, few studies have been done regarding the security, toxicity and impact of nanoparticles, especially during long-term treatments. It is necessary to analyze the effect over the corresponding tissues and organs, the possible accumulation when they are intravenously injected or the overexposure if NPs are locally administrated [4, 5].

A large variety of nanomaterials for efficient antibiotic drug delivery have been developed and their efficacy has been demonstrated [6]. Due to high thermal and chemical stability, high surface area and good biocompatibility, the interest on silica nanoparticles as a system to deliver drugs such as antibiotics is increasing [7, 8]. Colloidal silica is a very versatile material as it can be prepared in a wide variety of forms and sizes, its surface is easy to modify and it can be obtained from relatively cheap precursors. In this chapter, we will give an overview on the current development of nanosized silica particles and silica modified nanoparticles loaded with different antimicrobial agents for the prevention and treatment of infections.

### 2. Nitric oxide releasing silica nanoparticles

The antimicrobial activity of NO, a reactive free radical produced by inflammatory cells, has been demonstrated by a variety of approaches. NO production is part of an effective host response to infection. NO production by the inducible NO synthase isoform (NOS2) is stimulated by proinflammatory cytokines such as IFN $\gamma$ , TNF $\alpha$ , IL-1, and IL-2, as well

as by microbial products such as lipopolysaccharide and lipoteichoic acid. NO-donor compounds have been shown to inhibit or kill microbes when directly administered *in vitro*, demonstrating effectiveness against a remarkably broad range of pathogenic microorganisms including viruses, bacteria, fungi, and parasites [9].

Several strategies have been developed for delivering NO to bacteria, including NO-releasing silica nanoparticles. Nitric oxide releasing silica nanoparticles have been used to successfully control the formation of biofilms by microorganisms such as *Pseudomonas aeruginosa* and *Escherichia coli*. Two different types of precursor were used for nanoparticle synthesis, N-Methylaminopropyltrimethoxysilane (MAP3) and N-(6-inohexyl) aminopropyltrimethoxysilane (AHAP3). The authors found that the MAP3 silica nanoparticles had 1000-fold greater efficacy against *P. aeruginosa* biofilms than the AHAP3 nanoparticles [10]. The greater amount of NO released by MAP3 nanoparticles, the more rapid delivery leading to a greater instantaneous concentration of NO in solution and the smaller size of MAP3 nanoparticles that allow them to penetrate biofilm matrix more effectively could explain these results.

Nitric oxide-releasing nanoparticles prepared via co-condensation of a tetraalkoxysilane with an aminoalkoxysilane modified with diazeniumdiolate NO donors showed enhanced bactericidal efficacy and reduced cytotoxicity to healthy cells, compared to small molecule NO donors. Confirmation of particle association with *P. aeruginosa* cells helped to elucidate the differential toxicity observed between macromolecular and molecular NO donors. The possible mechanism by which this association between bacteria membranes and nanoparticles occurs is not entirely understood but is most likely related to electrostatic and/or hydrophobic interactions resulting in high local concentrations of NO and more efficient delivery of NO to the bacterial cells [11].

Another possible approach is to use two tetraalkoxysilane precursors, tetramethoxy- and tetraethoxysilane (TMOS and TEOS) to synthesize the organically-modified hybrid silica via co-condensation with amine-bearing silanes, followed by exposure to 5 atm of NO under basic conditions [12, 13]. By this method, NO-releasing silica nanoparticles showed improved NO storage and release properties, which could be tailored via the TMOS or TEOS content. Carpenter *et al.*, studied the bactericidal efficacy of NO-releasing silica nanoparticles as a function of particle size [14]. A reverse microemulsion synthesis was used to prepare amine-functionalized silica nanoparticles of 50, 100, and 200 nm. N-Diazeniumdiolate nitric oxide (NO) donors were subsequently formed on secondary amines. The bactericidal efficacy of the NO-releasing nanoparticles against *Pseudomonas aeruginosa* after 2 h was greater for smaller nanoparticles. The faster diffusion rate of smaller particles allows for a more rapid association with bacteria. As such, a larger portion of the stored NO is likely to be delivered to the bacteria from the 50 nm particles compared to the 100 and 200 nm particles, thereby lowering the necessary particle dose and overall NO concentrations required for effective killing. Although the explanation for effectiveness of NO-releasing nanoparticles remains unclear, the rapid diffusion properties of NO may result in enhanced penetration into the biofilm matrix and thus improve efficacy against biofilm-embedded bacteria [15].

### 3. Metal modified silica nanoparticles

The biocidal effects of copper and silver nanoparticles have been widely reported. They are very effective in reducing the microbial density *in vitro*, but their cytotoxicity towards mammalian cells has also been found to be high. Moreover, Albers *et al* [16] reported that the antibacterial effects occurred at silver ion concentrations that were between 2 and 4 times higher than those inducing cytotoxic effects. The incorporation of silver and copper into silica nanoparticles may allow the reduction of the concentrations of metal ions needed to achieve antimicrobial concentrations. In this section we discuss the development of Si-Ag and Si-Cu nanoparticles that were found to be effective for antimicrobial applications.

#### 3.1. Silver-SiNP

Antimicrobial properties of silver have been known for centuries. Three possible mechanisms for bacteria growth inhibition by silver have been proposed: interference with electron transport, binding to DNA, and interaction with the cell membrane [17]. Indeed,  $\text{Ag}^+$  binds to thiol groups (-SH) in enzymes leading to their deactivation, with several important outcomes, especially in the mitochondrial energy metabolism. Silver ions can also bind to DNA, increasing the stability of the double helix and denaturing the DNA molecule. Although, only the ionized form of silver is responsible for the antimicrobial action [18]. Hence the antimicrobial properties of metallic silver are explained by the fact that the contact with water may lead to dissolution of silver ions from a surface or particle, acquiring the desired properties.

The antibacterial effects of Ag-SiO<sub>2</sub> hollow composite powders against *Escherichia coli*, *Staphylococcus aureus* and bacillus were reported. Hollow silica nanospheres and nanotubes were synthesized as hosts for the immobilization of silver. It was observed that both composites had excellent antibacterial performance but Ag-supported tubular hollow structure showed a stronger antibacterial ability than spherical hollow structure because they can retain higher silver contents as well as smaller and more dispersed silver nanoparticles [19]. The combination of silver and silica for the synthesis of nanoparticles has been widely studied. For example, spherical nanoparticles with a silver core and an

amorphous silica shell were successfully fabricated by using tetraethoxysilane as silica precursor and reducing silver nitrate with ascorbic acid. These nanoparticles had excellent antibacterial effects against *E. coli* and *S. aureus* [20]. It is worth mentioning that the good performance of core-shell Ag-Si nanosized particles was subject of patents [21, 22]. In a similar approach silver nanoparticles were immobilized onto the surface of magnetic silica composite to prepare magnetic disinfectant that exhibited enhanced stability and antibacterial activity. Indeed, silver nanoparticles inlaid  $\text{Fe}_3\text{O}_4\text{-SiO}_2$  magnetic composite ( $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-Ag}$ ) was successfully synthesized and its application as an antibacterial material in water disinfection was demonstrated [23]. Silver nanoparticles, with diameter of about 10 nm, were anchored homogeneously and tightly onto the silica coat of  $\text{Fe}_3\text{O}_4\text{-SiO}_2$  magnetic nanoparticles, which increased the antibacterial abilities by avoiding the aggregation of Ag nanoparticles. The minimum inhibitory concentrations of  $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-Ag}$  magnetic composite to *Escherichia coli* and *Staphylococcus aureus* were  $15.625 \text{ mg.L}^{-1}$  and  $31.25 \text{ mg.L}^{-1}$ , respectively, and the minimum bactericidal concentrations were  $250 \text{ mg.L}^{-1}$  and  $500 \text{ mg.L}^{-1}$ , respectively. In inactivation experiment,  $150 \text{ mg.L}^{-1}$  of  $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-Ag}$  disinfectant in 150 mL of normal saline solution could kill 99.9% of the tested bacteria within 60 min. Paper disk diffusion assay also showed excellent antibacterial abilities against both *E. coli* and *S. aureus*. The silica coat not only acted as a supporting matrix, but also enhanced the stability of the disinfectant. The obtained  $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-Ag}$  composite has a high magnetic saturation value of  $75 \text{ emu.g}^{-1}$ , indicating that it can be recovered from water for reuse through magnetic separation. Interestingly possible contamination of the environment by the disinfectant is avoided.

### 3.2. Copper-SiNP

Copper is a heavy metal whose usefulness as an antibacterial agent is widely known. It is an effective agent with relatively low toxicity towards mammals, which is especially important in antibacterial treatment. Metal ions commonly substitute for other metal ions of a similar size, which provides the basis for the toxicity of copper [17]. The structure of proteins and enzymes can be altered by copper, so that they can no longer perform their normal functions, as a result, the inactivation of bacteria is obtained [24].

Copper can be deposited on a supporting material, so that the releasing time of Cu can be delayed over a long period of time. For instance, copper was deposited on the surface of spherical silica nanoparticles, where nanoparticles served as seeds for continuous Cu metal deposition. The antibacterial properties of the Cu-SiO<sub>2</sub> nanocomposites were examined with disk diffusion assays and proved excellent antibacterial ability [25].

Maniprasad *et al.*, [26] reported the synthesis of core-shell copper-silica nanoparticles. Silica "seed" particles were first prepared by the base-catalyzed Stöber process, followed by an acid-catalyzed seeded growth of the Cu-silica shell layer around the core. The seed particle size was 380 nm and the shell thickness was 35 nm. Cu loading was estimated to be 98 ng of metallic copper per mg of CuSiO<sub>2</sub>. Antibacterial efficacy was evaluated against *E. coli* and *B. subtilis*, obtaining more effective antimicrobial activity for the core-shell NP than insoluble Cu hydroxide particles at equivalent metallic Cu concentration, suggesting improvement of Cu bioavailability due to the particle structure.

## 4. Surface-modified silica nanoparticles and antimicrobial molecules loading

Antibacterial solutions or surfaces require materials with high activity against pathogenic bacteria but nude silica nanoparticles showed no detrimental effects on bacteria (Figure 1).

Grafting methods represent a functionalization technique that provides an ordered secondary structure with new interesting properties, as a result of the high diversity of modification that could be introduced on the surface of nanoparticles leading to many applications such as antimicrobial and antifungal agents. In this way, polypeptide polymer-grafted silica nanoparticles (NPs) were synthesized from poly-L-lysine covalently attached and their efficacy as antimicrobial agents was proved on both gram-negative *E. coli* and gram-positive *Bacillus subtilis* [27]. The grafting of antibacterial polymer, poly(vinylbenzyltributylphosphonium chloride) ( $\text{poly}(\text{St-CH}_2\text{P}^+(\text{Bu})_3\text{Cl}^-)$ ), onto silica surface was achieved by radical graft polymerization of the corresponding monomer showing strong antibacterial activity which was retained even after the boiling in water for 24 h [28].

Silica nanoparticles could also be used to covalently link molecules with antimicrobial effect to their surface through the selection of proper linkers. In this sense, hybrid-silica nanoparticles (NPs) containing the FDA-approved antimicrobial triclosan (Irgasan) were found to be superior in killing bacteria, as compared with the free biocide [29]. Quaternary ammonium compounds have been considered as excellent antibacterial agents due to their effective biocidal activity, long term durability and environmentally friendly performance. Similarly, 3-(trimethoxysilyl)-propyldimethyloctadecylammonium chloride as a quaternary ammonium silane was applied for the surface modification of silica nanoparticles, providing antibacterial properties due to the hydrophobicity of the modified surface. Functionalized silica nanoparticles exhibited the enhanced inhibition performance against growth of Gram-negative, Gram-positive and *Deinococcus geothermalis* compared to pristine silica nanoparticles [30]. Furthermore, silica nanoparticles coated with a quaternary ammonium cationic surfactant, didodecyldimethylammonium bromide (DDAB) were tested against bacteria (*S. aureus*) and fungi (*C. albicans*) showing lower minimal inhibitory concentrations (MIC) against bacteria and fungi than soluble surfactant. These nanoparticles were able to immobilize between 45 and 275  $\mu\text{g}$

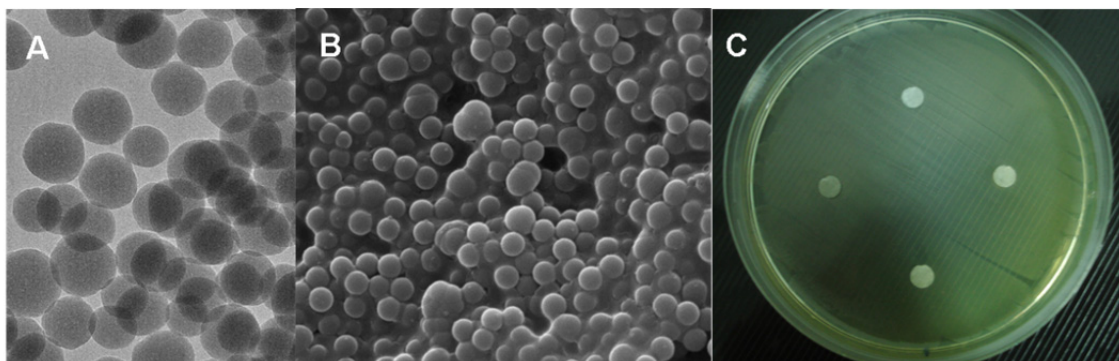
of DDAB per milligram of nanoparticle and due to the strong electrostatic interaction of the DDAB with the silica no measurable loss of antimicrobial activity was observed after suspension in aqueous solution for 60 days which confirms that the antimicrobial activity of the nanoparticle does not require the leaching of the surfactant from the surface of the NPs [31].

The adsorption of other antimicrobial agents on the surface of silica nanoparticles was also assayed by Jang *et al.*, who reported the fabrication of silica–poly(3-allyl-5,5-dimethylhydantoin-co-methyl methacrylate) (poly(ADMH-co-MMA)) core–shell nanoparticles as a biocidal polymeric agent using a seeded polymerization. The ADMH–MMA mixture was adsorbed on the surface of silica nanoparticles due to their hydrophobic properties and the radical polymerization was initiated. Halogenated derivatives of 3-allyl-5,5-dimethylhydantoin (ADMH) belong to the class of cyclic N-halamines which are often used as antimicrobial agents [32]. These N-halamine-functionalized silica–polymer core–shell nanoparticles displayed powerful antibacterial performance against both Gram-positive bacteria and Gram-negative bacteria, and their antibacterial activities have been greatly improved compared with their bulk counterparts [33].

In another attempt to develop silica nanoparticles with antibacterial activity, silica-coated Fe<sub>2</sub>O<sub>3</sub> nanoparticles were synthesized as carriers for the covalent immobilization and release of antimicrobial drug sparflloxacin where the silica overlayer acts as a physiologically conducive shell that also suppresses the extensive agglomeration of Fe<sub>2</sub>O<sub>3</sub> nanoparticles due to magnetic dipole–dipole attractions. These nanoparticles exhibited time-dependent drug release, with no measurable *in vitro* cytotoxicity, making them potentially relevant for nanomedicine applications specially in the treatment of urinary tract infections and against the major respiratory pathogens and typical pathogens that cause pneumonia [34]. The antibiotic gentamicin was entrapped into biodegradable silica and silica/ polyethylene glycol (PEG) xerogels as well. The particle sizes of the porous silica xerogel and porous silica-PEG were 190 to 395 and 220 to 342 nm, respectively, and the zeta potentials (surface charges) were –1.78 and –6.24, respectively. In this case, the drug molecules (31%) entrapped in the sol-gel matrix remained in biologically active form and the bactericidal effect was retained upon drug release. The *in vitro* drug release profiles of the gentamicin from the xerogel and that from the xerogel-PEG were distinctly different at pH 7.4 with a release of gentamicin of 57% in 33 h from the silica xerogel and with a release rate reaching 90% in 33 h for silica-PEG particles. These particles, silica xerogel and xerogel-PEG, were more effective in clearing the infection with *Salmonella enterica serovar Typhimurium* in the spleen and liver of mouse than was the same dose of free drug [35].

Enzymes can also be used as a strategy for the development of antimicrobial nanoparticles. In this sense, Lysozyme-coated mesoporous silica nanoparticles were reported as antibacterial agents that exhibit efficient antibacterial activity both *in vitro* and *in vivo* with low cytotoxicity and negligible hemolytic side effect. Lysozyme is a natural enzyme abundant in secretions, such as tears, saliva, and mucus of the mammalian and a part of the innate immune system against infection as it can cause damage of bacterial cell walls by catalyzing hydrolysis of 1,4-β-linkages between N-acetylmuramic acid and N-acetyl-d-glucosamine residues in peptidoglycan. The advantages found by the authors for this type of nanoparticle included the lower risk of development of resistance compared to antibiotics; selective damage of the bacterial walls; enhanced stability of Lysozyme (positively charged) by immobilizing it on the negatively charged silica via electrostatic interactions and a good antibacterial efficacy of Lysozyme nanoparticles when evaluated *in vivo* by using a intestine-infected mouse model as their minimal inhibition concentration (MIC) was fivefold lower than that of the free enzyme *in vitro* [36].

Another group of antimicrobial delivery systems are antifungal nanoparticles. In this case we can mentioned the covalent immobilization of amphotericin B, a potent antifungal agent approved by the FDA, widely used in clinical practice and effective against a large spectrum of fungi, into silica nanoparticles. These antifungal nanoparticle conjugates showed to be fungicidal against several strains of *Candida* sp., mainly by contact and they could be reused up to 5 cycles without losing their activity with no hemolytic or citotoxic effects [37]. The drug Itraconazole was also incorporated into ordered mesoporous (OMS) silica aiming an increase in its oral bioavailability. After loading itraconazole into OMS, its oral bioavailability was compared with the crystalline drug and the marketed product Sporanox in rabbits and dogs. After administration of crystalline itraconazole in dogs (20 mg), no systemic itraconazole could be detected but using OMS as a carrier the oral bioavailability of itraconazole compared well with the marketed product Sporanox, in rabbits as well as in dogs [38].



**Fig. 1** A) TEM images of silica nanoparticles, B) SEM images of silica nanoparticles and C) representative image of the disk diffusion method employed to assess antimicrobial activity of silica nanoparticles.

## 5. Bioglasses and bioceramics for antimicrobial applications

Bioactive glasses of the  $\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5$  composition have antimicrobial activity in aqueous solutions due to the release of their ionic compounds over time [39]. The release of the dissolution products result in a high pH environment [40], which is not well-tolerated by bacteria [41]. In addition, the release of silica has been also linked to the antibacterial bioactive glass effect [42]. The biocide efficiency of bioactive 45S5 Bioglass® derived glass-ceramic substrates against common Gram positive and Gram negative bacteria, and also against yeast have been reported [43]. Moreover, the shift from micro- to nano-sized bioglass materials afforded a ten-fold increase in silica release and solution pH elevation by more than three units. As a result, the killing efficacy was substantially higher for the nanomaterial against all tested strains of *Enterococcus faecalis* [44]. However, their antibacterial efficacy in human teeth is still inferior to that of other materials so that attempts have been made to spike bioactive glass with antimicrobial agents to increase its antimicrobial efficacy. Gentamicin sulfate (GS) was incorporated into mesoporous bioactive glasses with different composition, surface properties and materials forms such as powders and discs with different shape and sizes. The GS loading and releasing behavior demonstrated the key influence of the bioactive glass composition. Particularly higher  $\text{SiO}_2/\text{CaO}$  ratio led to higher amount of GS loading and faster GS release rate in simulated body fluids. Furthermore, the GS release rate of disk samples was slower than that of powder samples and a slight increase in the GS release rate was observed when decreasing the thickness and diameter of disks suggesting that the material form is also one factor which affects the release rate [45].

A particular case where composite scaffolds could be used is the application of an implantable antitubercular composite scaffold drug delivery system (CS-DDS). In this system, a beta-tricalcium phosphate ( $\beta\text{-TCP}$ ) bioceramic scaffold was coated with mesoporous silica nanoparticles and bioactive glass. Rifampicin and isoniazide were both loaded onto the scaffolds. This composite system showed much higher rifampicin and isoniazid loading capacities than pure  $\beta\text{-TCP}$  scaffold due to the mesoporous structure of the bioceramics. Compared to the complete *in vitro* release of both drugs over three days from the pure  $\beta\text{-TCP}$  scaffold, the CS-DDS displayed a sustained co-release pattern, allowing to keep concentrations higher than their effective values to kill mycobacterium tuberculosis for more than 30 days [46].

**Table 1** Representative silica nanoparticles with antimicrobial activity

Material type	Modification/ Molecule added	Silica precursor	Microorganism tested	References
Nitric Oxide-Silica NP	Nitric oxide	aminoalkoxysilanes	<i>E.coli/S.aureus/S.epi dermidis/C. albicans</i>	10
		aminoalkoxysilanes	<i>Pseudomona auroginosa</i>	10-11-14
		TMOS or TEOS with aminoalkoxysilanes		12-13
Metal –Silica NP	Silver	Sodium silicate (hollow)	<i>E.coli/S.aureus</i>	19
		TEOS		20
		TEOS-Fe <sub>3</sub> O <sub>4</sub> (magnetic)	-	23
	Copper	TEOS	<i>E.coli/S.aureus/E.clo acae/C. albicans/ B.subtilis</i>	25-26
Surface modified and molecule-loaded Silica NP	Poly-L-lysine	Ludox Silica Sol	<i>E.coli/B.subtilis</i>	27
	N-halamine polymers	Colloidal Silica NP	<i>E.coli/S.aureus</i>	32-33
	Triclosan	3- isocyanatopropyltriethox ysilane	<i>E.coli/S.aureus</i>	29
	Quaternary ammonium compounds	Colloidal Silica NP	<i>A. oryzae/P. ochrochloron/E. coli /S. aureus/ C. albicans</i>	30-31
	Antibiotics	TEOS:Fe <sub>2</sub> O <sub>3</sub> :APTES TEOS/TEOS-PEG	<i>Salmonella enterica serovar Typhimurium</i>	34-35
	Lysozyme	APTES	<i>E.coli</i>	36
	Antifungal agents	Colloidal Silica NP/APTES	<i>C.albicans / C. tropicalis / C. parapsilosis/ C. krusei / C. glabrata</i>	37-38
Bioglasses and bioceramics	-	Bioactive glass 45s5	<i>E.coli/M.luteus E.faecalis</i>	43-44
	Gentamicin	Bioactive glass M58s and 58s modified with dodecyl alcohol	-	45
	Rifampicin and isoniazide	B-tricalcium phosphate bioceramic and silica NP	<i>M.tuberculosis</i>	46

## 6. Conclusion

There is increasing interest in developing biomedical devices combining therapeutic and antibacterial potential. Silica-based nanostructured materials appear particularly promising in this area as they combine mechanical stability and biocompatibility with a very versatile chemistry allowing the control of dimensions, morphology and surface properties. Hence, it is possible to develop antibacterial agents via grafting or encapsulation processes that locally destroy bacteria, without being toxic to the surrounding cells and tissues (Table 1).

From a fundamental point of view, the possibility for antibacterial molecules to preserve their properties after immobilization on silica surface raises important questions about their mode of action, at the cell membrane level or intracellularly. In addition, although silica is usually considered as a biologically-inert material, the interactions of its soluble forms with cells are still a matter of intense research that has important implications for the present topic.

Considering applications, the next challenge is this area to integrate nanocarriers within scaffold materials, such as soft or hard tissue repair devices or stents, while preserving their antimicrobial properties. Indeed, as discussed above, the

efficiency of nanoscale materials is partly related to their easy diffusion within biofilms. As this capability may be lost upon integration, it is important to achieve a fine control of the drug release behavior to inhibit bacterial adhesion from the very beginning and achieve a sustained delivery over long time period. Here again, the flexibility and versatility of silica chemistry makes this material particularly promising for these applications

**Acknowledgements** María Lucia Foglia is grateful for their doctoral fellowship granted by the National Research Council (CONICET). Andrea Mathilde Mebert thanks Agencia Nacional de Promoción Científica y Tecnológica for her doctoral fellowship. The authors would like to acknowledge the support of grants from the University of Buenos Aires UBACYT 20020110100081 (to M.F.D) and from Agencia Nacional de Investigaciones Científicas y Técnicas BID 1728/OC-AR PICT 1783 and PICT 2012-1441. M.F.D. and T.C. thank the Argentina-France MINCYT-ECOS-Sud (project A12S01) and CONICET-CNRS programs for financial support.

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