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Antimicrobial Biomimetics

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1. Introduction

A vast territory for research is open from mimicking the behaviour of microorganisms to defend themselves from competitors. Antibiotics secreted by bacteria or fungi can be copied to yield efficient molecules which are active against infectious diseases. On the other hand, nanotechnology provides novel techniques to probe and manipulate single atoms and molecules. Nanoparticles are finding a large variety of biomedical and pharmaceutical applications, since their size scale can be similar to that of biological molecules (e.g. proteins, DNA) and structures (e.g. viruses and bacteria). They are currently being used in imaging (El-Sayed et al., 2005), biosensing (Medintz et al.,2005), biomolecules immobilization (Carmona-Ribeiro, 2010a), gene and drug delivery (Carmona-Ribeiro, 2003; Carmona-Ribeiro, 2010b) and vaccines (O´Hagan et al., 2000; Lincopan & Carmona-Ribeiro, 2009; Lincopan et al., 2009). They can also incorporate antimicrobial agents (antibiotics, metals, peptides, surfactants and lipids), can be the antimicrobial agent or used to produce antimicrobial devices. Antimicrobial agents found in Nature can sucessfully be copied for synthesis of novel biomimetic but synthetic compounds. In this review, synthetic cationic surfactants and lipids, natural and synthetic peptides or particles, and hybrid antimicrobial films are overviewed unraveling novel antimicrobial approaches against infectious diseases.

2. Biofilms, antimicrobial films and surfaces

2.1 Impregnation of materials and coatings with antimicrobials

The minimal conditions required for life on a given material are the presence of water or wet air, with a little dissolved gas, mineral salts and organic molecules so that in natural environments, biofilms can form on surfaces of materials (Lejeune, 2003). A biofilm is a structured consortium of bacteria embedded in a self-produced polymer matrix consisting of polysaccharide, protein and DNA. For human societies, the most detrimental property of surface-associated contaminants as biofilms is probably the expression of specific characters, such as increased resistance to detergents, disinfectants, antibiotics and immunological defenses (Hoiby et al., 2010). Many nosocomial infections are considered consequences of surface contaminations, since biofilms can be formed in indwelling medical devices and biomaterials, or even in equipments such as air conditioning and water-distribution networks (Mah & O´Toole, 2001; Hoiby et al., 2010). Besides, contaminated common hospital surfaces, such as door handles (Oie et al., 2002), stethoscopes (Cohen et al., 1997) and ward

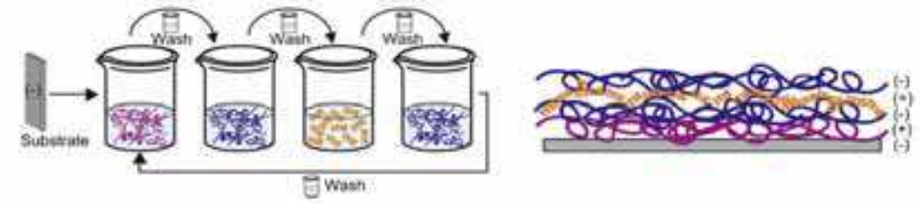
fabrics and plastics (Neely & Maley, 2000) can act as reservoirs of potentially harmful microbes. Upon being touched, these contaminated surfaces could lead to the spread of infection and propagate the contamination to other surfaces and patients in the vicinity (Page et al., 2009). Moreover, the device-related infections are usually associated with increased morbidity, mortality and additional hospital cost to patient (Tamilvanan et al., 2008). Antimicrobial films are required for packaging of food products, since microbial contaminations are responsible for enormous losses in food safety, conservation and shelf life (Cha & Chinnan, 2004; Dutta et al., 2009). Much effort has been devoted to the design of antimicrobial materials in form of particles, coatings or surfaces able to prevent surface contamination and/or erradicate the biofilm consortia (Tiller et al., 2001; Francolini et al., 2004; Furno et al., 2004; Zivanovic et al., 2007; Pereira et al., 2008; Ye et al., 2008; Caro et al., 2009; Avila-Sosa et al., 2010).

The first combinations of dental cements and resins with antibiotic drugs were described in the fifties (Colton & Ehrlich, 1953) whereas resorbable or soluble polymeric carriers which could deliver active drugs directly at the site of infection started to be described in the late seventies (Kopecek, 1977; Arai et al., 2010; Campoccia et al., 2010; Feng et al., 2010; Noel et al., 2010). Control, eradication or inhibition of biofilms and surface-related contaminations included development of novel materials, ranging from synthetic (Park et al., 1998; Hirota et al., 2005; Jampala et al., 2008; Pereira et al., 2008; Bryaskova et al., 2010) to natural and biodegradable compounds (Zhang et al., 1994; Cha & Chinnan, 2004; Pranoto et al., 2005; Maizura et al., 2007; Noel et al., 2010). Local antibiotic delivery systems have been proposed as alternative therapies to typical prophylactic antibiotic dosing (Frank et al., 2005). The most common drug carrier has been polymethylmethacrylate (PMMA) (McLaren, 2004; Nelson, 2004) but other materials could also be used as a local drug delivery system, especially in orthopaedic area, such as calcium sulfate (Heijink et al., 2006), collagen (Diefenbeck et al., 2006) and chitosan (Khor & Lim, 2003; Noel et al., 2010).

Different strategies for producing active films or surfaces have been described as summarized in Figure 1. The layer-by-layer (LbL) deposition consists in a LbL assembly of multiple thin films based on intermolecular electrostatic, hydrogen bonding, and/or covalent interactions between film components (Decher, 1997; Cui et al., 2008; Picart, 2008; Dvoracek et al., 2009; Agarwal et al., 2010; Shukla et al., 2010; Kharlampieva et al., 2009). Among other coating techniques, LbL assembly has the advantage of being a gentle, aqueous assembly process with nanometer level control over the composition of the layers. For example, Shukla et al. (2010) assembled films on silicon substrates which were plasma etched and immediately immersed in a solution containing a cationic polyelectrolyte, then water rinsed and then submerged in the polyanion of choice for the particular architecture being constructed also followed by water rinse step. After this the substrate was immersed in water solution containing the cationic antimicrobial amine-terminated ponericin G1 peptide and water rinsed again. Four deposition steps produced a tetralayered film with sucessive layers: $(\text{polycation/ polyanion/ ponericin G1/ polyanion})_n$, where n represents the number of deposited tetralayer repeats (Shukla et al., 2010). Another approach to produce antimicrobial films and coatings is the spin-coating technique (Pereira et al., 2008; Jausovec et al., 2008), which is based on the solubilization of polymer and antimicrobial compound in a volatile solvent, e.g. chloroform, followed by spin-coating of the solution on the surface of a glass slide or silicon wafer. The hybrid film is obtained from spinning and solvent evaporation (Pereira et al., 2008) (Figure 1). Graftings or covalent attachments of certain antimicrobial chemical moieties, such as pyridinium groups (Tiller et al., 2001) or

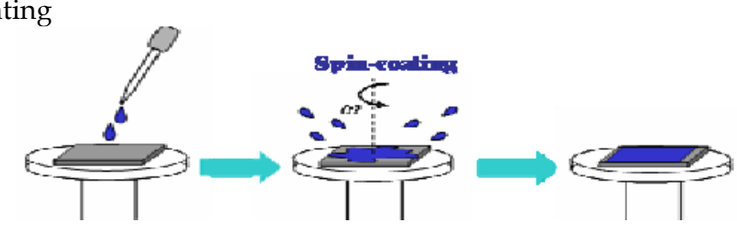
lysozyme (Caro et al., 2009) to surfaces can also be used to prepare antimicrobial materials. In an example of the plasma-enhanced method (Jampala et al., 2008), stainless steel substrates were pretreated with oxygen plasma and received a hexamethyldisiloxane layer. Residual gases were then pumped out and ethylene diamine plasma films deposited before substrate immersion in a hexyl bromide solution for deposition of the antimicrobial layer (Figure 1).

LbL deposition



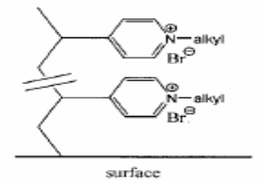
Shukla et al., 2010

Spin-coating



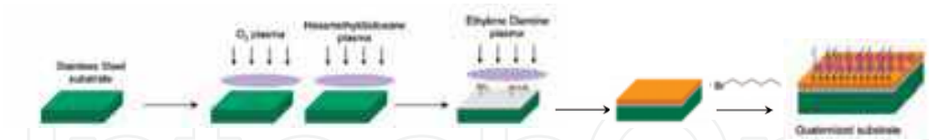
Pereira et al., 2008

Grafting



Tiller et al., 2001

Plasma-enhanced deposition



Jampala et al., 2008

Fig. 1. Methods for casting antimicrobial films on surfaces. Adapted from Tiller et al., 2001; Pereira et al., 2008. Adapted with permission from Jampala et al., 2008. Copyright 2008 American Chemical Society. Reprinted from Biomaterials, Shukla, A.; Fleming, K.E.; Chuang, H.F.; Chau, T.M.; Loose, C.R.; Stephanopoulos, G.N. & Hammond, P.T., Controlling the release of peptide antimicrobial agents from surfaces, 31, 2348-2357, Copyright (2010), with permission from Elsevier.

Surfaces modified by liposomes have already been recognized as an interesting and promising delivery vehicle for active and passive drug targeting purposes (Catuogno & Jones, 2003; Pinto-Alphandary et al., 2000; Jones, 2005). Liposomes can either disrupt on adsorption or adsorb intact, or a combination of both processes can occur (Carmona-Ribeiro, 1992; Carmona-Ribeiro & Lessa, 1999; Carmona-Ribeiro, 2003; Carmona-Ribeiro, 2010a,b). Hence, systems based on vesicles deposited on the surface of a biomedical device could limit

drug delivery to the area immediately surrounding the device, avoiding side effects in the rest of the organism (Vermette et al., 2002). Various strategies of liposome deposition on surfaces are available such as immobilization by hydrophobic interactions, covalent linkage and specific binding (Brochu et al., 2004). Pasquardini et al. (2008) reported the prevention of bacterial adhesion and colonization of polymeric surfaces through the immobilization of liposomes on polystyrene material. The surface was functionalized based on the deposition of covalently coupled lipid structures from antibiotic loaded vesicles, using either deposition of cationic vesicles on negatively charged surfaces or formation of covalent linkages between functionalized lipids and amines enriched surfaces. The lipid film, which was deposited on the polymeric surface, was used for loading and delivering a specific active agent, which was rifampicin, in a cationic liposome, to *Staphylococcus epidermidis* (Pasquardini et al., 2008). An artificial bone scaffold combined with liposomes was recently developed for therapy and prevention of refractory bacterial infections (Zhu et al., 2010). The porous β-tricalcium phosphate (β-TCP) was combined with liposomal gentamicin to form a complex drug carrier, which could release an initial high dose of antibiotic from the matrix, and a further sustained release of free gentamicin from the liposome allowing treatment and prevention of post-operative osteomyelitis (Zhu et al., 2010).

Pathogenic bacteria secrete virulence factors such as toxins and lipases that actively damage cell membranes and tissues around infected wounds, while nonpathogenic bacteria do not (or not at high concentration) (DiRita et al., 1991; Zhang & Austin, 2005). On this basis a 'smart' wound dressing system modified with antimicrobials encapsulated on lipid vesicles was developed, which only released an encapsulated antimicrobial agent in the presence of pathogenic bacteria, without responding to commensal/harmless bacteria (Zhou et al., 2010). The specificity towards pathogenic bacteria is particularly desirable given the importance of the normal microflora in providing a natural defense against infection (Tagg & Dierksen, 2003). Importantly, this would minimize the evolutionary pressure for the selection of antibiotic resistant microorganisms and prolong the efficacy and shelf life of the encapsulated antimicrobial (Hecker et al., 2003). Figure 2 illustrates this responsive antimicrobial system.

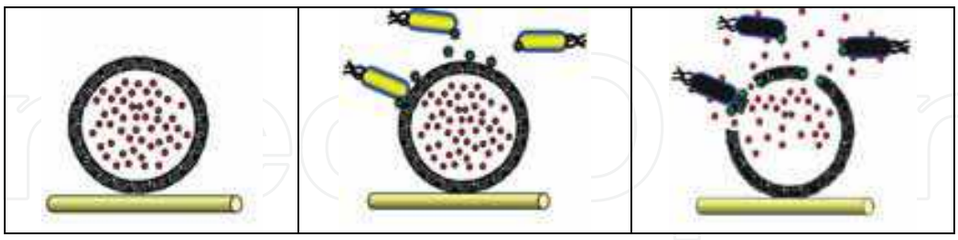


Fig. 2. Responsive antimicrobial system based on liposomal encapsulation of antimicrobials and drug release triggered by toxin secretion from pathogenic bacteria. Adapted with permission from Zhou et al., 2010. Copyright 2010 America Chemical Society.

Hydrogel matrices such as carbopol 940 or poly(ethylene glycol) gelatin incorporated liposomes improving the viscosity of the topical formulation and its retention time at the site of administration (Hosny, 2010). The bioadhesive properties of the gel ensured a sustained release of antibiotics from the liposomes. Alternatively, plain broad-spectrum antimicrobials, without any carriers, have been incorporated into devices (Tebbs & Elliott, 1993; Bach et al., 1999; Donelli et al., 2002; Zalewska & Ginalska, 2009; Francolini & Donelli,

2010). The coating of device surfaces with one or two antimicrobial substances or entrapping of these agents within the device material are approaches often used to obtain devices with different antimicrobial spectra and durations of the antimicrobial effect (Donelli & Francolini, 2001; Darouiche, 2008; Zilberman & Elsner, 2008). These are eluted with the aim of preventing biofilm formation by killing early colonizing bacteria. However, sufficient antibiotic must be incorporated for the "user-lifetime" of the device, and such incorporation must not damage the properties of the material (Danese, 2002). The technique of delivery must guarantee a rapid release of the antibiotic from the carrier and local drug levels well above the minimal inhibitory concentration (MIC). The drug release must be restricted to a limited period of time to prevent development of resistant bacterial strains and bactericidal should be favoured over bacteriostatic antibiotics (Schmidmaier et al., 2006). One of the main drawbacks of most available antimicrobial-coated devices is the burst release of the adsorbed antibiotics in the first few hours, followed by a long-lasting phase of slow release at low concentrations (Munson et al., 2004). This behaviour can develop antimicrobial resistance (Danese, 2002).

Antimicrobial polyurethane systems were developed containing two antibiotics, cefamandole nafate and rifampicin (RIF), selected by their action spectrum and their functional groups to interact with the suitably functionalized polymer (Ruggeri et al., 2007). In other similar instances, polyethylene glycol (PEG) was used as a pore forming agent (Kim et al., 2000; Meier et al., 2004). Although PEG is biologically inactive, the channels formed inside the polymeric matrix facilitated drug flow. Hence antibiotics released from these antimicrobial polyurethane systems inhibited the bacterial growth and exhibited a synergistic action when both cefamandole nafate and rifampicin antibiotics were present. In particular, PEG10000-containing polymer was active against the RIF-resistant *Staphylococcus aureus* strain up to 23 days. These results suggest that the combined entrapping of antibiotics and pore formers in these novel polymer systems could be promising to prevent bacterial colonization (Ruggeri et al., 2007). Figure 3 illustrates the prevention of microbial colonization on such surfaces.

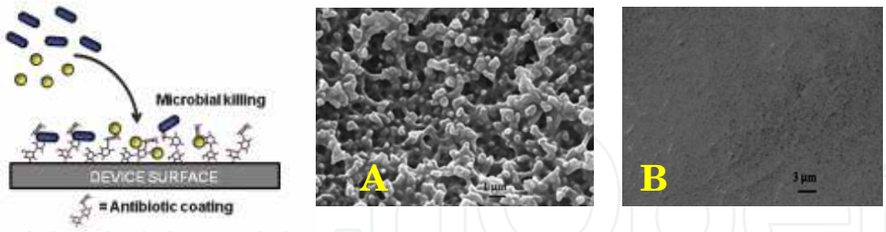


Fig. 3. Colonization of cocci (in yellow) and bacillus (in blue) on bare (A) or antibiotics-coated polyurethane surface (B). Adapted with permission from Ruggeri et al., 2007, Journal of Biomedical Materials Research, and from Francolini & Donelli, 2010, FEMS Immunology and Medical Microbiology. Copyright 2007 and 2010 John Wiley & Sons.

Hybrid antimicrobial biomaterials with potential to be applied as orthopaedic implants were recently prepared through immobilization of aminoglycoside antibiotics (amikacin or gentamicin) on hydroxyapatite ceramics (HAp), showing activity against *S. aureus*, *S. epidermidis*, *Pseudomonas aeruginosa* and resistance to biofilm formation (Zalewska & Ginalska, 2009). In fact, polymeric materials from both natural and synthetic origins are widely recognized as carriers for effective delivery of antimicrobial agents to treat the infections associated with orthopaedic implants. Resorbable polymeric materials such as

polylactides (Mader et al., 1997; Schmidmaier et al., 2006), copolymers of lactide and glycolide (Mader et al., 1997; Ambrose et al., 2003), polycaprolactone (Burd et al., 2001; Le Rey et al., 2003), hydroxyapatite and glass ceramics (Saito et al., 2002; Makinen et al., 2005; Zalewska & Ginalska, 2009), calcium sulfate (Nelson et al., 2002), and fibrin sealant implants (Mader et al., 2002) have already been investigated for use as antibiotic delivery systems. Prevention and treatment of osteomyelitis, particularly associated with orthopaedic implant surgery, have been the focus of many studies, since in most surgical procedures that include the incorporation of implants, the tissue-implant surface is especially prone to microbial contamination. Degradable polymer implant coating with antibiotics have been developed (Schmidmaier et al., 2006). For local antibiotic therapy, titanium K-wires to be implanted into the medullary canals of rat tibiae were coated with poly(D,L-Lactide) (PDLLA) loaded with gentamicin. Thereby, the onset of infections was prevented in 80-90% of animals thus treated (Schmidmaier et al., 2006). Since the PDLLA coating degrades by hydrolysis within 3−6 months of implantation with the products of degradation metabolized in the citric acid cycle (Hutmacher et al., 1996; Schmidmaier et al., 2001; Park et al., 2009), this local application of gentamicin from PDLLA-coated implants might support systemic antibiotic prophylaxis preventing implant-associated osteomyelitis.

Usnic acid as an alternative antimicrobial agent for device coating or impregnation has been loaded on polymer surfaces since it has the desirable properties of poor solubility in biological fluids and is not recomended for use in clinics for therapy. Polyurethanes adsorbed usnic acid and thereby there was inhibition of *S. aureus* biofilm formation (Francolini et al., 2004). Antiseptics have also been used to develop catheter materials (Brun-Buisson et al., 2004; Ostendorf et al., 2005; Rupp et al., 2005). A hydrophilic catheter incorporated with iodine, leading to a polyvinylpyrrolidone-iodine complex on the inner and outer surfaces of the catheter inhibited adhesion of *Staphylococcus* spp., *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*, during the time of iodine release (Jansen et al., 1992). Catheters incorporated with benzalkonium chloride also demonstrated a long-lasting antimicrobial activity against *Staphylococcus* spp., Gram-negative bacteria and *C. albicans* (Tebbs & Elliott, 1994). A polyurethane-based catheter impregnated with minute amounts of the antiseptic chlorhexidine and silver sulfadiazine was developed (Heard et al., 1998). This catheter was firstly coated only on the external surface and exhibited antimicrobial properties for nearly 15 days. A second generation of chlorhexidine-silver sulfadiazine was coated both internally and externally, and exhibited enhanced chlorhexidine activity, with a marked decrease in the colonization on these catheters (Brun-Buisson et al., 2004; Ostenford et al., 2005; Rupp et al., 2005).

Advantages of polymeric antimicrobial agents, when compared to conventional antimicrobial agents of low molecular weight, are their nonvolatile character, chemical stability, and low permeation through the skin of a man or animal. Thus, they may enhance the efficacy of some existing antimicrobial agents and minimize the environmental problems accompanying the residual toxicity of the agents, in addition to prolonging their lifetime (Akashi et al., 2001; Chen & Cooper, 2002; Gottenbos et al., 2002). Synthetic polymers with functional groups, especially when the functional group is a antimicrobial, active group, such as the quaternary nitrogen, are receiving considerable attention (Kenawy & Mahmoud, 2003; Li et al., 2006; Pereira et al., 2008; Melo et al., 2010).

Quaternary ammonium salts are commonly employed as disinfectants, and effective against a wide variety of Gram-positive and Gram-negative bacteria (Tapias et al., 1994; Campanhã et al., 1999; Gilbert & Moore, 2005; Carmona-Ribeiro et al., 2006). Various cationic and

antimicrobial architectures have been tested such as polyelectrolyte layers (Tiller et al., 2001; Thome et al., 2003; Codling et al., 2003; Cen et al., 2003; Li et al., 2006; Vieira & Carmona-Ribeiro, 2008), hyperbranched dendrimers (Chen & Cooper, 2000; Chen & Cooper, 2002; Abid et al., 2010) and long-chained amphiphiles (Abel et al., 2002; Haldar et al., 2005). The deposition of organic monolayers onto solid surfaces containing quaternary ammonium groups has been shown to prevent deposition and growth of bacterial biofilms (Kugler et al., 2005). Molecules with a net positive charge are able to kill microorganisms both in solution (Fidai et al., 1997; Friedrich et al., 2000) or upon attachment or adsorption to surfaces (Isquith et al., 1972; Endo et al., 1987; Tiller et al., 2001; Thome et al., 2003; Kugler et al., 2005; Pereira et al., 2008) or particles (Vieira et al., 2003; Vieira & Carmona-Ribeiro, 2008). Particularly interesting were the cationic liposomes (Tapias et al., 1994; Sicchierolli et al., 1995; Campanhã et al., 1999) or cationic bilayer fragments composed solely of dioctadecyldimethylammonium bromide or DODAB due to their intrinsic microbicidal property (Vieira & Carmona-Ribeiro, 2001; Lincopan et al., 2003; Lincopan et al., 2005).

Polymeric bactericides are more potent than their monomeric counterparts (Kenawy et al., 2007). Surfaces with cations deposited on them were shown to kill microbes upon contact in the 1980s (Speier & Malek, 1982) especially when treated with hydrophobic polycations (Klibanov, 2007). These cationic materials electrostatically attract a microorganism cell towards the treated surface, resulting in the puncturing of microbial cell envelope and subsequent cell death (Klibanov, 2007). Impregnation of polymers with quaternary ammonium compounds (QAC) was also achieved from deposition of alternate anionic and cationic polyelectrolyte layers where cetyltrimethylammonium bromide (CTAB) was the antimicrobial agent included in the cationic layer (Dvoracek et al., 2009). Films exposure to humidity allowed CTAB diffusion out of the film and bacterial growth inhibition in neighbouring regions. On silicon wafers, hybrid films, produced from spin-coating of a chloroformic solution of poly(methylmethacrylate) (PMMA) polymer and DODAB cationic lipid, exhibited remarkable antimicrobial activity against *E. coli* (Pereira et al., 2008). Antimicrobial PMMA/DODAB films are illustrated in Figure 4.

Fig. 4. PMMA films impregnated with a quaternary ammonium (QAC) lipid DODAB kill *E. coli* upon contact. In green, live, and in red, dead *E. coli* cells. Adapted with permission from Pereira et al., 2008. Copyright 2008 American Chemical Society.

Polymers of pyridinium derivatives were highly effective against Gram-positive bacteria (Kawabata & Nishiguchi, 1988). Pyridinium derivatives with alkyl bromides were covalently attached to glass slides and designed to create surfaces that kill airborne bacteria on contact (Tiller et al., 2001). These surfaces were able to kill more than 90% of deposited *S. aureus* cells and more than 99% of deposited *S. epidermidis*, *P. aeruginosa* and *E. coli* cells in a dry state. The bacteria cells were sprayed onto the surfaces to simulate the deposition of airborne bacteria. These tethered amphipatic polycations, as well as polimyxin B and soluble cationic antimicrobials, probably share a similar mechanism of attacking bacteria, by displacing the divalent cations that hold together the negatively charged surface of the

lipopolysaccharide network, thereby disrupting the outer membrane of Gram-negative bacteria. It is also possible that after destroying the outer membrane permeability barrier, the cationic groups of the tethered polymers further penetrate into the inner membrane, producing leakage (Vaara, 1992). Regarding Gram-positive bacteria, the action of immobilized polycations probably requires penetration of the cationic groups across the thick cell wall to reach the cytoplasmic membrane (Friedrich et al., 2000). Bromide salts of quaternized polyvinylpyridine (QPVP) with linear aliphatic chains of 2 and 5 carbon atoms were adsorbed onto silicon wafers, and lyzozyme molecules were adsorbed onto these polycations (Silva et al., 2009). The antimicrobial effect of lyzozyme bounded to the pyridinium derivative layers or to silicon wafers was evaluated with enzymatic assays using *Micrococcus luteus*. After 15 min of interaction with bacteria, pure QPVP with 5 carbons presented the best antimicrobial action, followed by pure QPVP with 2 carbons, mixtures of lyzozyme and QPVP with 5 carbons, pure lyzozyme and mixtures of QPVP with 2 carbons and the enzyme. When quaternary ammonium salts are linked to the polymer backbone by longer spacers, as in the case of QPVP with 5 carbons, their larger mobility favoured the biocidal effect. After one hour of interaction, all systems yielded 100% of death.

Antimicrobial silver particles alone or in combination with other metals or elements, such as carbon or platinum (Ranucci et al., 2003) or copper (Mclean et al., 1993) were also used to impregnate biomaterials (Davenas et al., 2002). Thin polymeric films prepared by the LbL method assembled oppositely charged polyelectrolytes, loaded with silver nanoparticles and presented differential cytotoxicity representing a good approach to manage microbial burden in wounds without impairment of wound healing (Agarwal et al., 2010). Impregnation of biodegradable polymer matrix with silver nanoparticles showed strong bactericidal effect against *E. coli*, *S. aureus* and *P. aeruginosa* (Bryaskova et al., 2010).

Silver has also been extensively used for the development of infection-resistant catheters. Polyurethane catheters in which carbon, silver and platinum particles are incorporated led to an electrochemically driven release of silver ions in the outer and inner vicinities of the catheter surface, demonstrating low catheter-related bloodstream infections (Ranucci et al., 2003). Silver-containing zeolite compounds received approval of Food and Drug Administration (FDA) for being used as food contact surfaces (Joerger, 2007). Silver-zeolites have already been incorporated into polymeric films yielding antimicrobial properties (Kamisoglu et al., 2008; Zampino et al., 2008; Fernández et al., 2010). Polymer composites of plasticized poly(vinylchloride) pellets with silver zeolites demonstrated activity against *S. epidermidis* and *E. coli* (Zampino et al., 2008), while polyurethane composites with silver zeolites showed antimicrobial action against *E. coli* (Kamisoglu et al., 2008) and polylactid acid-polylactide (PLA)/silver zeolite composites also presented activity against *S. aureus* and *E. coli*, with silver being effectively released from the films (Fernández et al., 2010). The silver-containing materials usually rely on the diffusion of Ag^+ ions from the material and their subsequent action on adherent microbes as broad spectrum antimicrobials (Lansdown, 2006).

2.2 Coatings with covalent modifications

The surfaces of medical devices can be simply modified with the application of external coating substances onto them. Thereby, alterations of material surfaces may lead to changes in specific and non-specific interactions with microorganisms and, thus, reduce microbial adherence. Medical devices made out of a material that would be antiadhesive or at least colonization resistant would be the most suitable candidates to avoid colonization and subsequent infection (Duran, 2000; Chandra et al., 2005; Hou et al., 2007).

One possible approach to inhibit microbial contamination of surfaces is to prepare a surface to which microbes find it hard to become attached. This is a preventive strategy, where the aim is to prevent microbial adhesion to the surface in the first place (Page et al., 2009). One well established method for preventing the adhesion of microbes, proteins and mammalian cells to surfaces is to coat them with a layer of poly(ethylene glycol) (PEG) (Page et al., 2009). PEG modification of polyurethane surfaces inhibited microbial adhesion (Park et al., 1998; Ostuni et al., 2001; Hou et al., 2007). The current method involves the deposition of a self-assembled monolayer, over a substrate, followed by functionalization of the monolayer with PEG. PEG polymeric surfaces are antimicrobial firstly because of the steric repulsion between PEG and the microbial cell envelope. The dynamic movement of PEG chains tethered to the surface, coupled with their lack of binding sites further hamper microbe adhesion (Page et al., 2009). For protecting stainless steel surfaces against protein and/or bacterial adhesion, thin films including the glycosidase hen egg white lysozyme (HEWL) and/or PEG were covalently bound to flat substrates pretreated with poly(ethylene imine) (PEI) (Caro et al., 2009). The ability of these modified surfaces to prevent protein adsorption and bacterial adhesion together with their biocide properties were tested employing bovine serum albumin (BSA), and the bacteria *Listeria ivanovii* and *Micrococcus luteus*. The cografting of PEG and HEWL resulted in a surface with both antiadhesive and antibacterial properties (Caro et al., 2009). Figure 5 illustrates these antiadhesive and antibacterial surfaces grafted with HEWL and PEG.

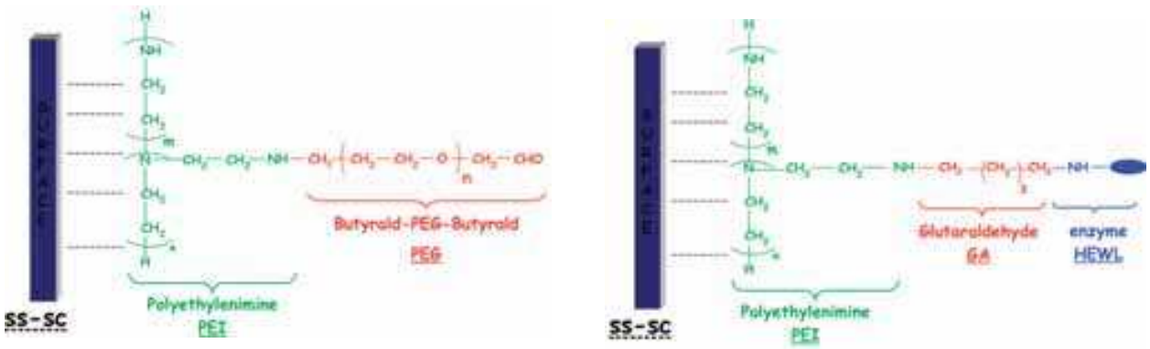


Fig. 5. Antiadhesive and antibacterial surfaces on stainless steel (SS) with graftings of poly(ethylene glycol) (PEG) or hen egg white lyzozyme (HEWL). Adapted with permission from Caro et al., 2009. Copyright 2009 American Chemical Society.

Inhibition of *C. albicans* biofilm formation was achieved by adding 6% polyethylene oxide (PEO) to polyurethane surfaces (Chandra et al., 2005). Similarly, biofilm formation by *C. albicans* and *Candida tropicalis* was inhibited on a silicone rubber voice prosthesis treated with a colloidal palladium/tin solution (resulting in a thin metal coat) (Dijk et al., 2000). On similar surfaces of hydrophobic polyurethanes modified with hydrophilic polyethylene oxide, adhesion of *S. epidermidis* was abolished (Patel et al., 2003; Patel et al., 2007). These modified surfaces significantly inhibited *S. epidermidis* biofilm formation over 48 h *in vitro* (Patel et al., 2007).

Polymers with zwitterionic head groups were also applied as surface coatings, preventing microbial contamination on surfaces. The zwitterionic nature of the polymer head group mimics that found in the lipid bilayer of biological membranes imparting biocompatibility and non-thrombogenic character to these materials. Several examples of this concept are

available from the literature such as polymers based on phosphorylcholine (Lewis, 2000; Rose et al., 2005; Hirota et al., 2005), sulfobetain and carboxybetaine (Cheng et al., 2007). The zwitterionic head groups increased hydrophilicity of the material, leading to reversible interactions between incident microbes and the surface and discouraging adhesion of cells, both mammalian and microbial (Cheng et al., 2007). Similarly, surfaces containing immobilized long-chain N-alkylated polyvinylpyridines and structurally unrelated N-alkylated polyethylenimines were reported to be lethal to *S. aureus*, *S. epidermidis*, *P. aeruginosa* and *E. coli* (Lin et al., 2002). The structure-activity analysis revealed that for surfaces to be bactericidal, the immobilized long polymeric chains have to be hydrophobic, but not excessively so, and positively charged.

Grafted or smeared on the surface, surfactants or polymers carrying electric charges could also modify the physico-chemical properties of the interface and decrease the binding ability of the colonizing organisms (Mireles et al., 2001). Synthetic vascular grafts such as polytetrafluoroethylene (PFTE) prostheses are easily accessible to pathogens after inserted into the patient. The lipophilicity of these PTFE grafts has been modulated with benzalkonium chloride (Harvey & Greco, 1981; Greco et al., 1982) or tridodecylmethylammonium chloride (Harvey et al., 1982), or incorporating drugs into biodegradable polymer carriers (Gollwitzer et al., 2003). Recently, new lipid-based formulations to incorporate antibiotics for anti-infective action in grafts were developed. In this case, PFTE grafts were coated with lipophilic agents such as poly-lactid acid or tocopherol acetate as carriers for gentamicin and teicoplanin, in order to release high drug concentrations locally and completely inhibit bacterial colonization on the implant (Matl et al., 2008). A recent study also reported the covalent attachment of quaternary ammonium groups to stainless steel and porous filter paper (cellulose) surfaces, through low-pressure plasma-enhanced functionalization (Jampala et al., 2008). The grafting of quaternary ammonium groups on these surfaces yielded stable and very efficient bactericidal properties, with activity against *S. aureus* and *Klebsiella pneumoniae*.

Another different and recent approach is the concept of modifying a surface with bacteriophages, in order to produce an antimicrobial surface (Curtin & Donlan, 2006). Bacteriophages are viruses that infect prokaryotic cells, which contain a core nucleic acid, usually double-stranded DNA (dsDNA), within a protein or lipoprotein capsid (Guttman et al., 2004; Hanlon, 2007). As obligate parasites of bacteria, the bacteriophages bind to microbial surfaces, injecting their genetic material and replicating within the bacterial host. If phage replication is a lytic process, it will result in the lysis of the host cell (Sulakvelidze et al., 2001). The characteristics of lytic phages, such as target specificity, rapid bacterial killing, and amplification at the site of infection, make them possible candidates as antimicrobial therapeutic agents (Deresinski, 2009). A phage-modified surface is certainly an interesting antimicrobial approach, especially because microorganisms currently resistant to antibiotics do not show resistance to phages. However, a few problems have to be considered. Firstly, the inherent specificity of phages to bacterial species, and further, bacteria can become resistant to phages (Stone, 2002). Thus, phage-treated surfaces should constantly be monitored. One study demonstrated the successful use of a developed wound dressing, containing lytic bacteriophages, to treat some skin infections that were not responding to conventional antimicrobial therapy (Stone, 2002). A biodegradable polymer wound dressing impregnated with ciprofloxacin, benzocaine, chymotrypsin, bicarbonate, and 6 lytic phages (Pyophage) with activity against *P. aeruginosa*, *S. aureus*, *E. coli*, *Streptococcus* spp. and *Proteus* spp. was also reported (Markoishvili et al., 2002). Another research showed the action of

catheters pre-treated with a coagulase-negative staphylococci phage reducing significantly *S. epidermidis* biofilm formation (Curtin & Donlan, 2006). Finally, the use of bacteriophages has been recently reported as a promising approach in the control of *S. epidermidis* and *P. aeruginosa* biofilm formation when catheters are pretreated with a cocktail of bacteriophages, thus reducing the 48-h mean biofilm cell density by 99.9%, even if few biofilm isolates were reported to be resistant to these phages (Fu et al., 2010). Approximate 90% reduction in both *Proteus mirabilis* and *E. coli* biofilm formation on bacteriophage-treated catheters when compared with untreated controls followed impregnation of hydrogel-coated catheter sections with a lytic bacteriophage (Carson et al., 2010).

2.3 Biodegradable antimicrobial materials

There has been a growing interest over the past few years in applications of biopolymers due to their renewable, sustainable and biodegradable properties (Zivanovic et al., 2007). One of the most popular biopolymers is chitosan. Chitosan is a cationic biopolymer obtained by N-deacetylation of chitin, which is known to be the second most abundant biopolymer in nature and is the major component of exoskeleton of crustaceans (Roberts & Wood, 2000). This biopolymer has been found to be nontoxic, biodegradable, biocompatible in addition to having antimicrobial characteristics (Park et al., 2002; Jayakumar et al., 2007). In view of these qualities, chitosan films have been used as a packaging material for the quality preservation of a variety of food products (Park et al., 2004). Blending of chitosan and polyethylene oxide (PEO) produced films with good antimicrobial effect against *E. coli* (Zivanovic et al., 2007). Chitosan-based films have the potential to be used in the food industry as active packaging materials to inhibit food-borne pathogens and in the pharmaceutical industry for controlled release of active compounds (Zivanovic et al., 2007; Noel et al., 2010).

Different theories have been put forward to explain the antimicrobial mode of action of chitosan such as chitosan interaction with intracellular targets, eg DNA (Rabea et al., 2003), chitosan chelating activity (Rabea et al., 2003) or chitosan perturbation of the cell membrane (Helander et al., 2001; Zakrzewska et al., 2005; Je & Kim, 2006). Others considered that a sequence of rather "untargeted" molecular events would take place simultaneously or successively. The initial contact between the polycationic chitosan macromolecule and the negatively charged cell wall polymers driven by electrostatic interaction between chitosan and teichoic acids in the cell wall would disrupt the equilibrium of cell wall dynamics, and cause ultimate cell death (Raafat et al., 2008).

Bioactive chitosan films can incorporate other antimicrobial agents, enabling to improve its antimicrobial efficacy (Quintavalla & Vicini 2002). A degradable chitosan sponge was loaded with the antibiotics amikacin or vancomycin for therapy after a traumatic injury or surgery with sustained release of the antibiotics for 72 hours, representing very high release levels needed for preventing early-stage infection (Noel et al., 2010). Chitosan-coated plastic films, alone or loaded with antimicrobial agents, were evaluated for their effect against *Listeria monocytogenes*, a food-borne pathogen with ability to survive and grow at refrigeration temperatures, tolerant to relatively high concentrations of salt and able to cause high fatality rate associated with listeriosis (Ye et al., 2008). These chitosan-coated films inhibited this pathogen growth in a concentration-dependent manner whereas chitosan-coated films impregnated with antibiotics were considerably more effective against *L. monocytogenes*. The antimicrobial activity of chitosan film proved against food pathogenic

bacteria (*E. coli*, *S. aureus*, *Salmonella typhimurium*, *L. monocytogenes* and *Bacillus cereus)* has also been enhanced by incorporation of garlic oil, potassium sorbate and nisin (Pranoto et al., 2005). Edible films or coatings are prepared from proteins, polysaccharides and lipids (Cagri et al., 2004) and reduce the risk of pathogen growth on food surfaces (Quattara et al., 2000; Pranoto et al., 2005; Seydim & Sarikus, 2006; Maizura et al., 2007). As chitosan is a potentially edible material, it has been used as a coating material for different types of foods (Coma et al., 2002; Coma et al., 2003; Zivanovic et al., 2005; Fernandez-Saiz et al., 2006). Incorporation of natural spices such as oregano, rosemary, garlic and lemongrass essential oils into edible films has been used to inhibit the growth of microorganisms (Quattara et al., 2000; Pranoto et al., 2005; Seydim & Sarikus, 2006; Maizura et al., 2007). Addition of essential oil of Mexican oregano (*Lippia berlandieri* Schauer) as antimicrobial agent to edible films of chitosan or starch inhibited *Aspergillus niger* and *Penicillium* spp. growth at low concentrations in the films hampering mould growth (Avila-Sosa et al., 2010).

Polymeric bioactive films laced with an assortment of antimicrobial agents, such as nisin (Kim et al., 2002; Lee et al., 2003; Mauriello et al., 2005; Nguyen et al., 2008), essential oils (Pranoto et al., 2005; López et al., 2007; Avila-Sosa et al., 2010) and bacteriocins (An et al., 2000; Mauriello et al., 2004; Ercolini et al., 2006; Ghalfi et al., 2006) have been described. Addition of the antimicrobial peptide nisin efficiently inhibited growth of *L. monocytogenes* in films of gelatin and corn zein (Ku & Song, 2007). Several reviews are available on preparation, characterization and determination of antimicrobial activity of these films and novel materials (Cutter, 2002; Quintavanalla & Vicini, 2002; Cagri et al., 2004; Cha & Chinnan, 2004; Cutter, 2006; Joerger, 2007; Dutta et al., 2009). Nisin has been the antimicrobial most frequently found in films for food packaging (Kim et al., 2002; Lee et al., 2003; Mauriello et al., 2005; Nguyen et al., 2008). Its small molecular size allows the production of films that release this peptide upon contact with food or liquid (Gill & Holley, 2000; Cutter et al., 2001). A self-assembled bacterial cellulose film containing nisin prevented *L. monocytogenes* and total aerobic bacteria growth on the surface of vacuum-packaged processed meat products (Nguyen et al., 2008). These cellulose pellicles were produced by *Gluconacetobacter xylinus* K3 and then impregnated with nisin, yielding active cellulose films with potential applicability as antimicrobial packaging films. Biodegradable polylactid acid (PLA) polymeric films impregnated with nisin also killed foodborne *L. monocytogenes*, *E. coli* O157:H7 and *Salmonella enteritidis* and was proposed as a good material to make bottles or films, or coatings for use in liquid or solid food packaging (Jin & Zhang, 2008). Similarly to nisin, some antimicrobial films have also been prepared from bacteriocins to prevent food contamination with *L. monocytogenes* (Mauriello et al., 2004; Ercolini et al., 2006; Ghalfi et al., 2006).

The desire for natural ingredients and the realization that plants harbour antimicrobial compounds have led to the production of a number of films with extracts from plants (Pranoto et al., 2005; Kim et al., 2006; Seydim & Sarikus, 2006). In fact, plants have exceptional ability to produce cytotoxic agents and there is an ecological rationale that antimicrobial natural products should be present or synthesized in plants following microbial attack to protect the producer from pathogenic microbes in its environment (Gibbons, 2005). Moreover, natural products are both fundamental sources of new chemical diversity and integral components of today's pharmaceutical compendium and more than 300 natural metabolites with antimicrobial activity have been reported in the period 2000-2008 (Saleem et al., 2010). As such, there has been an increase in the use of essential oils as an alternative to conventional synthetic antimicrobial agents. Essential oils that contain higher concentrations of phenolic compounds, such as carvacrol, eugenol, and thymol also

possess strong antibacterial properties against foodborne pathogens and display a wide range of other biological effects, including antioxidant and antimicrobial properties. The mode of action is considered to be the disturbance of the cytoplasmic membrane, disrupting the proton motive force, electron flow, and active transport, and/or coagulation of bacteria cell contents (Burt, 2004). López et al. (2007) prepared flexible films of polypropylene and polyethylene/ethylene vinyl alcohol copolymer added of the essential oil of cinnamon (*Cinnamomum zeylanicum*), oregano (*Origanum vulgare*) and clove (*Syzigium aromaticum*) and determined their activity against a wide range of microoganisms such as Gram-negative or -positive bacteria, moulds and yeasts showing specially more pronounced antifungal activities that persisted for more than two months after films preparation (López et al., 2007). Oregano and cinnamon essential oils were recently incorporated on the same polymeric material completely inhibiting *L. monocytogenes*, *Salmonella choleraesuis*, *C. albicans* and *Aspergillus flavus* growth (Gutiérrez et al., 2010).

The enzyme lysozyme has been another natural choice for the preparation of antimicrobial films (Park et al., 2004; Souza et al., 2010). Lysozyme is a food grade antimicrobial enzyme with bacteriostatic, bacteriolytic and bactericidal activity, particularly against Gram-positive bacteria, and efficient in controlling the growth of a great number of food pathogens (Souza et al., 2010). In humans, lysozyme is found in a wide variety of fluids, such as tears, breast milk, and respiratory and saliva secretions, as well as in cells of the innate immune system, including neutrophils, monocytes, macrophages, and epithelial cells participating of the innate defense response against invading microorganisms (Jolles & Jolles, 1984). This enzyme acts on bacteria by hydrolyzing the ß-1,4 glycosidic bonds between N-acetylmuramic acid (MurNAc) and N-acetylglucosamine (GlucNAc), resulting in degradation of peptidoglycan (PG), and subsequent microbial cell lysis (Schindler et al., 1977). The effective incorporation and release of lysozyme in chitosan films was used to reinforce the antimicrobial activity of chitosan (Park et al., 2004). Lysozyme has already been embodied in several biodegradable matrices yielding antimicrobial films and surfaces (Park et al., 2004; Fernández et al., 2008). In films of sodium caseinate lysozyme was released in a controlled manner so that sustained antimicrobial activity against *S. aureus* and *Micrococcus lysodeikticus* could be achieved (Souza et al., 2010).

3. Antimicrobial particles

3.1 Inorganic, metal and composite particles

The use of geological nanomaterials to heal skin infections has been known since the earliest recorded history, and specific clay minerals may prove valuable in the treatment of bacterial diseases, including infections for which there are no effective antibiotics, such as Buruli ulcer and multidrug-resistant infections (Williams & Haydel, 2010). A French green clay (rich in Fe-smectite) has been used in clinics for healing Buruli ulcer, a necrotizing fasciitis ('flesh-eating' infection) caused by *Mycobacterium ulcerans* (Falkinham et al., 2009). However, little is known about the physicochemical properties involved in the antibacterial activity of many minerals.

The mineral $CsAg0_2$ demonstrated broad bactericidal activity against pathogenic *Escherichia coli*, extended-spectrum beta-lactamase (ESBL) *E. coli*, *Salmonella enterica* serovar Typhimurium, *Pseudomonas aeruginosa* and *Mycobacterium marinum*, and a combined bacteriostatic/bactericidal effect against *Staphylococcus aureus*, penicillin-resistant *S. aureus*, methicillin-resistant *S. aureus* (MRSA) and *Mycobacterium smegmatis*, whereas another

mineral with similar structure and bulk crystal chemistry, $CsAr0_2$, had no effect on or even enhanced bacterial growth (Haydel et al., 2008). This mineral particulate heated to 200 or 500 ^oC still retained bactericidal activity, whereas heated or nonheated cation-exchanged $CsAg0_2$ no longer killed *E. coli*. Natural mineral mixtures were recently identified with antibacterial activity against a broad-spectrum of bacterial pathogens (Cunningham et al., 2010). Mineral-derived aqueous leachates also exhibited antibacterial activity, revealing that chemical, not physical, mineral characteristics were responsible for the observed activity. Chelation of these minerals with EDTA or desferrioxamine eliminated or reduced antibacterial action suggesting a role of an acid-soluble metal species, particularly Fe(3+) or other sequestered metal cations, in mineral toxicity. Testing the bactericidal effect of the heated product, many toxins were eliminated from consideration (e.g., microbes, organic compounds, volatile elements) and several redox-sensitive refractory metals that are common among antibacterial clays were identified (Williams & Haydel, 2010).

Inorganic active agents with antimicrobial activity can be based on a variety of inorganic nanostructured materials, such as titanium dioxide (Fu et al., 2005), silver (Jeong et al., 2005a; Rai et al., 2009) and silver-based nanostructured materials (Nishino & Kanno, 2008; Kittler et al., 2009), zinc oxide (Li et al., 2007), copper (Cubillo et al., 2006), gallium (Valappil et al., 2008) or gold (Park et al., 2006; Zhang et al., 2008) plus their composites (Sambhy et al., 2006).

Metallic and inorganic particles can be loaded into different organic carriers, like liposomes (Park et al., 2005), nano- and micro-capsules (Shim et al., 2002) or dendrimers (Raveendran et al., 2006) finding many applications in the industry of fabrics (Gorensek et al., 2010; Dastjerdi & Montazer, 2010), plastic (Roe et al., 2008; Xu et al., 2010) or biomaterials for drug delivery (Sharma et al., 2004; Pandey & Khuller, 2004; Hardi-Ianderer et al., 2008).

Titanium dioxide nanoparticles have antibacterial (Fu et al., 2005; Daoud et al., 2005) and self-cleaning properties (Bozzi et al., 2005). Copper nanoparticles embedded into submicron particles of sepiolite ($Mg_8\ Si_{12}\ O_{30}\ (OH)_4\ (H_2O)_4\ 8H_2O$) also demonstrated strong bactericidal properties (Cubillo et al., 2006) despite the lower antibacterial activity of copper when compared to silver nanoparticles (Pape et al., 2002). Grace & Pandian (2007) have used gold nanoparticles as carriers core coated by antibiotics like streptomycin, gentamycin and neomycin showing that gold nanocomposites have an intense antibacterial efficiency against various Gram-negative and Gram-positive bacteria, like *E. coli*, *P. aeruginosa*, *S. aureus* and *Micrococcus luteus*. They concluded that metal nanoparticles may change the metabolite pathway and the release mechanism of bacterial cells. Therefore, Au/drug nanocomposites were more efficient than drug alone. Park et al. (2006) loaded gold nanoparticles inside lipid liposomes, reporting an increased fluidity and permeability of barrier of the lipid and provided a kind of thermally sensitive liposome. Consequently, these systems showed potential as controlled release delivery system at particular temperatures (Park et al., 2006).

Silver has been employed since ancient times to fight infections and control spoilage (Tokumaru et al., 1984). Silver nanoparticles are antibacterial and multi-functional displaying low toxicity to human cells (Jeong et al., 2005a; Rai et al., 2009; Dastjerdi et al., 2009). Its antimicrobial effect at low concentrations is therapeutic against over 650 disease-causing organisms in the body (Jeong et al., 2005a,b; Lok, 2006). The ability of silver to prevent biofilm formation has also been demonstrated (Stobie et al., 2008). The most common synthesis of silver nanoparticles is the chemical reduction of a silver salt solution by a reducing agent such as $NaBH_4$, citrate, or ascorbate (Nickel et al., 2000; Leopold & Lendl, 2003; Khanna & Subbarao, 2003; Sondi et al., 2003).

Nanocomposites from polymers and silver particles have also been described; silver introduction into poly(styrene-co-acrylic acid) copolymer enhanced antibacterial activity by increasing ionic mobility (da Silva Paula et al., 2009). Silver nanoparticles inside phosphate-based, biodegradable ceramic particles were released in the presence of a growing microorganism (Loher et al., 2008). This effect was based on the microorganism requirements for mineral uptake during growth, creating a flux of calcium, phosphate and other ions to the microorganism. The growing microorganism dissolved the carrier releasing the silver nanoparticles. These biodegradable silver carriers in materials and polymer coatings enabled the creation of self-sterilizing surfaces (Loher et al., 2008). Metal nanoparticles with bactericidal effects can be affixed on various surfaces for prevention or protection purposes in specific applications, such as infirmaries, clothing, different surfaces, food protection and packing and water treatment (Ruparelia et al., 2008). Contrary to effects of ionic silver, the antimicrobial activity of colloidal silver particles is influenced by particle dimensions: the smaller the particles, the greater the antimicrobial effect due to its larger surface area to get in contact with the bacterial cells (Morones et al., 2005; Panacek et al., 2006; Pal et al., 2007).

In spite of several reports on the antimicrobial activity of silver nanoparticles (Sondi & Salopek-Sondi, 2004; Pal et al., 2007; Kim et al., 2007; Travan et al., 2009; Li et al., 2010), the mechanism of inhibitory effects of Ag ions on microorganisms is not yet fully elucidated. Some studies reported that the positive charge on the Ag ion would be crucial for antimicrobial activity (Dragieva et al., 1999; Hamouda et al., 1999; Dibrov et al., 2002). However, negatively charged silver nanoparticles also killed Gram-negative bacteria in a nanoparticle concentration –dependent manner (Sondi & Salopek-Sondi, 2004). The activity was also closely associated with the formation of "pits" in the cell wall of bacteria plus nanoparticles incorporation, accumulation and permeability increase of the bacterial cell membrane (Sondi & Salopek-Sondi, 2004). Damage of bacterial cell membrane with observations of pits and gaps on the cells was related to reduction of activity of some enzymes, leakage of sugars and proteins and cell death (Li et al., 2010). Silver nanoparticle shape also affected antibacterial effect against *E. coli*: truncated triangular silver nanoplates displayed stronger biocidal action than spherical or rod-shaped nanoparticles (Pal et al., 2007).

The use of microbial cells for the biosynthesis of nanosized materials has emerged as a novel approach for the synthesis of metal nanoparticles, particularly based on the main reaction of reduction/oxidation, where microbial enzymes with reducing or anti-oxidant properties are usually responsible for reduction of metal ions compounds into their respective metalic particles (Gericke & Piches, 2006a; Prathna et al., 2010). Metal particles can be obtained from biosynthesis by microorganisms and plants (Durán et al., 2005; Mohanpuria et al., 2008). Bacteria are known to produce inorganic materials either intra- or extracellularly. Microorganisms are considered as a potential biofactory for the synthesis of gold (Ahmad et al., 2003a; Ahmad et al., 2003b; Sastry et al., 2003; Gericke & Piches, 2006b), silver (Fu et al., 2000; Fu et al., 2006; Gericke & Piches, 2006a) and cadmium sulphide nanoparticles (Fu et al.,1999).

Silver nanoparticles were biosynthesized by *Klebsiella pneumoniae* (Shahverdi et al., 2007), *Staphylococcus aureus* (Nanda & Saravanan, 2009), *Escherichia coli* (Gurunathan et al., 2009) or *Brevibacterium casei* (Kalishwaralal et al., 2010). In combination with antibiotics, such as vancomycin and clindamycin, silver nanoparticles biosynthesized by *K. pneumoniae* exhibited enhanced activities against *S. aureus* (Shahverdi et al., 2007). Curiously, silver particles synthesized by *S. aureus* exhibited activity against resistant strains of *Staphylococcus*

sp. such as the methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE) (Nanda & Saravanan, 2009).

Fungi have also been widely studied for the biosynthesis of nanoparticles, and when compared to bacteria, they could be used as a source for the production of large amounts of nanoparticles. This is associated with the fact that fungi secrete large amounts of proteins, which directly translate to higher productivity of nanoparticle formation (Mohanpuria et al., 2008). Several fungus species have been employed to synthesize silver nanoparticles: *Phaenerochaete chrysosporium* (Vigneshwaran et al., 2006), *Phoma glomerata* (Birla et al., 2009), *Trichoderma viride* (Fayaz et al., 2010) and *Aspergillus clavatus* (Saravanan & Nanda, 2010; Verma et al., 2010). The biosynthesized nanoparticles showed antimicrobial activities alone (Verma et al., 2010; Saravanan & Nanda, 2010) or combined with antibiotics (Birla et al., 2009; Fayaz et al., 2010). Several plants have also been investigated for their role in the synthesis of nanoparticles (Torresday et al., 2002; Bali et al., 2006). The advantage of using plants to synthesize nanoparticles is that they are easily available, safe to handle and possess a broad variability of metabolites that may act in reduction reactions (Prathna et al., 2010). Gold (Torresday et al., 2002; Song et al., 2009), silver, nickel, cobalt, zinc and copper nanoparticles were obtained from biosynthesis by plants (Bali et al., 2006). Antibacterial properties of silver nanoparticles synthesized by plants like *Azadirachta indica* (Tripathi et al., 2009) or *Acalypha indica* (Krishnaraj et al., 2010) were recently reported. These particles were incorporated onto cotton disks, showing activity against *E. coli*. Leaf extracts were also used to synthesize silver nanoparticles with antimicrobial activity against water born pathogens such as *E. coli* and *Vibrio cholerae*.

3.2 Polymeric, lipid-based and hybrid particles

Biocompatible and biodegradable polymers have been extensively used in clinics for controlled drug release. Polymeric nanoparticles can be formed through self-assembly of copolymers, consisting of hydrophilic and hydrophobic segments or through linear polymers, such as poly (alkylacrylates) and poly (methylmethacrylate). A variety of biodegradable polymers have been used to form nanoparticles, including poly(lactic acid) (PLA), poly(glycolid acid) (PGA), poly(lactide-co-glycolide) (PLGA) and polyethylene glycol (PEG) (Sharma et al., 2004; Pandey & Khuller, 2004; Hardi-Ianderer et al., 2008; Zhang et al., 2010). Antimicrobial drugs can be adsorbed to the nanoparticles during polymerization or covalently conjugated to the nanoparticles surface after they are formed (Zhang et al., 2010). Polystyrene (PS) and poly(styrene-co-styrene sulfonate) particles coated with silver nanoparticles by gama-irradiation induced reduction of Ag ions yielding microbicidal composite particles against *S. aureus* (Oh et al., 2006). Another study described PS particles coated with poly(ethylene-co-butylene) copolymer containing a polymethacrylate block activated with amino or octyl bromide bactericidal moieties (Lenoir et al., 2005). The antimicrobial activity was directly related to the concentration of coated PS particles. Amphotericin B (AmB)-loaded poly(ε-caprolactone) nanospheres have therapeutic efficacy against *Leishmania donovani* (Espuelas et al., 2002) and *C. albicans* (Espuelas et al., 2003), when compared to free drug. Rifampicin-loaded polybutylcyanoacrylate nanoparticles have also shown enhanced antibacterial activity both *in vitro* and *in vivo* against *S. aureus* and *Mycobacterium avium* due to an effective delivery of drugs to macrophages (Skidan et al., 2003). Chitosan, a natural biopolymer, has antimicrobial and antifungal activity (Sudarshan et al., 1992; Jeon et al., 2001). Chitosan nanoparticles prepared

and loaded with antimicrobials or antibiotics (Portero et al., 2002) or metals (Qi et al., 2004) further enhance their antimicrobial action. Chitosan nanoparticles themselves or with adsorbed copper ions inhibited bacterial growth, with copper-loaded ones exhibiting higher activity due to higher surface charge density enhancing the affinity with the negatively charged bacteria membrane (Qi et al., 2004).. Polymeric particles of poly(4-vinyl pyridine), synthesized and chemically modified to become positively charged, were used for in situ silver and copper metal nanoparticle synthesis and presented antimicrobial action against *S. aureus*, *P. aeruginosa*, *E. coli* and *Bacillus subtilis* (Ozay et al., 2010).

Charged polymers or polyelectrolytes have often been used to produce nanostructured particles (Vieira & Carmona-Ribeiro, 2008; Melo et al., 2010). Cationic polymers can be potent antimicrobial agents (Codling et al., 2003; Kuegler et al., 2005). Cationic poly(arylene ethylene) conjugated polyelectrolytes have recently been reported as potent dark biocidals against *P. aeruginosa*, due to its high lipophilicity and the presence of accessible quaternary ammonium groups (Corbitt et al., 2009). The layer-by-layer (LbL) procedure (Decher & Hong, 1991) was used to produce hybrid antimicrobial and cationic particles from dioctadecyldimethylammonium bromide (DODAB) bilayer fragments (BF) supporting consecutive layers of the anionic polymer carboxymethylcellulose (CMC) and the cationic polyelectrolyte poly(diallyldimethylammonium) chloride (PDDA) (Melo et al., 2010). Both cationic microbicides, DODAB and PDDA, were combined in a single supramolecular assembly. These assemblies in form of small or large particles were obtained from small or large DODAB BF concentrations, respectively. The assemblies DODAB BF/CMC/PDDA exhibited potent antimicrobial activity against *P. aeruginosa* and *S. aureus*. The antimicrobial effect was similar for particles with 100 or 500 nm of mean diameter and dependent only on the amount of positive charges on particles (Melo et al., 2010). These hybrid particles also delivered AmB to *C. albicans* (Vieira & Carmona-Ribeiro, 2008). Cationic lipid, antibiotic and cationic polyelectrolyte nanostructured in each particle effectively attacked the fungus. Figure 6 shows these assemblies which were microbicidal with or without drug.

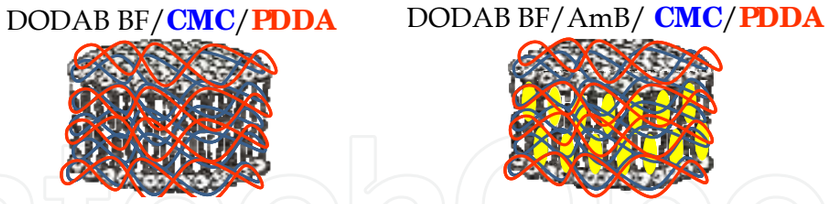


Fig. 6. Antimicrobial particles of cationic lipid (DODAB) and polyelectrolytes (CMC and PDDA), with or without amphotericin B (AmB). Adapted from Vieira & Carmona-Ribeiro, 2008 and adapted with permission from Melo et al., 2010. Copyright 2010 American Chemical Society.

Other interesting approaches were immobilization of bacteriophages active against a variety of food-borne bacteria by physisorption to modified, cationic silica particles (Cademartiri et al., 2010) or use of low-density lipoproteins (LDLs) from human plasma for delivering drugs inside the cells and treat intracellular infections (Hu et al., 2000). Biopolymer particles from lipoproteins can readily be obtained from human plasma by density gradient ultracentrifugation (Kader et al., 1998). A lipid core is surrounded by a monolayer of phospholipids, in which cholesterol and apolipoprotein-B are present. Other human plasma

lipoproteins, the high-density lipoproteins (HDLs) particles, have also been related with antimicrobial properties against *Staphylococcus epidermidis*, due to apolipoprotein A1 (Tada et al., 1993) or related with protection against trypanosome infection, due to native human HDLs containing haptoglobin-related protein (Hpr), apolipoprotein L-I (apoL-I) and apolipoprotein A-I (apoA-I) (Shiflet et al., 2005).

Dendrimers also possess several unique properties that make them a good nanoparticle platform for antimicrobial drug delivery. They are highly ordered and regularly branched globular macromolecules, with a core, layers of branched repeat units emerging from the core and functional end groups on the outer layer of repeat units (Grayson & Frechet, 2001). The branched nature of dendrimers provides huge surface area to size ratio, allowing great reactivity with microorganisms and drug loading capacity (Florence, 2005). Moreover, using antimicrobial drugs to synthesize dendrimers, they can become a potent antimicrobial for themselves. Dendrimer biocides may contain quaternary ammonium salts as functional end groups displaying greater antimicrobial activity against bacteria than small drug molecules, due to a high density of active antimicrobials on the dendrimer surfaces. The polycationic structure of dendrimer biocides facilitates the initial electrostatic adsorption to negatively charged bacteria, increasing membrane permeability and allowing more dendrimers to enter the bacterial cell (Chen et al., 2000; Chen & Cooper, 2002). Dendrimers have also been used as a vehicle to develop antimicrobial properties in textile fabrics (Ghosh et al., 2010; Klaykruayat et al., 2010). The poly(amidoamine) (PAMAM) dendrimer was modified to obtain quaternary ammonium groups as antimicrobial moieties or loaded with silver compounds. Both modified PAMAM structures were applied to cotton and nylon fabrics, exhibiting significant biocidal activity against *S. aureus* for each type of modified dendrimer (Ghosh et al., 2010). Cotton fabrics were impregnated with chitosan modified with antimicrobial PAMAM dendrimers, which imparted good activity against *S. aureus* to the fabrics when compared to fabrics with unmodified chitosan (Klaykruayat et al., 2010).

Dendrimeric structures were effective against mature biofilms, completely inhibiting *E. coli* (Hou et al., 2009) or *P. æruginosa* (Johansson et al., 2008) biofilm formation and inducing complete dispersion of both bacterial established mature biofilms, in a clear advantage with the majority of antimicrobial agents that are ineffective against already formed biofilms. Furthermore, dendrimers design can mimick the active conformation of linear antimicrobial peptides (Janiszewska & Urbanczyk-Lipkowska, 2007; Bruschi et al., 2010). The synthesis of a family of these peptidic dendrimers also showed antimicrobial properties against *S. aureus*, *E. coli* and *C. albicans* (Janiszewska & Urbanczyk-Lipkowska, 2007). Pini et al. (2005) reported the synthesis of an antimicrobial peptide in monomeric and dendrimeric form, obtaining activity against *E. coli* of the dendrimeric peptide much higher than that of the monomeric form. In fact, multimeric peptides offer several advantages with respect to their monomeric counterparts, due to improved stability in the presence of degrading enzymes as peptidases and proteases (Bruschi et al., 2010). A recent review reported the current state of therapeutic potential of the dendrimer systems in wound healing, bone mineralization, tissue repair, anticoagulant, anti-inflammatory and anticancer therapy (Gajbhiye et al., 2009).

Among the classical cationic surfactants, quaternary ammonium compounds (QACs) are the most useful antiseptics and disinfectants (Merianos, 1991; Frier, 1971). Since 1935 the antibacterial activity of the long-chained quaternary ammonium salts has been disclosed (Domagk, 1935). The fourth generation of quaternary antimicrobials included several mono-

and dialkyl dimethylammonium and polymeric quaternary ammonium salts (Petrocci et al., 1979). QACs are membrane active agents (Hugo & Frier, 1969; Furhop & Wang, 2004) that can cause lysis of spheroplasts and protoplasts suspended in sucrose (Salton, 1968; Davies & Field, 1969; Denyer, 1995; Russel et al., 1999). The cationic agents hypothetically react with phospholipid components in the cytoplasmic membrane, thereby producing membrane distortion and protoplast lysis under osmotic stress (Cabral, 1992; Russel & Chopra, 1996). Another possible mechanism for QACs action might be their inhibition and blockade of potassium channels in Gram-negative bacteria (Raja & Vales, 2009). The positive charge on microbial cells has been often correlated with the biocidal action (Isquith et al., 1972; Endo et al., 1987; Tapias et al., 1994; Sicchierolli et al., 1995; Fidai et al., 1997; Friedrich et al., 2000; Campanhã et al., 2001; Kugler et al., 2005). Dioctadecyldimethylammonium bromide (DODAB) (Tapias et al., 1994; Campanhã et al., 1999; Pereira et al., 2008; Melo et al., 2010), cetyltrimethylammonium bromide (CTAB) (Vieira & Carmona-Ribeiro, 2006; Dvoracek et al., 2009) and benzyldimethyldodecylammonium chloride (BDMDAC) (Ferreira et al., 2010) are some examples of quaternary ammonium compounds used to prepare antimicrobial particles.

Supramolecular assemblies of cationic lipid such as the bilayer fragments (BF) or the large bilayer vesicles have already been established as antimicrobial agents (Tapias et al., 1994; Sicchierolli et al., 1995; Martins et al., 1997; Campanhã et al., 1999; Carmona-Ribeiro, 2000; Campanhã et al., 2001; Lincopan et al., 2003; Carmona-Ribeiro, 2003; Carmona-Ribeiro et al., 2006; Vieira & Carmona-Ribeiro, 2008). In particular, DODAB is a cationic bilayer-forming synthetic lipid with a high chemical stability and well-described anti-infective properties (Carmona-Ribeiro et al., 2006). Adsorption of DODAB cationic bilayers onto bacteria cells changes the sign of the cell surface potential from negative to positive, with a clear relationship between positive charge on bacterial cells and cell death (Campanhã et al., 1999). DODAB BF also affected viability of *Candida albicans* (Campanhã et al., 2001; Vieira & Carmona-Ribeiro, 2006). Simultaneous determination of *C. albicans* viability and eletrophoretic mobility as a function of DODAB concentration also yielded good correlation between yeast surface charge and cell viability. Micromolar DODAB concentrations effectively killed bacteria, but DODAB concentrations required to kill yeast cells were much higher than those required to kill bacteria. Mammalian cells in culture were still more resistant to DODAB than fungi (Carmona-Ribeiro et al., 1997). DODAB indeed exhibits differential cytotoxicity, an important property for therapeutic uses. DODAB bilayer fragments (BF), by themselves or combined with particles, can produce lipid-based biomimetic assemblies or particles with antimicrobial activity. Synthetic amphiphile bilayers prepared from DODAB or other synthetic lipid, sodium dihexadecyl phosphate (DHP), were deposited onto oppositely charged polystyrene microspheres, forming bilayer covered lattices (Carmona-Ribeiro & Midmore, 1992). These homodisperse, DODAB bilayer-covered polystyrene sulfate (PSS) particles were combined with DNA, yielding supramolecular assemblies of PSS/DODAB/DNA (Rosa et al., 2008). Over a low concentration range of DNA, PSS/DODAB/DNA assemblies were cationic, colloidally stable and highly cytotoxic against *E. coli* cells, while from DNA concentration corresponding to charge neutralization, neutral or anionic assemblies, PSS/DODAB/DNA exhibited low colloid stability, high polydispersity and low antimicrobial activity.

Other important application of lipid based biomimetics refers to formulation of hydrophobic drugs. Aqueous miconazole (MCZ) aggregates were solubilized and/or colloidally stabilized by bilayer-forming synthetic lipids such as DODAB or DHP dispersions (Pacheco

& Carmona-Ribeiro, 2003). Drug particles became colloidally stable in the presence of charged bilayer fragments. At high drug to lipid molar proportion (P), when bilayer fragments covered drug particles, formulations were stable and highly effective. At low P, the drug became soluble in its monomeric form at the borders of the bilayer fragments (Vieira & Carmona-Ribeiro, 2001; Pacheco & Carmona-Ribeiro, 2003; Lincopan et al., 2003). The formulations were also effective and stable despite the toxicity due to the large concentration of cationic lipid (Lincopan et al., 2005; Lincopan et al., 2006). The results showed that synthetic bilayer fragments offered extra solubilization sites useful as receptive surfaces at their hydrophobic borders. The MCZ particles covered with DODAB BF showed a synergistic action between lipid and drug against *C. albicans* (Lincopan & Carmona-Ribeiro, 2006). At high P, addition of chaotropic K_2HPO_4 converted MCZ aggregates into negatively charged particles with affinity for cationic lipid, which then surrounded each drug particle with a cationic layer. In these formulations DODAB and MCZ acted synergistically against yeast. Biomimetic PSS/DODAB/DNA and MCZ drug particles are illustrated in Figure 7.

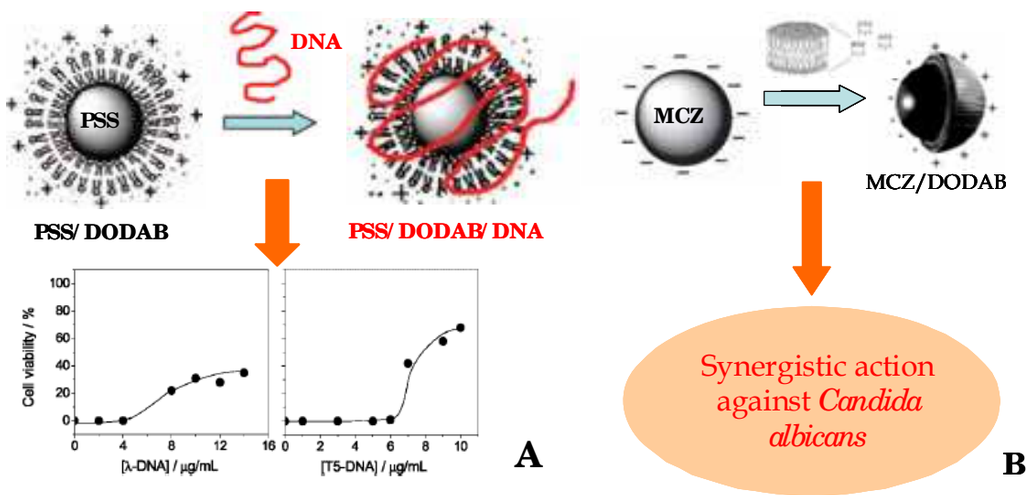


Fig. 7. Biomimetic particles: PSS/DODAB/DNA against *E. coli* (A); MCZ/DODAB against *C. albicans* (B). Adapted with permission from Rosa et al., 2008. Copyright 2008 American Chemical Society. Adapted with permission from Lincopan & Carmona-Ribeiro, 2006. Copyright 2006 Oxford University Press.

Lipids such as fatty acids, triglycerides, steroids, partial glycerides and waxes can also be used to produce solid nanoparticles (Zhang et al., 2010). As in oil-in-water nanoemulsions where a dispersed oil phase is stabilized in a water phase by an emulsifying layer of surfactant, nanoparticles composed of solid lipids such as stearic acid or solid lipid nanoparticles (SLN) (Müller et al., 2000) have been stabilized with polymers or surfactants such as poloxamer 188, polysorbate 80, lecithin, polyglycerol methylgluco distearate, sodium cocoamphoacetate or saccharose fatty acid esters and used to carry drugs, peptides or proteins (Martins et al., 2007). Advantages of SLN are their composition (biocompatible compounds), the fast and effective production process, including the possibility of large scale production, the avoidance of organic solvents in the production procedures, and the possibility to produce concentrated lipid suspensions. However, the drug loading capacity of conventional SLN is limited because of the formation of a perfect lipid crystal matrix and

other colloidal structures such as micelles, liposomes, mixed micelles and drug nanocrystals might be also present in the aqueous dispersion (Wissing et al., 2004). The preparation of SLN involves a first step of emulsification in hot water by stirring 10% of melted solid lipid such as stearic acid, 15% of surfactant and up to 10% of co-surfactant via microemulsions. Next, the warm microemulsion is dispersed under stirring in excess cold water. Finally, ultrafiltration or liophylization remove water excess and increases the SLN concentration (Fundaro et al., 2000; Igartua et al., 2000; Mehnert & Mäder, 2001).

SLNs are considered good drug carriers to obtain sustained release of antibiotics (Faustino-Vega et al., 2009; Han et al., 2009). SLNs can act as promising carriers for sustained ciprofloxacin release in infections (Jain & Banerjee, 2008) or to enhance the bioavailability of tobramycin from antibiotic-loaded SLN in the aqueous humor for topical ocular delivery (Cavalli et al., 2002). SLNs also represent a good carrier for intracerebral delivery of drugs, since these nanocarriers can not only mask the blood brain barrier limiting characteristics, but may also protect the drug from chemical and enzymatic degradation (Tiwari & Amiji, 2006). Besides, reduction of toxicity of drugs to peripheral organs can also be achieved with the SLN delivering the drugs directly to the central nervous system. Another possible application of SLNs is to deliver azole antifungal drugs to superficial fungal infection patients (Gupta et al., 2008). SLNs can also facilitate the delivery of anti-tuberculosis drugs such as rifampicin, isoniazid and pyrazinamide to the lungs as well as to the lymphatic system (Pandey & Khuller, 2005). Nimje et al. (2009) reported the selective delivery of rifabutin, another antituberculosis drug, to alveolar tissues, using drug-loaded solid lipid nanoparticles, increasing the therapeutic margin of safety and reducing side effects.

4. Liposomes in antimicrobial chemotherapy

Many infections are localized within phagocytic cells in the reticuloendothelial system (liver and spleen), in the blood stream, or in granuloma in various tissues and are possibly targets for liposomal drug delivery and therapy (Richarson, 1983). Examples of such infectious diseases are brucellosis, leprosy, tuberculosis, and listeria, all of them caused by intracellular bacteria.

Liposomes have been extensively used as carriers of antimicrobial and antineoplastic drugs (Lopez-Berestein, 1987). They are usually produced from naturally occurring, biodegradable and non-toxic phospholipids (Furneri et al., 2000). Liposomes have been designed to release drugs into an extracellular or intracellular compartment to reach their site of action (Fielding, 1991). The ability of liposomes to alter drug distribution depends largely on their size and surface properties (Fielding, 1991). Thus, liposomal encapsulation of antibiotics helps to increase their therapeutic index with mode of action related to increasing the drug concentration at the site of infection and/or reducing its toxicity (Schiffelers et al., 2001a). Organs rich in cells from the reticuloendothelial system (RES) preferentially take up liposomes, e.g. liver, spleen, lung and bone marrow (Gregoriadis, 1976a; Gregoriadis, 1976b). Targeting of liposomal antibiotic to bone marrow might achieve a high concentration of the drug in bone tissues. For extracellular bacteria, the enhanced antibacterial effect may be due to a fusion mechanism of the liposomal formulation with bacteria. The phagocytosis of antibiotic-loaded liposomes yields therapeutic intracellular drug concentrations and consequently enhanced killing of intracellular microorganisms, such as *S. aureus*, *E. coli*, *Brucella abortus* and *Mycobacterium avium* (Schiffelers et al., 2001a).

Most studies regarding liposomal antibiotics deal with aminoglycosides, quinolones, polypeptides, and β-lactams (Drulis-Kawa & Dorotkiewicz-Jach, 2010). The many advantages of liposomes as antibiotic carriers are improved pharmacokinetics and biodistribution, decreased toxicity, enhanced activity against intracellular pathogens, target selectivity, enhanced activity against extracellular pathogens, and efectiveness in overcoming bacterial drug resistance. The variety of liposomal formulations allows the design of effective antibiotic formulations and subsequent therapeutic success (Abeylath & Turos, 2008; Jia et al., 2008).

Traditional antibiotic therapy of staphylococcal osteomyelitis by a single drug or a drug combination is ineffective in producing complete sterilization of infected bones. Ciprofloxacin and vancomycin were encapsulated in a cationic, anionic or neutral liposomal formulation (Kadry et al., 2004). Cationic liposomes entrapped the highest percentage of antibiotics, and enhanced antibacterial activity above that of the free antibiotics; they were used for therapeutic trials to treat chronic staphylococcal osteomyelitis induced in rabbits. These liposomal formulations showed much lower nephrotoxicity than that induced by free drugs. Several other papers describe liposomal formulations against pathogenic microorganisms such as *P. æruginosa* (Okusanya et al., 2009), *K. pneumoniæ* (Gubernator et al., 2007), *E. coli* and *S. aureus* (Beaulac et al., 1998). The antibiotics chosen for encapsulation were mostly fluoroquinolones and aminoglycosides.

Encapsulation of gentamicin in liposomes can be used to achieve intracellular delivery and broaden the clinical utility of this drug. pH-dependent liposomal fusion with cells could be achieved due to the presence of phosphatidylethanolamine (PE) and the pH-sensitive lipid N-succinyldioleoyl-PE (Cordeiro et al., 2000). The pharmacokinetics and biodistribution of the free and liposomal gentamicin were examined in mice bearing a systemic *Salmonella enteric* serovar Typhimurium infection. Encapsulation of gentamicin in pH-sensitive liposomes significantly increased the concentrations of the drug in plasma compared to those of free gentamicin.

Liposomes of DMPC/CHOL (molar ratio 2:1) containing gentamicin showed better activity against *P. æruginosa* than the free drug (Rukholm et al., 2006). For a highly resistant *P. æruginosa* strain there was a 16-fold reduction in MIC for the liposomal gentamicin. Similar results in MIC reduction were obtained for liposomes of DPPC/CHOL (molar ratio 2:1) containing amikacin, gentamicin, and tobramicin (Mugabe et al., 2006). Long-circulating liposome encapsulated gentamicin demonstrated superior antibacterial activity over the free drug in a single-dose study of immunocompetent rats with *K. pneumoniæ* pneumonia (Schiffelers et al., 2001b). Multilamellar liposomes carried gentamicin for treatment of mice lethally infected with *Brucella abortus* (Vitas et al., 1997). The use of free or liposomal gentamicin in liposomes with a negative net charge did not produce a protective effect. Only the cationic liposomes had a therapeutic effect against infection. Pulmonary delivery of rifampicin encapsulated in liposomes was reported (Deol & Kuller., 1997; Vyas et al., 2004; Zaru et al., 2007; Changsan et al., 2009). Lung-specific Stealth liposomes made of phosphatidylcholine, cholesterol, dicetylphosphate, O-steroyl amylopectin and monosialogangliosides/ distearylphosphatidylethanolamine-poly (ethylene glycol) 2000 for the targeted delivery of anti-tuberculosis drugs to the lung have been described (Deol & Kuller, 1997). Modification of surface of stealth liposomes by tagging O-stearylamylopectin resulted in the increased affinity of these liposomes towards lung tissue of mice. Regarding tissue distribution, these liposomes showed more accumulation in lungs than in reticuloendothelial system of the normal and tuberculous mice. Isoniazid and rifampicin

encapsulated in liposomes were less toxic to peritoneal macrophages than the free drugs. The same formulations administered at one-third of the recommended doses showed a sustained release of the drugs in the plasma (5 days), lungs, liver and spleen (7 days) (Labana et al., 2002). Vyas et al. (2004) formulated aerosolized liposomes incorporating rifampicin via a cast-film method employing egg phosphatidylcholine- and cholesterol-based liposomes. Liposomes coated with alveolar macrophage-specific ligands demonstrated preferential accumulation in alveolar macrophages, maintaining high concentrations of rifampicin in the lungs even after 24 h after inhalation. Other tuberculostatic drugs such as pyrazinamide (El-Ridy et al., 2007) and rifabutin (Gaspar et al., 2008) were also formulated in liposomes stressing the great versatility and potential of the nanocarriers. Rifampicin-encapsulating liposomes were nontoxic to respiratory associated cells, including bronchial epithelial cells, small airway epithelial and alveolar macrophages (Changsan et al., 2009). Furthermore, the liposomes did not activate alveolar macrophages to produced interleukin-1, tumor necrosis factor-α, or nitric oxide at a level that would cascade to other inflammatory effects. The MIC against *Mycobacterium bovis* was smaller for liposomes containing rifampicin than for free rifampicin.

Liposomal formulations for important antifungal drugs such as amphotericin B (AmB) were first described by Lopez-Berestein and coworkers (Lopez-Berestein, 1987). Systemic fungal infections are often the cause of mortality in patients with hematological malignancies and certain other conditions associated with profound immunosuppression. The majority of such infections are caused by *Aspergillus* and *Candida* species (Potter, 2005). Voriconazole and lipid-associated AmB have been shown to be effective in the first-line therapy (Potter, 2005). Nebulized liposomal AmB formulations are effective, safe, and convenient for the prevention of *Aspergillus* infection in lung transplant patients (Monforte et al., 2010). A novel method was developed to incorporate polyene antibiotics, nystatin and AmB, into liposomes prepared from the mixture of phosphatidylcholine and cholesterol (7: 3) or phosphatidylcholine, cholesterol, and cardiolipin (7: 3: 1) plus the amphiphilic polymer N-vinylpyrrolidone showing higher antifungal activity than non-immobilized antifungal antibiotics (Yamskov et al., 2008). Other water-soluble complexes of AmB and polyvinylpyrrolidone were compared with AmB for antifungal activity, and were less haemolytic and cytotoxic than AmB showing cytotoxicity similar to AmBisome (Charvalos et al., 2006). AmB-loaded cationic liposome gels were formulated with 1, 2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1, 2-dioleoyl-3-trimethylammonium-propane (DOTAP), and cholesterol (CH) at a molar ratio of DOPE: DOTAP: CH of 4:5:1 in thermosensitive gel composed of poloxamer 407 and poloxamer 188. AmB-loaded cationic liposome gels were more stable and less toxic than free AmB. These gels containing cationic liposome may become useful for vaginal delivery of AmB (Kang et al., 2010).

Disadvantages of liposomal antibiotics are associated with chemical and physical instability mainly due to the hydrolysis of ester bonds or the oxidation of unsaturated acyl chains of the lipids used to construct the liposomal vesicles (Sharma & Sharma, 1997; Storm & Crommelin, 1998; Carmona-Ribeiro, 2003). Besides hydrolysis, peroxidation of unsaturated acyl chain bonds is also possible (Storm & Crommelin, 1998). Oxidation and/or hydrolysis can be prevented by adding antioxidant components or by freeze-drying or by storage at low temperature (Storm & Crommelin, 1998). The physical instability of liposomal drugs leads to drug leakage from the lipid vesicles. Under physiological conditions, stability is usually low and depends on the interaction of the liposomal membranes with components of body fluids (Gregoriadis, 1995). This is a very unfavourable situation, especially as the

best results of antibacterial activity of liposomal drugs in vitro are observed for positively charged or fluid liposomes (Drulis-Kawa et al., 2006). The presence of anionic lipids in liposomal vesicles also favours the binding of serum proteins to the vesicle surface (Briones et al., 2008).

Encapsulation efficiency depends on the type of lipids and on the hydrophobic-hydrophilic character of the drug. There are several instances of low encapsulation efficiency of antibiotics depending on type of the lipid. Gubernator et al. (2007) obtained meropenem and gentamicin (hydrophilic drugs) encapsulation efficiency in the range of 2.7–5.7% for a cationic fluid formulation. Lutwyche et al. (1998) showed that 25–33% of total gentamicin was associated with the outer surface of anionic liposomes composed of DOPE lipid, so a gentamicin encapsulation capacity of 2.8% was obtained in the anionic formulation DOPE/DOPS/PEG. Low encapsulation efficiency was also obtained by others (Lutwyche et al., 1998; Omri & Ravaoarinoro, 1996) making liposomal formulations much more expensive than conventional antibiotic treatment (Kshirsagar et al., 2005).

Since the major requirement to form a supramolecular assembly of the bilayer type is a cylindrical molecular geometry (Israelachvili et al., 1977), bilayer vesicles and liposomes can be obtained not only from expensive phospholipids but also from several other synthetic amphiphiles such as dialkyldimethylammonium bromide or chloride (Kunitake et al., 1977), sodium dihexadecylphosphate (Mortara et al., 1978, Carmona-Ribeiro et al., 1991) and many other molecules (Furhhop & Fristch, 1986; Segota & Tezak, 2006). For synthetic lipids such as dioctadecyldimethylammonium bromide (DODAB), chemical stability is superior to the one exhibited by the phospholipids since the hydrocarbon chains are saturated and ester functionalities are absent from DODAB chemical structure. The properties and applications of vesicles and bilayer fragments composed solely of synthetic lipids have been reviewed in the literature (Carmona-Ribeiro, 1992; Carmona-Ribeiro, 2001; Carmona-Ribeiro, 2003; Carmona-Ribeiro, 2006; Carmona-Ribeiro, 2007; Carmona-Ribeiro, 2010a; Carmona-Ribeiro, 2010b).

DODAB bilayers adsorb or become adsorbed onto negatively charged biomolecules such as proteins (Carvalho & Carmona-Ribeiro, 1998; Lincopan & Carmona-Ribeiro, 2009), DNA (Kikuchi & Carmona-Ribeiro, 2000; Rosa et al., 2008), biological structures such as microorganisms (Martins et al., 1997; Campanhã et al., 1999; Campanhã et al., 2001; Pacheco et al., 2004; Carmona Ribeiro, 2006) or mammalian cells (Carmona-Ribeiro et al., 1997) or drugs (Vieira & Carmona-Ribeiro, 2001; Lincopan et al., 2003; Pacheco & Carmona-Ribeiro, 2003; Lincopan et al., 2005; Carmona-Ribeiro, 2006; Lincopan & Carmona-Ribeiro, 2006; Vieira et al., 2006; Vieira & Carmona-Ribeiro, 2008). In antimicrobial chemotherapy, DODAB revealed excellent microbicidal properties (Vieira & Carmona-Ribeiro, 2001; Pacheco & Carmona-Ribeiro, 2003; Lincopan et al., 2003; Lincopan et al., 2005; Vieira et al., 2006; Carmona-Ribeiro, 2006; Lincopan & Carmona-Ribeiro, 2006; Vieira & Carmona-Ribeiro, 2008) besides outstanding versatility to formulate several antimicrobial drugs (Vieira & Carmona-Ribeiro, 2001; Lincopan et al., 2003; Pacheco & Carmona-Ribeiro, 2003; Lincopan et al., 2005; Vieira et al., 2006; Lincopan & Carmona-Ribeiro, 2006; Carmona-Ribeiro, 2006; Vieira & Carmona-Ribeiro, 2008). AmB and MCZ self-assemble and solubilize at hydrophobic sites of DODAB bilayer fragments in water solution exhibiting *in vivo* therapeutic activity (Vieira & Carmona-Ribeiro, 2001; Pacheco & Carmona-Ribeiro, 2003; Lincopan et al., 2003; Lincopan et al., 2005; Vieira et al., 2006; Carmona-Ribeiro, 2006). In order to formulate hydrophobic drugs with the DODAB lipid at high drug-to-lipid molar ratios, the "sticky" property of chaotropic dihydrogen phosphate anion converted MCZ or

AmB drug particles into negatively charged particles (Figure 7). Thereafter, anionic drug particles could be coated by the DODAB cationic lipid (Lincopan & Carmona-Ribeiro, 2006; Vieira et al., 2006). These formulations were tested against *Crytpococcus neoformans* and *Candida albicans* and were very effective. Coalescence of bilayer fragments around drug granules encapsulated drug particles at high drug-to-lipid molar ratios (Pacheco & Carmona-Ribeiro, 2003; Lincopan & Carmona-Ribeiro 2006; Vieira et al., 2006; Vieira & Carmona-Ribeiro, 2008). *In vivo* activity of the DODAB/AmB formulation against systemic candidiasis was evaluated from survival and tissue burden experiments in comparison to the classical drug formulation Fungizone (Lincopan et al., 2003). Effective AmB dose in the novel DODAB/AmB formulation was lower than AmB dose in Fungizone but gave the same therapeutic result: 100% survival (Lincopan et al., 2003). From tissue burden experiments, DODAB/AmB efficacy was also equivalent to the one exhibited by Fungizone regarding elimination of *Candida albicans* colonization in spleen and kidneys. In contrast to Fungizone, which is the traditional AmB formulation using deoxycholate, the novel formulation exhibited low nephrotoxicity (Lincopan et al., 2005). Synthetic and charged bilayer fragments are opening new perspectives for delivery of water insoluble drugs. In the specific case of the synthetic cationic lipid DODAB, bilayer fragments present antimicrobial activity, solubilize fungicides such as AmB and MCZ, stabilize hydrophobic drug particles, are therapeutically effective *in vivo*, and sometimes exhibit synergism with the drug carried.

5. Antimicrobial peptides

Antimicrobial peptides (AMPs) are widely distributed in nature, being produced by bacteria, plants, and a wide variety of animals – both vertebrates and invertebrates (Zasloff, 2002; Brogden, 2005; Pereira, 2006; Rossi, 2008). These compounds are also considered to be key players in innate immunity against microorganisms (Devine et al., 2002; Song et al., 2005). Although AMPs produced by animal and plants and those produced by bacteria certainly function in entirely different settings, the production of bacterial AMPs may also be thought of as a type of defense, since the peptides kill invading bacteria that compete with the AMP-producer for nutrients. The AMPs produced by bacteria seem overall to be more potent than the ones produced by eukaryotes, the former peptides being active at pico- to nanomolar concentrations and the latter at micromolar concentrations (Fimland et al., 2005). AMPs are generally small peptides consisting of 5-50 amino acid residues and are highly positively charged (Hancock, 1998) amphipathic molecules with well defined hydrophobic and hydrophilic regions (Zasloff, 2002; Toke, 2005). AMP´s found in nature exhibit a wide variety of structures and amino acid sequences with amphiphilic nature and positive charge as the only common factors between them (Melo et al., 2009). These properties permit the peptide to fold into an amphiphilic structure in three dimensions, often upon contact with membranes, so they form separate patches rich in positively charged and hydrophobic amino acids. Folded peptides fall into four broad structural groups: β-sheet peptides stabilized by two to four disulfide bridges (for example, human α- and β-defensins, plectasin or protegrins); α-helical peptides (for example, LL-37, cecropins or magainins); extended structures rich in glycine, proline, tryptophan, arginine and/or histidine (for example, indolicidin); and loop peptides with one or disulfide bridge (for example, bacteriocins) (Hancock & Sahl, 2006). Among the bacteriocins of Gram-positive bacteria, there is a particular group, the lantibiotics (lanthionine-containing peptide antibiotics), which are characterized by thioether-based intramolecular rings resulting from

post-translational modifications of serine (or threonine) and cysteine residues (for example, nisin and mersacidin) (McAuliffe et al., 2001). Lanthionine rings, some of which represent conserved binding motifs for recognition of specific targets, create segments of defined spatial structures in the peptides (Hsu et al., 2004). These ring structures also provide stability against proteases and against the antigen-processing machinery, since antibodies against highly cross-bridged antibiotics are very difficult to obtain.

Hundreds of peptide antibiotics have been described in the past half-century (Perlman & Bodansky, 1971; Kleinkauf & Dohren, 1988; Hancock et al., 1995). AMPs belong to two classes. They can be nonribosomally (gramicidins, polymyxins, bacitracins, glycopeptides, etc.) or ribosomally synthesized peptides. The former are often drastically modified and are largely produced by bacteria, whereas the latter are produced by all living species (including bacteria) as a major component of the natural host defense molecules of these species (Perlman & Bodansky, 1971; Kleinkauf & Dohren, 1988).

Non-ribosomally synthesized peptides can be described as peptides elaborated in bacteria, fungi, and streptomycetes that contain two or more moieties derived from amino acids (Perlman & Bodansky, 1971; Kleinkauf & Dohren, 1988). By definition even the longer peptidic molecules in this class are made on multienzyme complexes rather than being synthesized on ribosomes. Many of the antibiotics used in our society are peptide derived. For example, the natural penicillins can be dissected into residues of mono substituted acetic acid, L-cysteine and D-valine, while cephalosporin C, the basic building block of many semi synthetic cephalosporins comprises D-a-aminoadipic acid, L-cysteine, a,b-dehydrovaline, and acetic acid. The glycopeptides class of antibiotics including vancomycin and teicoplanin have sugar-substituted peptide backbones (Hancock & Chapple, 1999). Another example is daptomycin lipopeptide, an important reserve antibiotic against multiple resistant Gram positive bacteria.

Cationic peptides such as polymyxin B (net charge of +5) and gramicidin S (net charge of +2) exhibit different selectivities. The first is selective to Gram-negative bacteria whereas the second exhibited activity against Gram-positive and Gram-negative bacteria plus *Candida albicans* (Kondejewski et al., 1996). The cationic antimicrobial peptides act on cells by self-promoting their uptake across the cytoplasmic membrane interfering with the cytoplasmic membrane functionality as a barrier. In contrast, the gram-positive-specific antibiotic bacitracin works by inhibiting the transfer of cytoplasmically synthesized peptidoglycan precursors to bactoprenol pyrophosphate. Other antibiotic peptides of nonribosomal origin, the streptogramins, are protein synthesis inhibitors (Hancock & Chapple, 1999).

Ribosomally synthesized peptides are produced by eukaryotes and represent crucial components of their defense systems against microorganisms, being widely distributed in nature and produced by mammals, birds, amphibians, insects, plants, and microorganisms. Although they form a diverse group of peptides as judged by their primary structures, they are often cationic, amphiphilic and most of them kill bacteria by permeabilizing their cell membranes. Their positive charge presumably facilitates interactions with the negatively charged bacterial phospholipid-containing membranes and or acidic bacterial cell walls, whereas their amphiphilic character enables membrane permeabilization. Classification from chemical functionalities may be used for these AMPs from a high content of a certain amino acid, most often proline, intramolecular disulfide bridges, and content of α-helical structure (Hancock & Chapple, 1999; Papagianni, 2003).

Antibiotics primarily generated by bacteria and fungi have led to dramatic improvement in the ability to treat infectious diseases and significant increase in food animal production. They represent one of the major scientific and medical advances of the 20th century (Gordon

et al., 2005; McPhee & Hancock, 2005). Although antibiotic therapy is still the first choice to combat microbial infections in humans and animals, the prevalence of bacterial resistance to conventional antibiotics is a growing public health concern. This has driven the search for new antimicrobials that are broadly effective and less likely to induce antimicrobial resistance (Sang & Blecha, 2008). While conventional antibiotics are active only against bacteria and/or fungi, AMPs have a broader range of applications against bacteria, fungi, parasites, enveloped viruses and cancer. A large variety of AMPs synthesized by bacteria belong to the group of bacteriocins which are not ribosomally synthesized (Papagianni, 2003). Bacteriocins are small, heat stable peptides that bacteria use to compete against other bacteria of the same species (narrow spectrum) or against bacteria of other genera (broad spectrum) (Cotter et al., 2005). The majority of Class I and Class II bacteriocins are active in the nanomolar range against Gram-positive bacteria in closely related species or in a broad-spectrum manner for many species. The most promising bacteriocins as antibiotics are produced by lactic acid bacteria (LAB) with the core genera including *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus* and *Streptococcus*. Examples of such peptides are nisin (Cotter et al., 2005; Dufour et al., 2007), mersacidin (pre-clinical test to treat Gram-positive infections) (Hancock & Sahl, 2006) and lacticin (against mastitis infections) (Gardiner et al., 2007). Table 1 illustrates AMPs diversity.

Origin	Class	Examples	Antimicrobial activity	Reference
Lactic Acid Bacteria LAB	Class I and II Bacteriocins	Lantibiotics Class I: nisin, mersacidin; non-lantabiotics Class II: pediocin, PA1, enterocin AS48	Nanomolar range, activity against closely related or broad-spectrum Gram-positive bacteria	Willey et al.,2007 Field et al.,2008
Bacteria (*E.coli*)	Bacteriocins	Colicins, microcins	Nanomolar range, activity against Enterobacteriaceae	Duquesne et al.,2007 Nes et al.,2007
Fungi	Fungal Defensins	Plectasin	Activity multiple resistant Gram-positive	Mygind et al.,2005
Plants	Plant Defensins	Ib-AMP1-4 and cyclotides	Micromolar range: antifungal, anti-HIV, anti parasites	Colgrave et al.,2008 Ireland et al.,2008 Marcos et al.,2008
Insects/ amphibians	Insect/ amphibian cationic peptides	Cecropin A, mellitin, magainins, temporins	Micromolar range active against multidrug-resistant bacteria	Bechinger, 1997; Giacometti et al.,2003
Arachnida/ vertebrates	Venom toxins/ b-defensins	Defensin-like toxins (DLTs) in venom, and b-defensins	Micromolar range, active against multidrug-resistant bacteria mostly in a salt-dependent manner	Yeaman & Yount, 2007; Warren et al.,2008
Mammals	α-Defensins q-Defensins b-Defensins	Human neutrophil defensins, enteric and epithelial defensins	Micromolar range active against multidrug-resistant bacteria, and fungi and viruses	Selsted & Ouellette, 2005; Lehrer, 2007
Higher vertebrates	Cathelicidins	Human LL-37, porcine PR-39, bovine indolicidin	Micromolar range active against multidrug-resistant bacteria, and fungi and viruses	Zanetti, 2005
Humans	Others	Lactoferricin, and antimicrobial domain of lysozyme	Micromolar range active against multidrug-resistant bacteria	Brogden, 2005

Table 1. Antimicrobial peptides diversity of origin, class and antimicrobial activity. Adapted from Sang & Blecha, 2008.

Bacillus species are efficient AMPs factories. Their AMPs are active against Gram-positive microorganisms, with some presenting broader activity against Gram-negative bacteria and fungi (Katz & Demain, 1977). The soil isolate *B. cereus* 8A produces an antibacterial substance, cerein 8A, which inhibits several Gram-positive bacteria including *Bacillus* spp., *Streptococcus* spp. and *Listeria monocytogenes* (Bizani & Brandelli, 2002). Iturins are lipopeptides produced by *Bacillus subtilis* that show antifungal activities against various pathogenic yeasts and molds. The antifungal activity of iturin is related to their interaction with the cytoplasm membrane of target cells leading to an increase in K^+ permeability (Maget-Dana & Peypoux, 1994). Another antifungal lipopeptide complex produced by the *Bacillus subtilis*, the fengycin, was found inhibitory to filamentous fungi but not yeast (Vanittanakom et al., 1986). The mechanism of fengycin action was revealed as a two-state transition controlled by the lipopeptide concentration – one state being monomeric, not deeply anchored and nonperturbing lipopeptide and other burried, aggregated form responsible for membrane leakage and bioactivity (Deleu et al., 2008).

A soil microorganism identified as *Bacillus megaterium* was found to produce several antibiotics (Pueyo et al., 2009). Analysis both by electron spray ionization (ESI) and matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (MS) identified these substances as lipopeptides. Predominant peaks at m/z 1,041 and m/z 1,065 revealed ions which were compatible with surfactins and lichenysins, respectively. Two other ions m/z 1,057 and m/z 1,464 were further studied by collision-induced dissociation (CID) unveiling an iturin A at the first and fengycins A and B at the second m/z peaks. The CID spectrum of the m/z 1,464 ion also suggested the existence of fengycins A and B variants in which Ile was changed to Val in the position 10 of the peptide moiety. This mixture of lipopeptides isolated from *B. megaterium* was very effective against *B. cereus*. The culture did not grow after the exposure to 12 µg/mL of the lipopeptides mixture for 30 minutes.

Many AMPs are produced by fungi. The most widely used and historic antibiotic to date, penicillin, was from the fungus *Penicillium chrysogenum*, previously named *Penicillium notatum*. Plectasin is the first identified fungal defensin derivated from *Pseudoplectania nigrella*, a black saprophytic asomycetes. This defensin was active against antibiotic-resistant strains of *Streptococcus pneumoniae* with rates similar to penicillin and vancomycin presented, efficacy in treating peritonitis and pneumonia in mice, and showed therapeutic potential as antifungal compound (Mygind et al., 2005). Anafp, another antifungal peptide obtained from the culture supernatant of *Aspergillus niger* inhibited various yeast strains as well as filamentous fungi at low concentrations (Lee et al., 1999). A novel antifungal peptide named 'AcAFP' from *Aspergillus clavatus* exhibited thermostability and is promising due to its thermostability at 100°C for 1 h and strong inhibitory activity against mycelial growth of several molds including *Fusarium oxysporum*, *Fusarium solani*, *Aspergillus niger*, *Botrytis cinera* and *Alternaria solani* (Skouri-Gargouri & Gargouri, 2008). A 6.0-kDa antimicrobial peptide from *Aspergillus clavatus* ES1, designated as AcAMP, was isolated by a one-step heat treatment, was sensitive to proteolytic enzymes, stable between pH 5.0 and 10.0, and heat resistant (15 min at 100°C) (Hajji et al., 2010). AcAMP exhibited antibacterial activity against several Gram-positive and -negative bacteria. Based on all these features, AcAMP can be considered as a promising new member of the restraint family of ascomycete antimicrobial peptides that might be used in biological control of plant diseases and also for potential applications in food preservation.

The mode of action of the cationic and amphiphilic AMPs has been associated with their electrostatic attraction to the microbial cell surfaces, which contain negatively charged and acidic polymers, such as lipopolysaccharides (Gram negative bacteria), and wall-associated teicoic acids (Gram-positive bacteria). They transit the outer membrane of the Gram negative bacteria via self-promoted uptake (Hancock & Lehrer, 1998). Subsequently these peptides contact the anionic surface of the cytoplasmic membrane and insert in a manner such that they initially straddle the interface of the hydrophilic head groups and the fatty acyl chains of membrane phospholipids. After insertion into the membrane, antimicrobial peptides act by either disrupting the physical integrity of the bilayer, via membrane thinning, transient poration and/or disruption of the barrier function, or translocate across the membrane and act on internal targets (Hancock & Sahl, 2006).
Several complex and controversial models describe these subsequent events, including the reorientation of peptide molecules perpendicular to the membrane to form either barrel-stave or toroidal channels, the breakdown of membrane integrity as a result of the swamping of membrane charge by a 'carpet' of peptides at the interface, the detergent-like dissolution of patches of membrane and the formation of peptide-lipid aggregates within the bilayer (Jenssen et al., 2006). Each of these successfully predicts the ability of cationic antimicrobial peptides to break down the cytoplasmic membrane, but only the toroidal channel and aggregate models explain the action of certain peptides on cytoplasmic targets. Indeed, the action of many peptides cannot be explained by disruption of membrane permeability barriers, as discussed in several reviews (Yeaman & Yount, 2003; Jenssen et al., 2006; Peschel & Sahl, 2006). Figure 8 shows mechanisms of action for conventional antibiotics and AMPs.

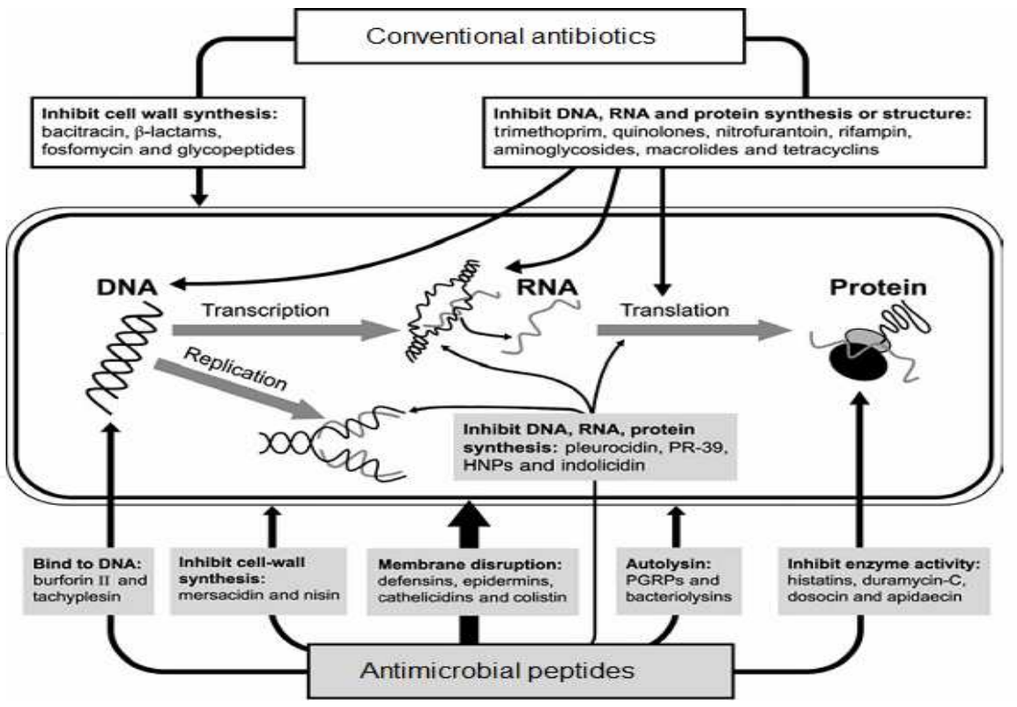


Fig. 8. Mechanism of action for conventional antibiotics and AMPs. Reproduced with permission from Sang, Y. & Blecha, F., Antimicrobial peptides and bacteriocins: alternatives to traditional antibiotics, Animal Health Research Reviews, 9, 2, 227-235, 2008. Copyright 2008 Cambridge Journals.

Bacitracin, β-lactams and glycopeptides action is related to the inhibition of cell wall synthesis whereas trimethoprim, quinolones, nitrofurantoin, rifampin, aminoglycosides, macrolides and tetracyclines inhibit DNA, RNA or protein synthesis. However, recent observations suggest that AMPs besides insert and damage of the cytoplasmatic membranes of target cells, peptides may also interact with intracellular targets such as DNA and RNA, presumably interfering with their metabolic functions and thus leading to cell death (Brogden, 2005; Hale & Hancock, 2007). They can alter cytoplasmic membrane septum formation; inhibit cell wall synthesis; inhibit nucleic acid and protein synthesis; or inhibit enzymatic activity (Brogden, 2005).

Antibiotics and AMPs have a mixed history so does the development of their applications. Polymyxin B and gramicidin S have been used in the clinic and as topical over-the-counter medicines for a long time, and the cationic lantibiotic nisin has been used as an antimicrobial food additive. In contrast, despite several series of clinical trials, only one of the new generation (designer) cationic antimicrobial peptides has demonstrated efficacy in phase 3 clinical trials. Nevertheless, given their exceptionally broad activity spectra, which for a single peptide can include activity against Gram-negative and Gram-positive bacteria, fungi as well as viruses and parasites, still substantial interest remains in exploiting the potential of these molecules (Hancock & Sahl, 2006).

Some AMP-based antibiotic formulations are at preclinical stages with some proceeding to clinical trials (Andrès & Dimarcq, 2005; Gordon et al., 2005; McPhee & Hancock, 2005; Hancock & Sahl, 2006). Nisin, a LAB lantibiotic, is one of few examples of AMP-based antibiotic therapies that have been commercialized. AMP-based drugs derived from insect cecropin B and bovine indolicidin have progressed to clinical trials to treat wounds or skin-related infections in humans, applications that may also be used in veterinary medicine (Hancock & Sahl, 2006; Scott et al., 2007). Some drugs under testing are derivatives of AMPs that have been modified to improve their antimicrobial activity. These modifications include introducing non-natural residues like D-amino acids, addition of C-terminal amidation and catalysis of cyclic formation, which are believed to improve stability and activity against targeted micro-organisms as shown in natural bacteriocins, plant cyclotides and primate q-defensins (Lehrer, 2007; Bansal et al., 2008; Ireland et al., 2008). Optimized design of synthetic peptides based on knowledge from natural AMP studies (the concept of 'designer AMPs') may provide a feasible way to increase novel drug development (Scott et al., 2007; Jenssen et al., 2008). Short antimicrobial peptides with nine and eleven residues were developed against several clinically important bacterial and fungal pathogens such as *E. coli*, *P. aeruginosa*, *S. aureus*, *C. albicans* and *Fusarium solani* (Qi et al., 2010). Twelve analogues of previously reported peptides BP76 (KKLFKKILKFL) and Pac-525 (KWRRWVRWI) were designed, synthesized, and tested for their antimicrobial activities. Two of eleven amino acid peptides, P11-5 (GKLFKKILKIL) and P11-6 (KKLIKKILKIL), have very low MICs of 3.1–12.5 μg/mL against all five pathogens. The MICs of these two peptides against *S. aureus*, *C. albicans* and *F. solani* are four to ten times lower than the corresponding MICs of the reference peptide BP76. P9-4 (KWRRWIRWL), newly designed nine-amino acid analogue, also has particularly low MICs of 3.1–6.2 microgram/mL against four of the tested pathogens; these MICs are two to eight times lower than those reported for Pac-525 (6.2–50 micrograms/mL). These new peptides (P11-5, P11-6 and P9- 4) also exhibit improved stability in the presence of salts, and have low cytotoxicity as shown by the haemolysis and MTT assays. From the results of field-emission scanning electron microscopy, membrane depolarization and dye-leakage assays, were propose that these peptides exert their action

by disrupting lipid membranes. Molecular dynamics simulation studies confirm that P11-6 peptide maintains relatively stable helical structure and exerts more perturbation action on the order of acyl tail of lipid bilayers (Qi et al., 2010). A series of AMP´s incorporating the un-natural amino-acids Tic-Oic have been developed. Herein the in vitro activity of these peptides, including ten new compounds, against eight potential bio-terrorism bacteria agents and three other bacterial strains were tested. These peptides exhibit a wide range of organism potency and selectivity (Venugopal et al., 2010).

Endogenous antibiotics are antimicrobial peptides called host defense peptides and participate in multiple aspects of immunity (inflammation, wound repair, and regulation of the adaptive immune system) as well as in maintaining homeostasis (Auvynet & Rosestein, 2009; Pathan et al., 2010). The possibility of utilizing these multifunctional molecules to effectively combat the ever-growing group of antibiotic-resistant pathogens has intensified research aimed at improving their antibiotic activity and therapeutic potential, without the burden of an exacerbated inflammatory response, but conserving their immunomodulatory potential. Because of their wide involvement in inflammatory response and the emerging role of inflammation in atherosclerosis, antimicrobial peptides have been proposed to represent an important link between inflammation and the pathogenesis of atherosclerotic cardiovascular diseases (Li, 2009). The synthesis of AMPs and the development of analogues is an option for their use in humans. Another interesting approach was to induce the endogenous production of these peptides, which would avoid the possible toxicity and adverse systemic reactions, as well as the difficulty to deliver them in integral form to the desired sites of action (Guani-Guerra et al., 2010). The increasing incidence of antibiotic-resistant bacterial infections is one of the greatest challenges faced by modern medicine with an obvious need for new effective and safe treatments. Thanks to AMPs multifunctional properties, the development of resistance by microorganisms towards AMPs is more difficult. Eventually, AMPs may become useful therapeutic tools.

6. Conclusion

Antimicrobial films and surfaces have been produced from impregnation of materials and coatings with antimicrobials, deposition of coatings with antimicrobial covalent modifications and biodegradable materials. These films prevent adhesion and colonization of pathogenic microorganisms and are important for designing biomedical devices and food packaging. Antimicrobial particles have been obtained from inorganic, metal and composite materials, polymers, lipids and a variety of hybrid combinations. They are important in disinfection, sterilization and in impregnation of materials to become antimicrobials. In therapy against infectious diseases, antimicrobial particles, liposomes and antimicrobial peptides provided several instances of improvement of the therapeutic index for a variety of formulations. The future will probably witness important novel developments in applied research regarding antimicrobial hybrid and composite systems by themselves or in efficient combinations with drugs.

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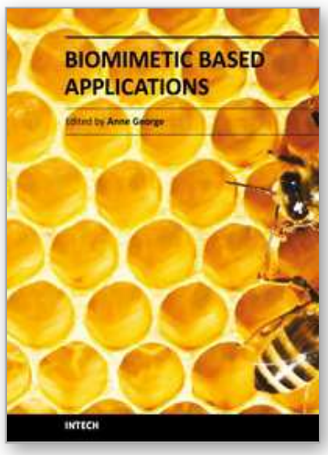

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The interaction between cells, tissues and biomaterial surfaces are the highlights of the book "Biomimetic Based Applications". In this regard the effect of nanostructures and nanotopographies and their effect on the development of a new generation of biomaterials including advanced multifunctional scaffolds for tissue engineering are discussed. The 2 volumes contain articles that cover a wide spectrum of subject matter such as different aspects of the development of scaffolds and coatings with enhanced performance and bioactivity, including investigations of material surface-cell interactions.

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