Chapter 1
Advances in Drug Delivery Strategies for Microbial Healthcare Products

Jose Manuel Ageitos and Marcos Garcia-Fuentes

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Abstract Biomacromolecules produced by microorganisms have been employed in healthcare ever since ancient times as part of fermented products or natural remedies, but from the discovery of penicillin in 1928 by Alexander Fleming, it is

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impossible to conceive medicine without microbial products. In addition to antibiotics, microorganisms produce secondary metabolites currently employed as anti-inflammatory, immunosuppressant, and antitumoral drugs, among others. As with any other well-established drugs, undesirable side effects may occur with these compounds due to excessive systemic drug concentrations, and their pharmacological activity can be lost by the development of resistance in the target cells. Besides, many microbial drugs have intrinsic physicochemical properties that limit their application in healthcare such as low aqueous solubility, low bioavailability, acute toxicity, and fast systemic and pre-systemic degradation.

Here we review the critical aspects of innovative strategies for microbial products of high interest for academia and healthcare industry. In order to improve some of the current drug limitations, researchers have explored multiple advanced formulation approaches based on disruptive technologies. By means of new biomaterials and nanotechnology, it is possible to maximize the possibilities for functionalization and interfacing with the biological environment, a characteristic that leads to unique properties as drug delivery carriers. These approaches have resulted in improved pharmacological effects and pharmaceutical characteristics as compared to classical formulations, representing the dawn of a new era in microbial healthcare products.

Abbreviations

FDA	Food and Drug Administration
GRAS	generally recognized as safe
MRSA	methicillin-resistant *S. aureus*
PEG	poly(ethylene glycol)
PEGylated	functionalized with PEG
PLGA	poly(lactic-*co*-glycolic acid)
TAT peptide	transactivator of transcription of human immunodeficiency virus (HIV1)
VRE	vancomycin-resistant enterococci
VRSA	vancomycin-resistant *S. aureus*

1.1 Introduction

Microorganisms are a fundamental source of products for human purposes. On the one hand, primary metabolites, such as alcohols, vitamins, amino acids, enzymes, or organic acids, are employed as nutritional supplements and as raw material for industrial biotransformation. On the other hand, secondary metabolites are employed by pharmaceutical industry to produce active pharmaceutical ingredients widely used in healthcare. Only related to healthcare industry, the estimated market of

microbes and microbial products is estimated as $187.8 billion by 2020 (Singh et al. 2017a). As part of these active pharmaceutical ingredients, it can be included anti-inflammatory, antitumoral, and antibiotic drugs, among others.

However, the applicability of these drugs can be hindered by their intrinsic physicochemical properties, such as limited solubility in aqueous environment, reduced intestinal absorption, enzymatic degradation, or interspecific metabolization, and thus can easily conduct to a lack of efficiency or acute toxicity induced by the increase of dose. The conventional approach consists of solubilization by means of surfactants for producing suspensions of these compounds; however, biocompatible surfactants are uneconomic and difficult to synthesize and often unable to eliminate the toxicity or improve the absorption. Another concern for conventional formulations, which makes well-established treatments into obsolete, is the emergence of antibiotic resistance in microorganism (Kalhapure et al. 2015). Antibiotics have been widely employed in medicine since the 1940s; however, due to their prolonged use and abuse, we have conducted the selection of resistant strains of microorganisms (de Miguel et al. 2016; Ageitos et al. 2017). Nowadays, infections with multiresistant microorganisms are becoming the main issue in nosocomial treatments (Inweregbu et al. 2005; WHO 2014). Other than searching for new drugs, researchers are focusing attention in drugs that, while having high antibiotic activity, have high toxicity. Those drugs have not been extensively employed and, therefore, less prone to resistance selection. It is required the reformulation of these drugs to find a therapeutic window where its toxicity is tolerable while maintaining their antibiotic activity. This dichotomy is usually solved with a precise controlled release or using specific carriers to bring the active pharmaceutical ingredients close to where they are needed and, in an ideal case, both solutions (Wong and Choi 2015). The controlled release of drugs was classically conducted by the design of drug delivery systems which allow the sustainable liberation of compounds based on the properties and inner structure of the materials. With the advances in material science, nowadays it is possible to design "smart" drug delivery systems with stimuli-responsive characteristics (Liu et al. 2016).

Nanotechnology is one of the best alternatives for the design of new formulations to improve existing therapies. This emerging area of medicine is based on the use of nanometric carries to significantly reduce the side effects of nonspecific treatments. Drug delivery systems can be classified regarding their properties such as size, composition, structure, and physical properties. There is some controversy regarding the size definition. Nanocarriers are defined materials in nanometric scale (10^{-9} m); however, in biological sciences the concept is dynamic, referring to particles smaller than 500 nm; in the case of microcarriers, the size spans between 0.1 and 100 μm. Regarding composition, the classification is clearer; thereby, metallic devices can be composed by pure metals (usually gold or silver) or metal oxides [iron(II, III)oxide (Fe_3O_4), gadolinium(III) oxide (Gd_2O_3), or titanium dioxide (TiO_2)]. Polymeric devices are generally composed by a polydisperse synthetic polymer, such as poly(lactic-*co*-glycolic acid) (PLGA), poly(lactic acid), poly(ethylene glycol) (PEG), methoxy poly(ethylene glycol), poly(vinyl alcohol), and poly(vinyl acetate), among others. Dendrimers are a special case of polymeric devices where the polymer have a low dispersion, being formed of repetitively branched molecules, such

as poly(propylene imine). Natural polysaccharides, such as chitosan, alginate, hyaluronic acid, starch, or dextran, are employed in formulations, as much as core or covering of polymeric devices. Both metallic and polymeric devices are generally named particles and, depending on size, as nanoparticles or microparticles; while amphipathic polymers produce micelles, lipid-based devices can be composed by a mixture of lipids or oils with emulsifiers in order to produce different structures such as nanoemulsions, lipospheres, solid lipid particles, micelles, liposomes, nanostructured lipid carriers, and cubosomes, among others. The main difference between those devices is the organization of the hydrophobic and hydrophilic regions (Fig. 1.1).

Furthermore, nanocarriers can be functionalized with biomarkers which allow the active delivery of the drugs by targeting ligands specific for a cell surface receptor molecule (Wong and Choi 2015). This mechanism allows a tight adhesion of the nanocarrier to the targeted cell surface, which may lead either to endocytosis or the drug release induced by other factors, such as pH, temperature, redox-responsible, or the presence of enzymes (Liu et al. 2016). The design of drug nanocarriers must be done taking into account some critical parameters, such as size, shape, or surface charge, the biological response they induce, and the employed administration route (Ageitos et al. 2016).

Examples of succeeding drug nanocarriers are the liposomal formulations approved by the US Food and Drug Administration (FDA). Doxil®/Caelyx™, a PEGylated (functionalized with polyethylene glycol) liposomal formulation of doxorubicin developed by Janssen, initially approved by the FDA for Kaposi's sarcoma treatment in 1995, was later approved for ovarian cancer (2005) and multiple myeloma (2008). This formulation improved site-directed delivery to disease and decreased systemic toxicity of free doxorubicin. Also for Kaposi's sarcoma treatment, in 1996, was approved DaunoXome® (Galen), a liposomal formulation of

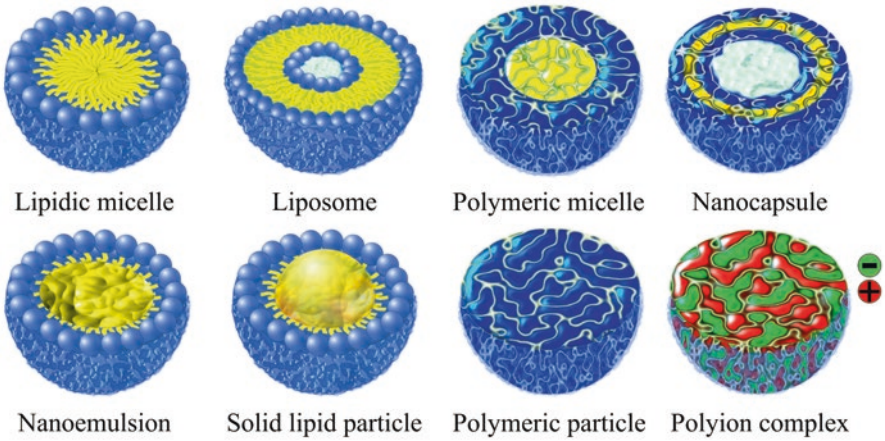

Fig. 1.1 Schematic representation of different nanocarriers described in this chapter. Blue areas represent hydrophilicity and yellow hydrophobicity

daunorubicin, which showed an increased delivery to tumor site and lowered the systemic toxicity arising from side effects of daunorubicin. The antifungal drug amphotericin B was also approved in two liposome formulations, Abelcet® (Sigma-tau) and AmBisome® (Gilead Sciences), both showing a reduction in the toxicity in comparison to free compound. Nowadays there are several microbial drugs based on nanomedicine in clinical trials, and it is expected that those numbers increase soon (Egusquiaguirre et al. 2012; Anselmo and Mitragotri 2016; Bobo et al. 2016; Anselmo et al. 2017).

In the current chapter, we are going to present recent formulations of well-established microbial drugs that can serve as example of the different ongoing approaches, highlighting the critical aspects as compared to classical formulations. It must be considered that the main part of the discussed works are only proofs of concept and will take time to reach the mark, considering that, as explained by Liu and collaborators, "these nanoplatforms are lack of standardized manufacturing method, toxicity assessment experience, and clear relevance between the pre-clinical and clinical studies, resulting in the huge difficulties to obtain regulatory and ethics approval" (Liu et al. 2016). However, authors consider that the works exposed here are an excellent point of reference and a valuable font of knowledge for "advances in drug delivery strategies for microbial healthcare products."

1.2 Anti-inflammatory and Immunosuppressant Drugs

1.2.1 Cyclosporine A

Cyclosporine A (Fig. 1.2) is a non-ribosomally synthesized cyclic peptide isolated from *Tolypocladium inflatum* and is widely used for treating psoriasis and arthritis due its immunosuppressant effect (Thell et al. 2014). Some of the limitations of cyclosporine A are its low bioavailability (Bravo González et al. 2002) derived from poor aqueous solubility and low intestinal permeability (Italia et al. 2007). Cyclosporine A has a narrow therapeutic window where nephrotoxicity, hepatotoxicity, and neurotoxicity have been reported (De Clercq and Holý 2005; Zhang et al. 2013). For these reasons, cyclosporine A is considered a model peptide in nanomedicine, and multiple formulations have been proposed for cyclosporine A delivery through a variety of routes (Wang et al. 2014). Here we will cover the major examples, and we direct the readers seeking further details to a recent review by Guada et al. (Guada et al. 2016b).

PLGA nanoparticles and microspheres have been developed for increasing the stability during the storage of cyclosporine A (Chacón et al. 1999). Orally administered cyclosporine A-loaded poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles showed a cyclosporine A controlled release for 5 days and lower nephrotoxicity than current cyclosporine A formulations (Sandimmune Neoral®) (Italia et al. 2007). Similar results were obtained by Guada and collaborators with cyclosporine A lipid nanoparticles, where these nanoparticles had improved pharmacological response

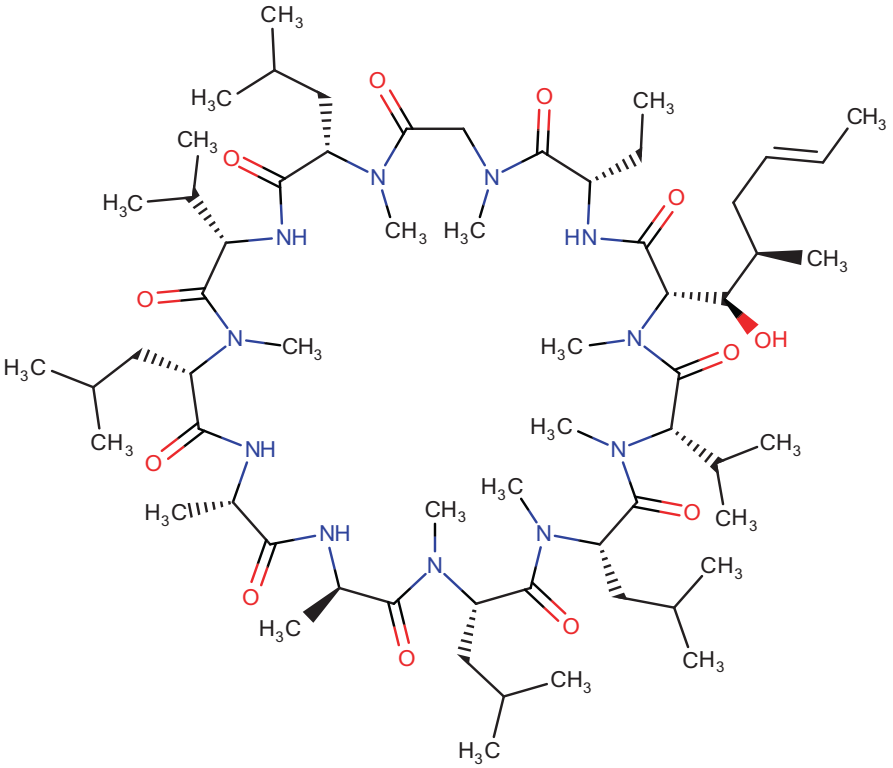

Fig. 1.2 Chemical structure of cyclosporine A. PubChem CID: 5284373

and less nephrotoxicity than Sandimmune Neoral® (Guada et al. 2016c). Wang et al. have found that lipid-based nanoscale drug delivery systems, such as nanostructured lipid carriers and self-microemulsifying drug delivery systems, were superior to polymeric nanoparticles for enhancing cyclosporine A oral bioavailability (Wang et al. 2014). Interestingly, cyclosporine A lipid-based devices failed to treat inflammatory bowel diseases (Guada et al. 2016a), while cyclosporine A encapsulated in poly(lactic acid) and poly(lactic-*co*-glycolic acid) (PLGA) microspheres showed a reduction in the inflammation of dextran sodium sulfate-induced colitis in animals (Fukata et al. 2011). In addition to the formulations mentioned above for the oral route, cyclosporine A poly-Ɛ-caprolactone nanoparticles showed the ability of penetrating human skin and to reduce inflammation in psoriasis skin models without the appearance of cytotoxicity (Frušić-Zlotkin et al. 2012). Recently, Leung et al. have described cyclosporine A-loaded mannitol porous nanoparticles for pulmonary delivery; those nanoparticles showed good aerosol performance and enhanced dissolution profile compared to spray-dried counterpart (90% in 10 min) (Leung et al. 2017).

Ocular delivery is a specialized type of topical route where other factors such as irritability and mucosal adhesion must be considered. Cationic polymers, such as chitosan, have better adhesion to negatively charged cornea and conjunctiva (Battaglia

et al. 2012), which are critical parameters to ensure an enhanced penetration in the eye of the active pharmaceutical ingredient. Sandri and collaborators investigated cyclosporine A-loaded solid lipid nanoparticles associated with chitosan; these cyclosporine A/solid lipid nanoparticles were biocompatible and enhanced the penetration of cyclosporine A according to in vitro and ex vivo experiments (Sandri et al. 2010). Chitosan nanoparticles have also shown a prolonged cyclosporine A release in vivo, with drug levels being detected both in vitreous and aqueous humor samples (Başaran et al. 2014). Cyclosporine A-poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles have also been studied for ocular delivery. In vitro studies of these nanoparticles confirmed the absence of cytotoxic effects in cell model, while released cyclosporine A retained its anti-inflammatory activity (Hermans et al. 2014). In vivo studies showed that cyclosporine A-loaded PLGA:Eudragit® RL nanoparticles produce a significant increase in cyclosporine A concentrations in rabbit tears in comparison to the commercial formulation (Aksungur et al. 2011). Cyclosporine A has been also assayed in nanomicelle formulations based on polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. These micelles showed good biocompatibility and delivered superior levels of cyclosporine A into the cornea in vivo as compared to commercial oil-based cyclosporine A preparations (Guo et al. 2015). Nanomicelles of methoxy poly(ethylene glycol)-hexylsubstituted poly(lactide) copolymers were also instilled ocularly, and authors found higher cyclosporine A cornea levels as compared to the systemic treatment of cyclosporine A (Di Tommaso et al. 2012).

1.2.2 Tacrolimus

Tacrolimus (fujimycin, Fig. 1.3) is an immunosuppressive macrolide lactone, inhibitor of calcineurin-dependent IL2 signaling, isolated from *Streptomyces tsukubaensis*, and is widely employed in clinical practice for prophylaxis of organ rejection (the liver, heart, kidney, pancreas, lung, and bone marrow) in patients

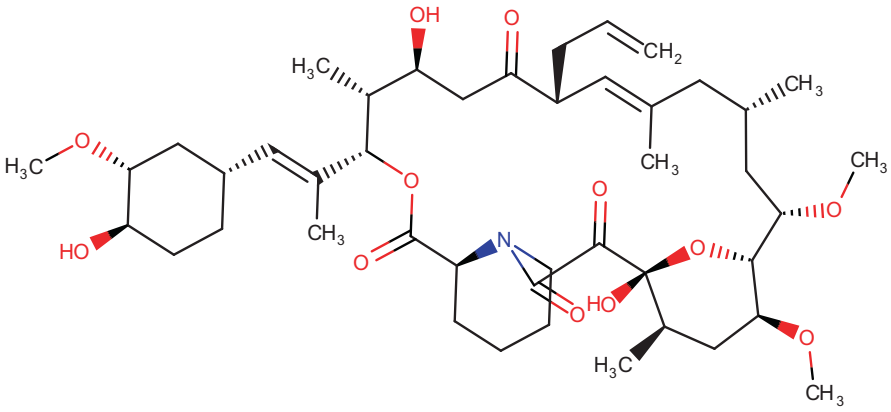

Fig. 1.3 Chemical structure of tacrolimus. PubChem CID: 445643

receiving transplantation (Borhade et al. 2008; Thell et al. 2014). The efficacy of tacrolimus is reduced by its low aqueous solubility and its metabolization in the gastrointestinal tract before absorption. Conventional formulations of tacrolimus have been related to several side effects, including hypertension, nephrotoxicity, and diabetes (Zamorano-Leon et al. 2016).

A few tacrolimus formulations have been tested for improving its bioavailability. For instance, tacrolimus has been formulated in self-microemulsifying drug delivery systems using combinations of various oils, surfactants/cosurfactants, and buffers. Tacrolimus-self-microemulsifying drug delivery systems showed higher bioavailability and immunosuppressive effect than the pure drug and the marketed formulation upon oral administration in an animal model (Borhade et al. 2008). Double-coated tacrolimus-loaded polymethacrylate nanoparticles encapsulated within hydroxypropyl methylcellulose were administered orally to rats and pigs. The researchers detected a 4.9-fold (rats) and a 2.45-fold (pigs) enhancement in relative oral bioavailability as compared to the commercial product (Nassar et al. 2009).

Nanocarriers can also provide targeting for reducing the side effects of tacrolimus. Shin and collaborators studied poly(lactic-*co*-glycolic acid) (PLGA) and PEGylated (functionalized with polyethylene glycol) PLGA nanoparticles loaded with tacrolimus for lymphatic delivery. Tacrolimus nanoparticles and a marketed formulation were intravenously administered to rats; as a result, authors found that concentrations of tacrolimus in mesenteric and axillary lymph nodes were higher for tacrolimus-poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles than for the marketed formulation (Shin et al. 2010). Yoshida et al. proposed another alternative for lymphatic delivery of this active pharmaceutical ingredient using oral oil formulations in rats. Authors found that oil formulations of tacrolimus increased the rate of lymphatic absorption 3- to 15-fold as compared with a solid dispersion formulation while keeping a lower tacrolimus concentration in blood (Yoshida et al. 2016).

Advanced formulations have also been designed to achieve sustained plasmatic levels of drug. For instance, tacrolimus has been loaded in PLGA or poly(lactic acid) microspheres and injected intramuscularly and subcutaneously; after a single injection, it achieves sustained blood levels for 2 weeks, allowing the prolongation of graft survival time in a rat model of heart transplantation (Kojima et al. 2015). Similar results were reported for tacrolimus-loaded in PEG-PLGA nanoparticles administered by gastric perfusion. Tacrolimus/PEG-PLGA nanoparticles produced longer tacrolimus retention time in plasma and increased survival time in a liver transplantation rat model, as compared to tacrolimus capsules (Xu et al. 2014).

Regarding topical applications, tacrolimus has been solubilized in methoxy poly(ethylene glycol)-hexylsubstituted poly(lactide) and loaded into a poly(acrylic acid) gel. The delivery of tacrolimus from this hydrogel formulation was found to be twice that of the commercial formulation in an induced psoriasis model (Gabriel et al. 2016). Another example is a tacrolimus/curcumin-loaded liposphere gel formulation that showed a reduction in lesion markers in an induced psoriasis model as compared to the commercial gel formulation (Jain et al. 2016).

1.3 Cardiovascular Protective Drugs

1.3.1 Lovastatin

Lovastatin (Fig. 1.4) is a highly lipophilic drug isolated from *Aspergillus terreus*, approved as a cholesterol-lowering statin drug by FDA (Chang et al. 2011). Lovastatin is an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase and cholesterol biosynthesis (Jun and Daxin 2016). Lovastatin has been described as an antitumoral drug since it induces cell death in myeloma plasma cells (van de Donk et al. 2002). Due to its lipidic nature, lovastatin has low oral bioavailability (lessthan5%) and short half-life (1–2 h) (Gu et al. 2011); therefore, several formulations have been designed to improve this limitation.

For instance, nanostructured lipid carriers loaded with lovastatin have shown improved pharmacokinetic and pharmacological properties than the free drug (Jun and Daxin 2016). In a similar manner, Gu and collaborators have developed lovastatin-loaded nanostructured lipid carriers functionalized with the major apoprotein of high-density lipoprotein (apoA-I) for targeting foam cells in atherosclerosis. They found that this strategy can deliver lovastatin to foam cells through the very low-density lipoprotein receptor pathway (Gu et al. 2011). Lovastatin has also shown the ability to induce expression of bone morphogenetic protein 2, which can be employed for fracture healing. However, this is only useful upon regional administration, due to oral administration of lovastatin resulted in poor peripheral delivery to the skeleton, since lovastatin was mainly metabolized in the liver. Garret and collaborators developed lovastatin-loaded poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles in the form of nanobeads and observed increased healing in bone fractures after a single injection in the fracture zone as compared to classical oral administration (Garrett et al. 2007).

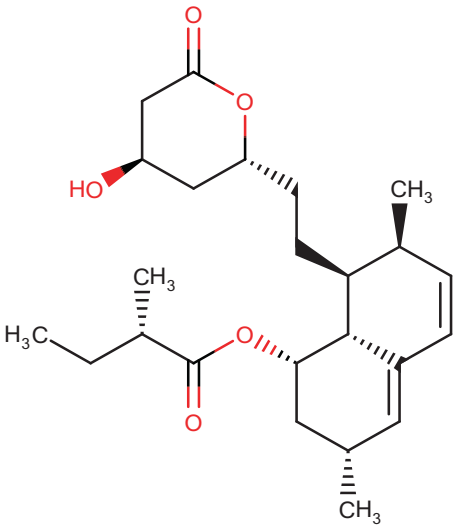

Fig. 1.4 Chemical structure of lovastatin. PubChem CID: 53232

1.3.2 Simvastatin

Simvastatin (Fig. 1.5) is another cholesterol-lowering drug derived synthetically from a fermentation product of *A. terreus*. Simvastatin has been used for the treatment of dyslipidemia, coronary heart disease, and specially hypercholesterolemia. Like lovastatin, simvastatin also shows low oral bioavailability. Simvastatin is a white to off-white, nonhygroscopic, crystalline power that is practically insoluble in water. This profile makes simvastatin a logical candidate for its encapsulation in amphipathic carriers (Wu et al. 2015). Zhang and coworkers have developed simvastatin-loaded solid lipid nanoparticles, which were able to triplicate the oral bioavailability of the unmodified simvastatin in rat models (Zhang et al. 2010). Simvastatin-loaded nanostructured lipid carriers have shown to be more efficient for attenuating the atherogenic risk of erythrocytes in hyperlipidemic rats as compared to a simvastatin suspension. Simvastatin-loaded nanostructured lipid carriers induced enhanced drug absorption and bioavailability, a prolonged half-life of simvastatin (Harisa et al. 2017). Bertha et al. have studied simvastatin-loaded poly(ethylene oxide) electrospinning fibers for the controlled release of this drug. Simvastatin fibers showed the ability of release drug for 12 h following zero-order release rate kinetics, which indicate a release mechanism governed by a non-Fickian diffusion process. Moreover, the release profile could be changed by modifying the drug/polymer ratio (Betha et al. 2015). Simvastatin has also been employed for breast adenocarcinoma, in the form of simvastatin loaded into polymeric nanoparticles, composed by a star-shaped cholic acid core grafted with poly(lactic-*co*-glycolic acid) (PLGA). Simvastatin-loaded cholic acid-PLGA nanoparticles showed higher cytotoxicity than pristine simvastatin or simvastatin loaded in linear PLGA nanoparticles. Simvastatin-loaded cholic acid-PLGA nanoparticles were effective in vitro and in vivo, where they effectively suppressed tumor growth in a BALB/c nude mice xenograft tumor model (Wu et al. 2015).

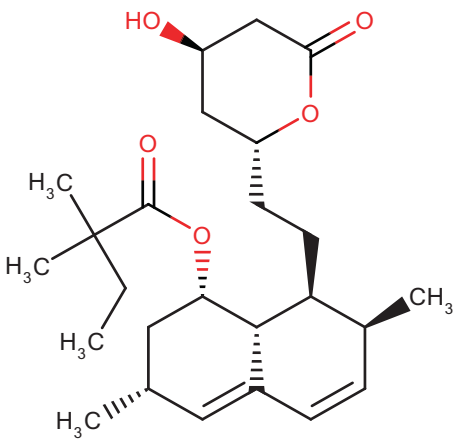

Fig. 1.5 Chemical structure of simvastatin. PubChem CID: 54454

1.4 Antitumoral Drugs

1.4.1 Aclarubicin

Aclarubicin (aclacinomycin A, Fig. 1.6) is an anthracycline anticancer drug isolated from *Streptomyces galilaeus*, employed in China and Japan for cancer treatment. Aclarubicin mainly follows two pathways in its cytotoxic activity; it inhibits DNA topoisomerase activity inhibiting the synthesis of nucleic acids and reduces the oxygen consumption in mitochondria (Iihoshi et al. 2017). Several formulation strategies focused on the active targeting of tumors have been conducted. Aclarubicin has been delivered in cationic albumin-conjugated PEGylated (modified with polyethylene glycol) nanoparticles for glioma chemotherapy in rats (Lu et al. 2007). These in vivo studies showed that aclarubicin concentration in the tumor was 3.3-fold higher than the one reached with a free aclarubicin preparation. This nanomedicine also increased the retention in the glioma, being the concentration of aclarubicin in the tumor 6.6-fold higher than the one reached with free drug 24 h postinjection (Lu et al. 2007). Jia et al. assayed aclarubicin-loaded solid lipid nanoparticles for targeted liver delivery by intravenous administration. This nanomedicine showed a sustained release of aclarubicin, together with high bioavailability; in vivo studies showed that the specific ratio of active pharmaceutical ingredient released in the liver was duplicated as compared to direct aclarubicin injection, while delivery in other organs was reduced significantly. Authors proposed that solid lipid nanoparticles accumulate in the liver by passive mechanisms after intravenous injection; they are absorbed by the reticuloendothelial system, leading to greatest drug accumulation in the liver, due to its size (70 nm) (Jia et al. 2014b).

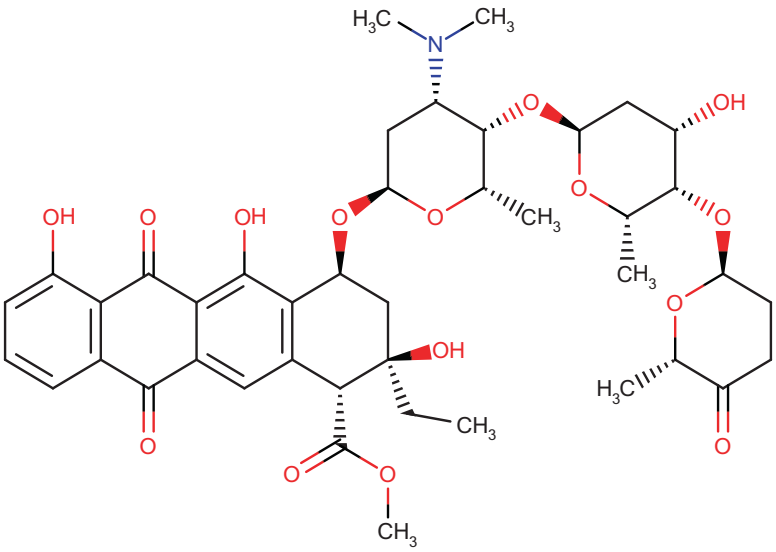

Fig. 1.6 Chemical structure of aclarubicin. PubChem CID: 451415

1.4.2 Bleomycin

Bleomycin (Fig. 1.7) is a mixture of basic glycopeptide antineoplastic antibiotics isolated from *Streptomyces verticillus* (Umezawa et al. 1966) and is commonly used in the treatment of lymphoma, squamous cell carcinomas, germ cell tumors, and malignant pleural effusion (Moeller et al. 2008; Zhang et al. 2011). Bleomycin's major components are bleomycin A_2 (55–70%) and bleomycin B_2 (25–32%) (Zhang et al. 2011; Yu et al. 2015). The cytotoxic activity of bleomycin is based on the free radical degradation of DNA after binding to guanosine-cytosine-rich portions (Dorr 1992). Bleomycin has pulmonary toxicity, and it is employed for the induction of pulmonary fibrosis models in mice (Moeller et al. 2008). Bleomycins are water-soluble molecules, which, combined with their high molecular weight, leads to low cell membrane permeability.

The improvement of bleomycin's action has been extensively studied by different drug delivery strategies (Yu et al. 2015), such as metallic nanoparticles (Shatskaya et al. 2013; Yang et al. 2016), nanoliposomes (Chiani et al. 2017), or microspheres (Nguyen et al. 2011). The objective of those strategies was to improve the cellular uptake, to enhance the lymphatic accumulation (Matsuru et al. 1979), to target cancerous cell receptors through folate receptors (Chiani et al. 2017), or to achieve sustained plasmatic levels and reduced side effects by controlled release formulations (Zhang et al. 2011). For instance, Kullberg and collaborators proposed bleomycin's immunoliposomes conjugated with trastuzumab for recognition of Her-2^+ breast cancer cells. Those immunoliposomes were functionalized with the pore-forming protein listeriolysin O to promote endosomal escape cell internalization. The authors observed that this formulation was able to specifically reduce the viability to Her-2-positive cells with an effective bleomycin concentration that was 57,000-fold lower than the one administered extracellularly (Kullberg et al. 2012).

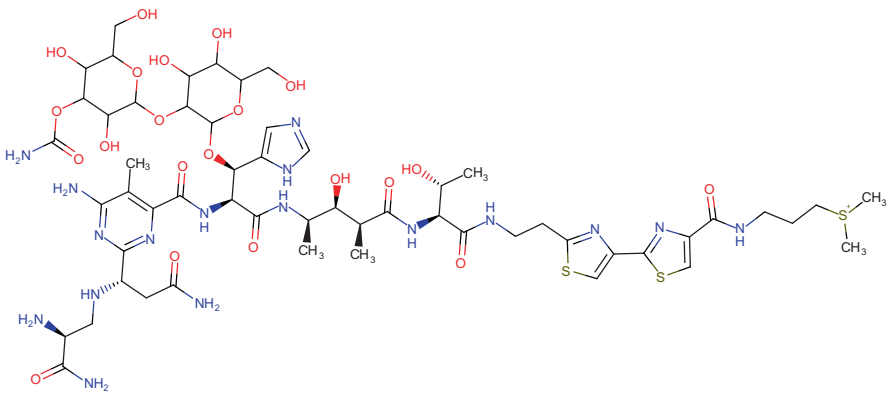

Fig. 1.7 Chemical structure of bleomycin. PubChem CID:5360373

1.4.3 Doxorubicin

Doxorubicin (Adriamycin, Fig. 1.8a) is a 14-hydroxylated version of daunorubicin (daunomycin, Fig. 1.8b), a chemotherapeutic drug isolated from *Streptomyces peucetius*. Daunorubicin has a broad antitumoral spectrum; however, its application became hindered by its high toxicity and side effects. In order to solve these limitations, novel "smart" stimuli-sensitive drug delivery systems that respond to pH, temperature, and magnetism have been proposed. For instance, Zang and collaborators developed daunorubicin-loaded titanium dioxide (TiO_2) nanoparticles. The fraction of daunorubicin released from daunorubicin-TiO_2nanoparticles increased three- to fourfold in acidic conditions as compared to pH 7.4. As the extracellular pH of tumors is lower than in healthy cell tissues, this allows to trigger daunorubicin release specifically in the tumor. In vitro studies have indicated that daunorubicin-TiO_2 nanoparticles enhance the delivery of daunorubicin to the tumors as compared to conventional administration and that they induce tumor apoptosis in a caspase-dependent manner (Zhang et al. 2012). Daunorubicin has also been investigated for antitumor therapy in combination with nanomedicines integrating also oxaliplatin. The drug combination was integrated in biodegradable amphiphilic polymeric mixed micelles that showed reduced systematic toxicity and greater synergistic effect than the combination of the same free drugs. The mixed micelles demonstrated in vivo lower toxicity and comparable or higher antitumor efficacy compared with the same drugs in small molecule formulation (Xiao et al. 2012).

Doxorubicin has been extensively studied in recent years, for instance, by their encapsulation in doxorubicin-loaded nanoparticles of poly(lactic-*co*-glycolic acid) coated with multilayers of chitosan/alginate. Multilayered nanoparticles showed superior in vivo tumor inhibition rates and decreased toxicity compared to doxorubicin-poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles and doxorubicin in solution (Chai et al. 2017). Malinovskaya et al. have further studied doxorubicin-loaded PLGA nanoparticles in U87 human glioblastoma cells and observed that nanoparticles penetrate cells by means of clathrin-mediated endocytosis and then they accumulate in lysosomes and some ultimately might be released into the

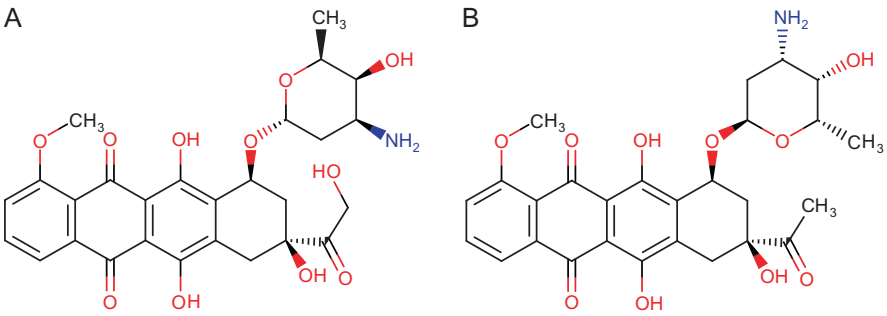

Fig. 1.8 Chemical structure of (**a**) doxorubicin and (**b**) daunorubicin. PubChem CID:31703 and 30323

nucleus (Malinovskaya et al. 2017). Another example is lithocholic acid-polyethylene glycol (PEG)-lactobionic acid nanoparticles loaded with doxorubicin. In vitro, those nanoparticles show high cellular uptake in a human liver cancer cell line triggered by the galactose-asialoglycoprotein receptor interaction; doxorubicin-lithocholic acid-PEG-lactobionic acid nanoparticles were able to suppress in vivo the tumor growth in an orthotopic mouse model of liver cancer (Singh et al. 2017b). Another approach for targeted delivery has been recently reported by Han and collaborators with doxorubicin-loaded angiopep-2 and the transactivator of transcription of the human immunodeficiency virus [TAT peptide, (Ageitos et al. 2016)] peptide dual-modified liposomes. Those complexes showed high binding efficiency to glioma cells, due to specific recognition of angiopep-2 by the low-density lipoprotein receptor-related protein-1 and the cell-penetrating properties of TAT peptide (Han et al. 2017). Pearce and collaborators have employed the prostate-specific membrane antigen receptor, which is overexpressed on many prostate cancers, on lymph nodes, and on bone metastases as therapeutic targets for a doxorubicin-loaded hyperbranched polymer carrier. In addition of their excellent in vitro efficacy, prostate-specific membrane antigen-doxorubicin-polymers did not show adverse toxicity and reduced volume of subcutaneous prostate tumors for in vivo studies (Pearce et al. 2017). An example of the refinement acquired in the design of targeted delivery strategies for doxorubicin is a recently proposed synergistic chemo-photothermal cancer treatment, based on doxorubicin-loaded multi-walled carbon nanotubes coated with poly(N-vinyl pyrrole), functionalized with folic acid and polyethylene glycol. This material allowed doxorubicin release in a pH-dependent manner and allowed the use of combined chemotherapeutical and photothermal treatments in vitro (Wang et al. 2017).

1.4.4 Mithramycin

Mithramycin (plicamycin, Fig. 1.9) is the most representative member of the aureolic acid family of tricyclic polyketides with antitumor activity produced by *Streptomyces argillaceus*, *S. plicatus*, *S. atroolivaceus*, and other *Streptomyces* species (Lombó et al. 2006). It has been described that mithramycin binds preferentially to the minor groove of guanosine-cytosine-rich portions of DNA, inhibiting their transcription (Lee et al. 1990) and inhibiting the binding of transcription factors like Sp1 (Liu et al. 2017). Mithramycin has been employed in the clinical treatment of testicular embryonal carcinoma, glioblastoma (Lombó et al. 2006), or in hypercalcemia in patients with metastatic bone lesions and Paget's disease (Nastruzzi et al. 2012). However, mithramycin has a narrow therapeutic range since it can cause severe hemorrhagic diathesis at doses up to 30 μg/Kg/day (Lee et al. 1990) and produce gastrointestinal, hepatic, kidney, and bone marrow toxicity

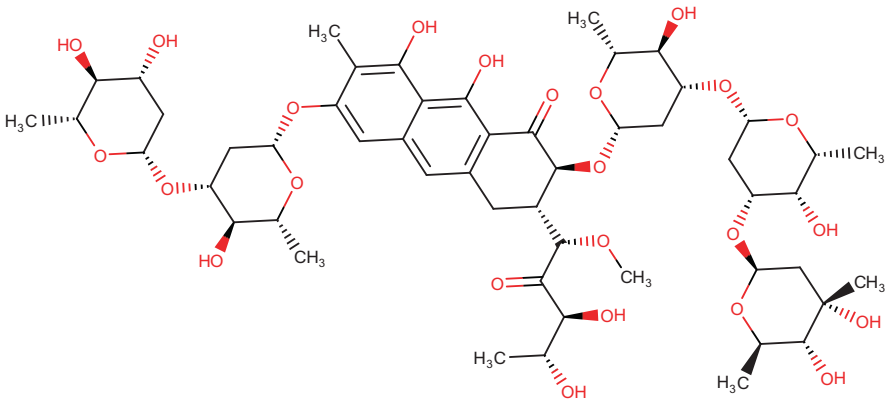

Fig. 1.9 Chemical structure of mithramycin. PubChem CID:163659

(Cohen-Sela et al. 2009). In order to increase absorption and tumor accumulation, Scott et al. designed polyethylene glycol(PEG)-poly(aspartate hydrazide) self-assembled micelles containing mithramycin derivatives that presented increased cytotoxicity to human A549 lung cancer cells. Those micelles had a pH-responsible behavior, inducing the release of mithramycin derivatives at the acidic environment typical of the tumor (Scott et al. 2011). For the treatment of pancreatic carcinoma, mithramycin-loaded methoxy poly(ethylene glycol)-poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles have been recently investigated (Liu et al. 2017). Mithramycin-nanoparticles showed excellent results in vitro and suppressed BxPC-3 tumor growth by 96% in xenograft models.

In addition to the antitumoral activity, new formulations have been assayed with other purposes. Cohen-Sela and coworkers developed a method for the encapsulation of mithramycin in PLGA nanoparticles, with high loading efficiency (80%), and applied this formulation for the treatment of restenosis (Cohen-Sela et al. 2009). Mithramycin-PLGA nanoparticles significantly inhibited RAW264 macrophages and smooth muscle cells and reduced the number of circulating monocytes in rabbits. However, the formulation failed to show a therapeutic effect in a restenosis in rat models. Mithramycin upregulates the expression of human γ-globin genes, which can be associated with a significant improvement in the clinical outcome of the patient with beta-thalassemia. Based on this premise, Nastruzzi and collaborators assayed mithramycin encapsulated in polymeric micellar nanoparticles (Nastruzzi et al. 2012). They found that this advanced formulation was able to reduce the inherent toxicity of the drug and that it induces a more pronounced effect on cell differentiation and γ-globin upregulation when compared to free mithramycin.

1.4.5 Mitomycin C

Mitomycin C (Fig. 1.10) is an antineoplastic antibiotic isolated in Japan in the 1950s from a culture of *Streptomyces caespitosus*. Mitomycin C generates oxygen radicals, alkylates DNA, and produces interstrand DNA cross-links, conducting selective inhibition of DNA synthesis and eliciting genetic recombination, sister chromatid exchange, chromosome breakage, and mutagenesis (Tomasz 1995). Mitomycin C is employed in the treatment of localized bladder cancer and as part of a cocktail chemotherapy of breast, prostate, pancreatic, and non-small cell lung cancers (Bachar et al. 2011). Mitomycin C treatments are associated with number of acute and chronic toxicities, such as severe decrease of blood cells in bone narrow (irreversible myelosuppression), hemolytic uremic syndrome, irritation, or infection (Cheung et al. 2005). Formulation strategies for mitomycin C are focused on improving its bioavailability due to its lipophilic character and on targeted delivery for reducing the side effects of the conventional treatments.

Controlled release formulations of mitomycin C have been designed by encapsulation in poly(lactic acid) nanoparticles upon mitomycin C association with soybean phosphatidylcholine. This association improves the liposolubility of mitomycin C by formation of a mitomycin C-soybean phosphatidylcholine complex (Hou et al. 2009). Besides these strategies aimed at controlling drug levels, other formulations have been developed to control the spatial distribution of the drug. For instance, mitomycin C-loaded hyaluronan-grafted particle clusters were able to produce the specific accumulation of the drug in tumors of epithelial origin (e.g., head and neck cancers) since they express the cell surface glycoprotein receptor for hyaluronan CD44. These hyaluronan clusters showed an increased therapeutic effect on head and neck cancers ex vivo as compared with free mitomycin C, while they did not affect normal cells (Bachar et al. 2011). Another example of targeted delivery is the design of folic acid-tagged (mitomycin C-soybean phosphatidylcholine complex/10-hydroxycamptothecin)-loaded micelles. These micelles have pH-dependent drug release and enhanced cellular uptake mediated by folic acid receptor interaction.

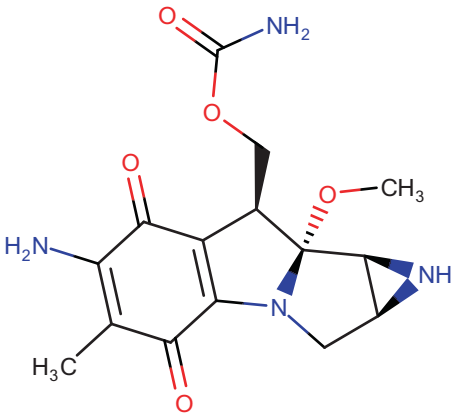

Fig. 1.10 Chemical structure of mitomycin C. PubChem CID:5746

Mitomycin C/10-hydroxycamptothecin-loaded folic acid micelles induced death of tumor cells in vitro and produced the inhibition of growth of tumor tissue in vivo, with low toxicity (Lin et al. 2015). Similar results were obtained with chemical analogs of folic acid such as methotrexate (an inhibitor of dihydrofolate reductase). PEGylated chitosan nanoparticles loaded with mitomycin C/methotrexate were internalized by folic acid receptor-mediated endocytosis and were effective in vivo and in vitro due to the synergic effect of these two drugs (Jia et al. 2014a).

In addition to systemic administration, mitomycin C can be delivered topically using formulations such as the recently reported mitomycin C imprinted poly(2-hydroxyethyl methacrylate-N-methacryloyl-L-glutamic acid) cryogel membranes (Öncel et al. 2017). Cryogel membranes showed low cytotoxicity and released mitomycin C following a non-Fickian diffusion with an initial burst release phase. For intravesical topical treatment focused on bladder tumors, Sun and collaborators proposed mitomycin C loaded onto an in-situ depot of chitosan, β-glycerophosphate, and Fe_3O_4 magnetic nanoparticles (Sun et al. 2016). Fe_3O_4-mitomycin C-chitosan/β--glycerophosphate allowed a sustainable release of mitomycin C in vitro and in vivo, increasing its retention time in the bladder (up to 72 h). Fe_3O_4-mitomycin C-chitosan/β-glycerophosphate increased the survival rate and inhibited the growth of bladder tumors during the in vivo tests, where they observed an improvement in tumor cell apoptosis as compared with conventional administration of mitomycin C (Sun et al. 2016).

1.4.6 Paclitaxel

Paclitaxel (Fig. 1.11) is an anticancer drug isolated in the late 1960s from the western yew, *Taxus brevifolia*; however, the natural abundance of paclitaxel in the bark of yew is only 0.01%–0.05%. Thus, the search for alternative sources of paclitaxel has been a main issue in the past decades. The isolation of several paclitaxel-producing endophytic fungi, such as *Taxomyces andreanae* or *Pestalotiopsis guepinii*, has opened the door to a sustainable paclitaxel source (Zhou et al. 2010). In this way, although the quest is still ongoing (Li et al. 2014; Ismaiel et al. 2017), nowadays paclitaxel can be considered as a drug with microbial origin. Paclitaxel has been approved in many countries for the treatment of ovarian and breast cancers. Its mechanism of action is based on arresting the cell cycle by disrupting the dynamic equilibrium within the microtubule system, inhibiting cell replication. Even though paclitaxel should be functional in most cancer cells, the drug has important solubility problems and side effects and might lack efficacy against some resistant cancers (Steffes et al. 2017).

Traditional formulation of paclitaxel (Taxol®) produces several side effects such as hypersensitivity, nephrotoxicity, neurotoxicity, vasodilatation, labored breathing, lethargy, and hypotension. In order to improve these main issues, several new formulations have been investigated (Nehate et al. 2014). For instance, Danhier and collaborators proposed paclitaxel-loaded polyethylene glycol (PEG)-functionalized

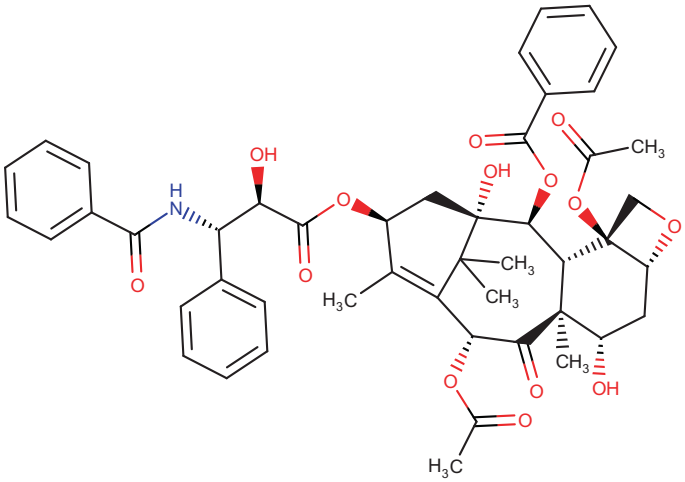

Fig. 1.11 Chemical structure of paclitaxel. PubChem CID:36314

poly(lactic-*co*-glycolic acid) (PLGA)-based nanoparticles. Paclitaxel-loaded nanoparticles showed higher efficacy than commercial paclitaxel formulations in vitro and in vivo, including greater inhibition in the growth of a transplantable lymphoid tumor (Danhier et al. 2009). Paclitaxel-loaded mixed micelles, composed of PEG-*block*-poly(propylene glycol)-*block*-PEG(poloxamer) and poly(ethylene oxide-*co*-propylene oxide) with a diameter of 25 nm, have been studied by Wei and collaborators. Paclitaxel-loaded mixed micelles showed higher toxicity than the commercial paclitaxel formulations in human lung adenocarcinoma cell lines (Wei et al. 2009). Recently, Steffes and collaborators have studied in detail paclitaxel-loaded cationic nanoliposomes with different loading ratio. Nanoliposomes with lower paclitaxel content (1–2 mol%) were more stable and more efficacious than nanoliposomes with higher loading ratio (≥3 mol%), both in release profiles and toxicity against prostate (PC3) and melanoma (M21) human cancer cells lines (Steffes et al. 2017).

In addition to nanoparticle systems, submicron/nanoscale PLGA implants have been assayed for paclitaxel release. Paclitaxel-loaded PLGA nanofiber discs, paclitaxel-loaded PLGA submicron-fiber discs, and paclitaxel-loaded PLGA microspheres entrapped in hydrogel matrices have been intracranially implanted in mice glioblastoma xenograft models. Paclitaxel-loaded nanoscale implants demonstrated optimal drug pharmacokinetics in the brain/tumor and significant tumor inhibition (Ranganath et al. 2010).

1.4.7 Prodigiosin

Prodigiosin (Fig. 1.12) is a natural red pigment produced by several bacterial genera including *Serratia*, *Streptomyces*, *Vibrio*, *Hahella*, *Zooshikella*, and *Pseudoalteromonas* (Dozie-Nwachukwu et al. 2017; Mazzoli et al. 2017), with a wide range of biological activity, including antimicrobial, antimalarial, immunosuppressive, or antitumor properties (Darshan and Manonmani 2015). Prodigiosin can induce apoptosis in cancer cells by several suggested mechanisms of action, such as copper-mediated cleavage of double-stranded DNA, phosphatase inhibition, or disruption of the pH gradient (Rastegari et al. 2017). This versatile pigment has been investigated for different administration routes, for instance, the group of Prof. Soboyejo has studied the controlled release of prodigiosin as breast cancer treatment in a variety of formulations, including thermosensitive poly(N-isopropylacrylamide) hydrogels, implants of poly-di-methyl-siloxane (Danyuo et al. 2014, 2015), biodegradable poly(lactic-*co*-glycolic acid) (PLGA) microparticles (Obayemi et al. 2016), and the free drug (Danyuo et al. 2016). Prodigiosin has also been encapsulated in chitosan microspheres and tested on breast cancer cells with promising results (Dozie-Nwachukwu et al. 2017). Recently, a prodigiosin grafted polysaccharide (β-cyclodextrin and chitosan)-coated magnetic nanoparticles, with lysosome enzymatic-triggered release, have been proposed. These magnetic nanoparticles targeted the GLUT1 receptor, which is overexpressed in cancer cells. Accordingly, prodigiosin-loaded chitosan magnetic nanoparticles showed greater efficacy on cancer cell lines than in noncancerous controls (Rastegari et al. 2017).

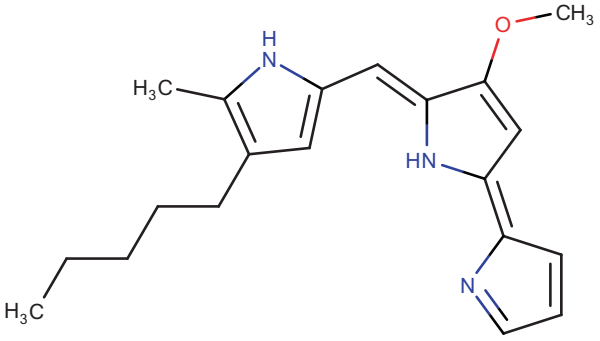

Fig. 1.12 Chemical structure of prodigiosin. PubChem CID:5351169

1.5 Antibiotic Drugs

1.5.1 Amphotericin B

Amphotericin B (Fig. 1.13) is a highly hydrophobic macrolide antifungal antibiotic employed to treat systemic fungal infections and leishmaniasis produced by *Streptomyces nodosus*. This drug has been employed in clinical from more than 60 years as a form of micellar suspension with sodium deoxycholate. However, this formulation produced severe adverse effects such as nephrotoxicity, anemia, and infusion-related side effects. In the 1990s, new formulations based on liposomes were marketed. Liposome-based amphotericin B retained the same activity than micellar amphotericin B while reducing the nephrotoxicity. However, both formulations required an intravenous administration (Serrano and Lalatsa 2017). Current investigations are trying to provide formulations for transmucosal delivery of amphotericin B, and herein we will cover some of the most recent research.

In order to improve oral absorption, amphotericin B-loaded cubosomes have been studied. This formulation increased the bioavailability of amphotericin B by 285% as compared to the commercial micellar suspension, while it did not show nephrotoxicity in animal models (Yang et al. 2012). For bioadhesive mucosal formulations, amphotericin B was encapsulated in core-shell structures formed by monomethoxy polyethylene glycol)-poly(ε-caprolactone) micelles. Amphotericin B/methoxy poly(ethylene glycol)-poly(Ɛ-caprolactone) micelles increased the solubility of amphotericin B yet reduced the overall toxicity, while when loaded in a buccal tablet system, they were able to suppress *Candida albicans* biofilm formation (Zhang et al. 2017a). The same research group also proposed amphotericin B-loaded methoxy poly(ethylene glycol)-poly(Ɛ-caprolactone)-graft-poly(ethylenimine) micelles for local candidiasis treatment. Authors obtained

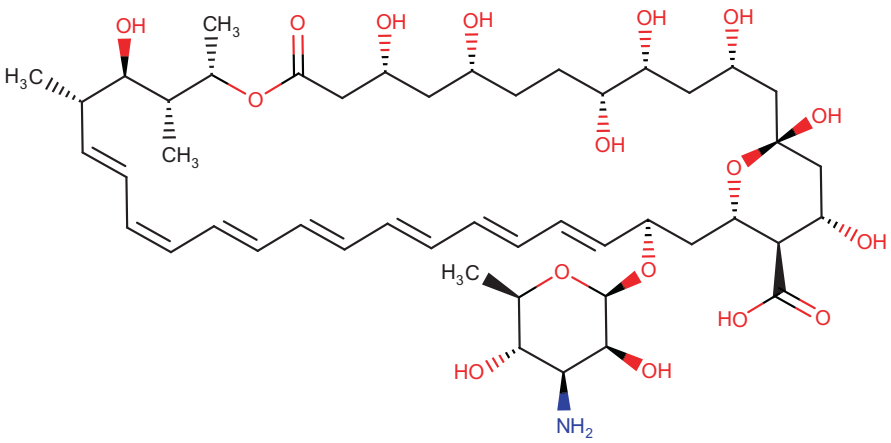

Fig. 1.13 Chemical structure of amphotericin B. PubChem CID:5280965

reduced in vitro cytotoxicity and nonsystemic in vivo toxicity while retaining the same activity against *C. albicans* than Fungizone® (Zhou et al. 2017).

Van De Ven and collaborators developed amphotericin B-loaded poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles and amphotericin B nanosuspensions for intraperitoneal administration, which both systems showed to be more effective in vitro and in vivo against the different *Leishmania* stages and axenic fungi in comparison with the free amphotericin B or marketed formulations (AmBisome® and Fungizone®) (Van De Ven et al. 2012). Jain and collaborators developed amphotericin B-loaded muramyl dipeptide conjugated to multimeric poly(propylene imine) dendrimers for targeting macrophages. These formulations showed a reduction in the hemolytic and cytotoxic effect in erythrocyte and macrophage cultures in comparison to commercial amphotericin B (AmBisome® and Fungizone®). The formulation also showed targeted delivery to macrophages in an in vivo leishmanial model (Jain et al. 2015). Amphotericin B loaded in poly(lactic-*co*-glycolic acid) (PLGA) and dimercaptosuccinic acid nanoparticles showed a preferential tropism for the lungs. This formulation did not produce in vitro hemolysis or in vivo toxicity, while it was able to treat lung fungal infection as commercial amphotericin B, but reduce the number of injections (Souza et al. 2015). Wang and collaborators proposed amphotericin B loaded into polymeric micelles of phenylboronic acid-functionalized polycarbonate/polyethylene glycol and urea-functionalized polycarbonate/PEG diblock copolymers. By means of different blend ratios, authors were able to produce the controlled release of amphotericin B while reducing hemolytic and nephrotoxic effects as compared to commercial amphotericin B colloidal suspension (Fungizone®) (Wang et al. 2016). Recently, it has been reported that amphotericin B-loaded poly(lactic-*co*-glycolic acid) (PLGA)-polyethylene glycol blend nanoparticles had a superior performance to amphotericin B-loaded PLGA nanoparticles, both nanoparticles inhibited in vitro amphotericin B-induced hemolysis and in vivo liver damage (Moraes Moreira Carraro et al. 2017). Another functionalization of PLGA nanoparticles has been performed with amphotericin B-loaded *O*-stearoyl mannose modified PLGA nanoparticles. Mannose-PLGA nanoparticles showed an improvement of intracellular internalization in ex vivo experiments, as compared with pristine amphotericin B-loaded PLGA nanoparticles while effectively treating visceral leishmaniasis in vivo of animal models (Ghosh et al. 2017).

1.5.2 Gentamicin

Gentamicin (Fig. 1.14) is a mixture of three aminoglycoside antibiotics (C1, C1a, and C2), produced by *Micromonospora purpurea*, and is effective against Gram-positive and Gram-negative bacteria; however, like all aminoglycosides, gentamicin is not effective when it is orally provided (Popat et al. 2007). On account of this, gentamicin is often employed in topical applications, especially in bone cements, where it has been employed clinically in various forms for nearly five decades to prevent or treat osteomyelitis (Aviv et al. 2007). This type of infections is difficult

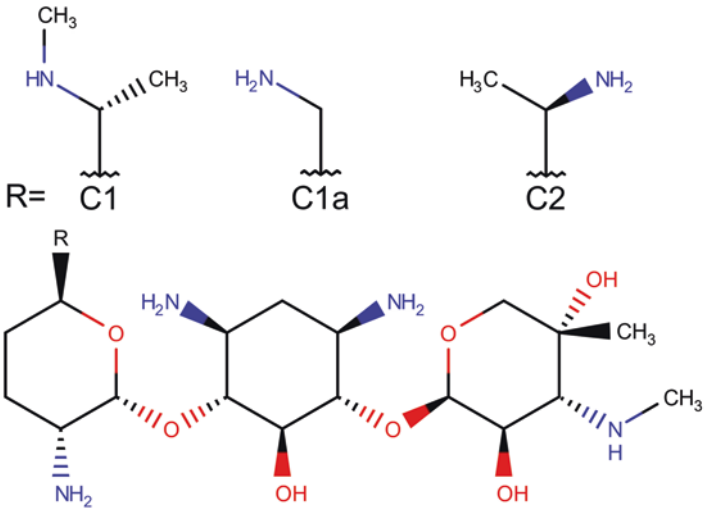

Fig. 1.14 Chemical structure of gentamicin. PubChem CID: 72395, 72396, 72397

to treat because antibiotics cannot readily reach the infection site in bone tissue and because the toxicity and adverse systemic effects of gentamicin, such as ototoxicity and nephrotoxicity, to increment the dosage of drug become infeasible (Swieringa et al. 2008). Besides, most of the classical bone cements were produced with non-biodegradable polymers, which often produce a strong burst release of only hours.

Aviv and collaborators investigated poly(lactic-*co*-glycolic acid) (PLGA) and poly(lactic acid) films for coating of orthopedic implants and observed a sustainable gentamicin release for 12–24 weeks in concentrations, sufficient to inhibit the growth of *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, or *Staphylococcus aureus* (Aviv et al. 2007). Gentamicin-loaded collagen fleeces have been evaluated in acute periprosthetic infections; the release of gentamicin to blood was detected at inhibitory concentrations for *P. aeruginosa*, *S. aureus*, and *Klebsiella* spp., without reaching toxic levels (Swieringa et al. 2008). Gentamicin-PLGA coating on porous magnesium scaffold also showed a controlled release of gentamicin and inhibited adhesion and biofilm formation of *S. epidermidis* and *S. aureus*. Besides this, PLGA-Mg improved the biocompatibility with human bone marrow stromal cells, as compared to porous magnesium scaffold without coating (Li et al. 2015). Pishbin and collaborators have proposed gentamicin-loaded bioactive glass/chitosan composite coatings of metal orthopedic implants. The coating produced an improved cell adhesion and osteogenesis while kept antimicrobial effects against *S. aureus* (Pishbin et al. 2014). Gentamicin has also been encapsulated in *d*-α-tocopheryl polyethylene glycol 1000 succinate micelles and subsequently loaded into a biocomposite material, based on titania nanotubes directly fabricated on titanium surface, coated with chitosan or PLGA. Gentamicin-*d*-α-tocopheryl polyethylene glycol 1000 succinate-chitosan-titania nanotubes showed controlled release of gen-

tamicin (3–4 weeks) and an enhanced osteoblast adhesion and antibacterial properties (Kumeria et al. 2015). Also for titanium coating, gentamicin has been loaded in silk fibroin nanoparticles from *Antheraea mylitta*. Gentamicin-silk fibroin nanoparticles deposited on titanium showed a sustained drug release, enhanced osteoblast adhesion, proliferation, and differentiation in comparison to bare titanium surface (Sharma et al. 2016). A case study of 100 patients with chronic osteomyelitis treated with gentamicin-loaded, calcium sulfate/hydroxyapatite biocomposite has shown that this treatment was able to eradicate the infection in the 96% of the cases with a single procedure (McNally et al. 2016).

Gentamicin-loaded materials have been employed for other purposes, for instance, polyvinyl alcohol/dextran hydrogels have been studied for gentamicin-loaded wound dressing. Gentamicin-loaded gels showed a positive effect of wound healing during in vivo studies and improved the physical properties of pure poly(vinyl alcohol) gels (Hwang et al. 2010). Gentamicin-loaded solid-reversed-micellar-solution-based solid lipid microparticles have been studied for intramuscular injection, being observed diffusion-controlled release profiles in vitro and in vivo rat model (Umeyor et al. 2012). Gentamicin-poly(lactic-*co*-glycolic acid) nanoparticles have shown the controlled release of the drug after intraperitoneal injection and improved the antimicrobial effect of gentamicin toward *P. aeruginosa* infection in a murine model (Abdelghany et al. 2012). In a similar manner, gentamicin-loaded poly(lactic-*co*-glycolic acid) nanoparticles showed a controlled release during 35 days and inhibited the growth of clinical isolates of *S. epidermidis* and *S. aureus* in vitro (Posadowska et al. 2015).

1.5.3 Polymyxin B

Polymyxin B (Fig. 1.15) is a positively charged cyclic antimicrobial peptide produced by *Paenibacillus polymyxa*, with activity against Gram-negative bacteria, especially for multidrug-resistant *P. aeruginosa*. Polymyxin B acts as surfactant, permeabilizing and depolarizing the cell membrane (Ageitos et al. 2017). Even

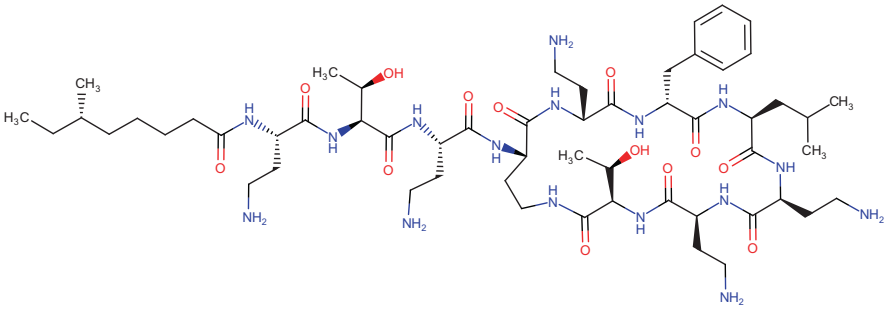

Fig. 1.15 Chemical structure of polymyxin B. PubChem CID:49800004

though polymyxin B is an effective antibiotic, its clinical use became limited due to its toxicity (mainly nephrotoxicity, ototoxicity, and neuromuscular blockade), protein binding (Brandenburg et al. 2012), and inefficient intestinal absorption (Chifiriuc et al. 2016).

In order to solve the abovementioned drawbacks, polymyxin B has been complexed with liposomes; although in general the bactericidal effect became reduced, it was possible to explore other administration routes, such as the lung. Interestingly, it was not detected in the presence of polymyxin B in the kidney or blood, while bacterial infection was reduced in comparison to conventional polymyxin B (Carmona-Ribeiro and Carrasco 2014; Alipour and Suntres 2014; Martin et al. 2015). Sodium alginate-cross-linked polymyxin B sulfate-loaded solid lipid nanoparticles have been assayed for reducing the toxicity and kept antimicrobial activity, and those solid lipid nanoparticles showed high inhibition capacity against the evaluated strains, with low cytotoxicity (Severino et al. 2015). Recently, it has been reported the vehiculation of polymyxin B in surfactants (poractant alfa); the formulation had a prophylactic in vivo effect on the lung function in neonatal pneumonia of rabbits (Stichtenoth et al. 2017). Sukhishvili and collaborators described an interesting application of polymyxin B/tannic acid films with pH-triggered release induced by bacterial growth. Polymyxin B/tannic acid films inhibited the growth of *S. epidermidis* or *Escherichia coli* while allowing the adhesion and proliferation of murine osteoblast cells (Zhuk et al. 2014). The same group has recently presented polymyxin B-loaded poly(methacrylic acid) hydrogel coatings, which released polymyxin B by the same mechanism (localized pH triggering), and authors proved that these coatings were able to inhibit the growth of *E. coli* even after repeated use or under flowing conditions (Albright et al. 2017). Also for coating applications, polymyxin B has been loaded into 2-hydroxyethyl methacrylate hydrogels on imprinted contact lenses (Malakooti et al. 2015) and as a cationic oral nanoemulsion with dexamethasone acetate for mucosa adhesion (Li et al. 2016). Based on the positive charge of polymyxin B, it is possible to perform polyion complexes based on electrostatic interactions with negatively charged polymers, such as poly(styrene sulfonate). Recently, polymyxin B-polyion complex nanoparticle colloidal suspensions have been reported with antibacterial activity against *P. aeruginosa* similar to free polymyxin B, while polymyxin B-polyion complex nanoparticles showed a gradual release of polymyxin B, which could reduce the toxicity at high doses (Insua et al. 2017a, b).

1.5.4 Nisin

Nisin (Fig. 1.16) is the most prominent member of the lantibiotic family, a group of ribosomally synthetized polycyclic antimicrobial peptides (AMPs) produced by *Lactococcus lactis* subsp. *lactis*, approved as a food preservative by the FDA (Ageitos et al. 2017). Nisins have been formulated in the form of nanoemulsions, nanoliposomes, nanoparticles, and nanofibers or immobilized to produce

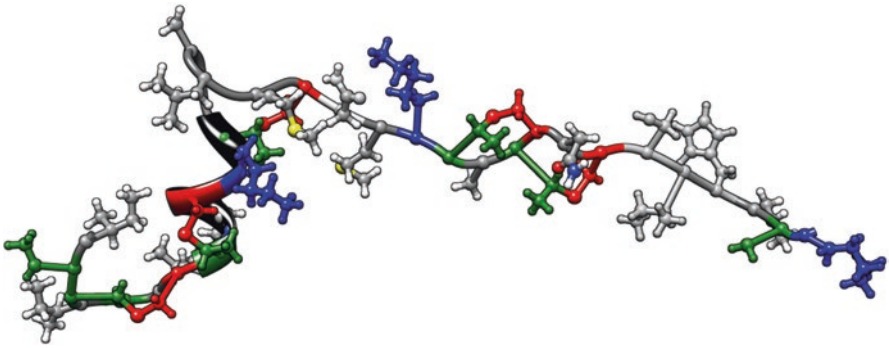

Fig. 1.16 Representation of the structure of nisin (PDB ID: 1WCO) depicting relevant residues. Red, cysteine. Green, uncommon amino acids. Blue, lysine

biodegradable films in order to increase its stability, allow a controlled release, or increase its activity range (Lemes et al. 2016; Khan and Oh 2016). Even if some of the formulation strategies resulted in a partial loss of activity (Carmona-Ribeiro and Carrasco 2014), nisin-loaded solid lipid nanoparticles have shown to inhibit *Listeria monocytogenes* and *Lactobacillus plantarum* grown for up to 20 and 15 days, respectively, compared to 1 and 3 days, respectively, for free nisin (Prombutara et al. 2012). Nisin incorporated with 2,3-dihydroxybenzoic acid in nanofibers of poly($_{D,L}$-lactide) and poly(ethylene oxide) was able to inhibit the biofilm formation by 88% after incubation with a methicillin-resistant *S. aureus* (MRSA) strain (Ahire and Dicks 2014). Based on the synergic effect, nisin-functionalized gold nanoparticles have been studied. The nanoparticles presented low cytotoxicity and lower minimum inhibitory concentration (MIC) (8- to 32-fold) than nisin for clinical isolates of *Enterococcus faecalis* and *S. aureus*, without the appearance of antibiotic resistance (Pradeepa et al. 2017).

1.5.5 Vancomycin

Vancomycin (Fig. 1.17) is a cyclic glycopeptide antibiotic, produced by *Amycolatopsis orientalis*, and is widely used for the treatment of Gram-positive bacterial infection, especially for MRSA. Vancomycin has long been considered as a "drug of last resort"; however, the appearance of vancomycin-resistant *S. aureus* (VRSA) or vancomycin-resistant enterococci (VRE) strains entailed the requirement of higher and more efficient dosage of vancomycin (Singh et al. 2014), which is a major concern, since vancomycin produces nephrotoxicity and hypersensitivity (Honary et al. 2014). Several strategies have been developed for enhancing the efficacy and reducing vancomycin toxicity. Improvement of intestinal viability of vancomycin has been conducted with vancomycin-Eudragit RS100-coated nanoparticles (Loveymi et al. 2012) or vancomycin-poly(lactic-*co*-glycolic acid) (PLGA)

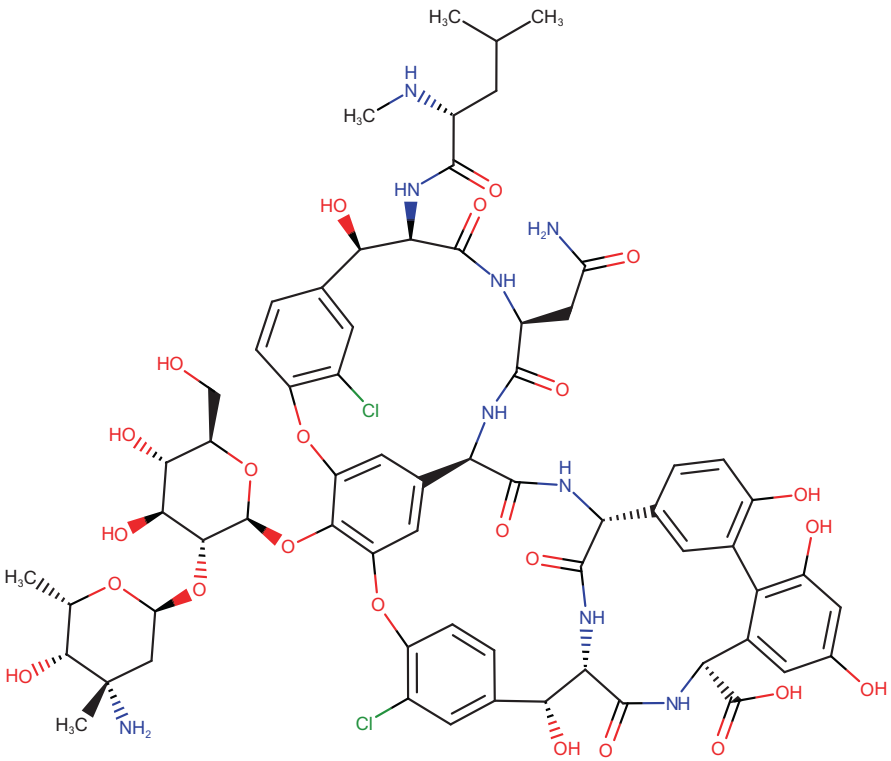

Fig. 1.17 Chemical structure of vancomycin. PubChem CID:14969

nanoparticles (Zakeri-Milani et al. 2013); in both cases, the intestinal absorption was higher than that of vancomycin solutions at the same concentrations.

The group of Concheiro has studied vancomycin loaded in different polymeric films, such as poly(propylene)films with cross-linked poly(acrylic acid) or interpenetrated networks of poly(acrylic acid) and cross-linked poly(acrylic acid) poly(*N*-isopropylacrylamide). All the films showed a pH-dependent vancomycin release and were able to reduce the formation of biofilms by MRSA (Ruiz et al. 2008). Further studies showed that direct grafting of poly(propylene) with gamma radiation produced the smart polymer *net*-poly(propylene)-*g*-poly(acrylic acid)-*inter-net*-poly(*N*-isopropylacrylamide), with temperature- and pH-responsible swelling; vancomycin-loaded-*net*-poly(propylene)-*g*-poly(acrylic acid)-*inter-net*-poly(*N*-isopropylacrylamide) films released vancomycin at adequate levels for killing bacteria attempting to adhere the surface of the film; this strategy seems suitable for functionalizing the surface of medical devices based on poly(propylene) (Muñoz-Muñoz et al. 2009). The group of Hu et al. has studied derivatized chitosan, vancomycin-loaded N-trimethyl chitosan nanoparticles (Xu et al. 2015), and vancomycin/N-trimethyl chitosan nanoparticles associated with composite beads of poly(trimethylene carbonate) (Zhang et al. 2017b) for the controlled release of van-

comycin. Both vancomycin/N-trimethyl chitosan nanoparticles and vancomycin/N-trimethyl chitosan nanoparticle-poly(trimethylene carbonate) had excellent antibacterial activity, while the combination of vancomycin/N-trimethyl chitosan nanoparticle-poly(trimethylene carbonate) was able to promote bone repair. Hachicha et al. studied vancomycin-loaded poly(lactic-*co*-glycolic acid) (PLGA) microparticles for continuous release in intraocular route (Hachicha et al. 2006). Vancomycin-loaded folic acid-tagged chitosan nanoparticles were able to reduce the minimum inhibitory concentration and minimum bactericidal concentration for VRSA strains. Authors concluded that folic acid tag was required for nanoparticle action (Chakraborty et al. 2010). Gu and collaborators described (vancomycin)-capped gold nanoparticles with an improved activity against VRE strains and Gram-negative bacteria (Gu et al. 2003). Comparable results were obtained by Mohammed Fayaz and collaborators with vancomycin-bound gold nanoparticles, which were able to reduce four times for *E. coli* and six times for VRSA the minimum inhibitory concentration as compared with free vancomycin (Mohammed Fayaz et al. 2011). Argenziano and collaborators have proposed an interesting approach for vancomycin delivery. Authors developed vancomycin-loaded nanobubbles, a core-shell nanostructure filled with a gas (perfluoropentane), with shell of dextran sulfate, where vancomycin was loaded. Vancomycin-nanobubbles allowed a controlled release of the active pharmaceutical ingredient and were generally more effective against MRSA than free vancomycin while reducing in vitro cytotoxicity on human keratinocytes (Argenziano et al. 2017).

1.6 Probiotic Microorganisms

Even though this chapter is focused on microbial compounds, it must also be taken into account that microorganism themselves can exert an important role in healthcare, as it is the case of probiotics. The Food and Agriculture Organization defines probiotic microorganisms as "live microorganisms, which when consumed in adequate amounts, confer a health effect on the host" (Morelli and Capurso 2012). Probiotics must survive to gastrointestinal tract in order to exert beneficial health effects (Calo-Mata et al. 2016); however, they lose viability due to the extreme conditions they are subjected (gastric acids, bile salts, proteases) (Arslan-Tontul and Erbas 2017). In view of the above, several formulations for the protection of probiotics have been developed. One example of coating technology is Phloral™, a combination of an anionic polymer based on starch, which cannot be digested by mammal amylases, but does bacterial ones, and Eudragit® S, a pH-activated polymer (Ambrogi et al. 2008; Dodoo et al. 2017). Dodoo and collaborators observed that lyophilized *Lactobacillus acidophilus* LA-5 has poor tolerance to simulated gastric fluid, while after encapsulation with Phloral®, viabilities of 90% were observed after the same treatment (Dodoo et al. 2017). Microencapsulation can produce single- or double-layered structures using techniques such as spray drying or

spray chilling. Arslan-Tontul and Erbas showed that the structure of the microcapsules will confer different survival rates to heat and gastric conditions of several probiotic microorganisms *Saccharomyces boulardii*, *L. acidophilus*, and *Bifidobacterium bifidum* (Arslan-Tontul and Erbas 2017). In general terms, single-layered microcapsules produced by spray drying (gum arabic and β-cyclodextrin) showed improved survivability, for instance, encapsulated microorganism survived after incubation at 80 °C, while non-encapsulated ones only bore at 50 °C. In order to increase the viability of probiotics during storage and gastrointestinal environment, pea protein-alginate microcapsules have been recently reported (Varankovich et al. 2017). *Lactobacillus rhamnosus* R0011 and *L. helveticus* R0052 were encapsulated in pea protein-alginate microcapsules with or without a chitosan coating, being observed that both formulations were able to protect the viability of probiotic microorganisms after incubation in simulated gastrointestinal environment. Moreover, chitosan-coated pea protein-alginate microcapsules were able to keep the viability of bacteria up to 9 weeks at room temperature (Varankovich et al. 2017). Besides the intrinsic prophylactic effect of probiotics, these microorganisms have been assayed for mitigating toxic side effects of chemotherapeutic agents; thus, Sharma et al. prepared microparticles containing 5-fluorouracil (pyrimidine analog that is an antineoplastic antimetabolite) and selected probiotic strain with high free radical scavenging activity. In vivo studies showed that microparticles with *L. rhamnosus* protected the colonic epithelium from the cytotoxic effect of 5-fluorouracil; these results open the door to a new solution for the problems associated with traditional chemotherapy (Sharma et al. 2017).

1.7 Conclusion

In the current chapter, we have summarized several novel strategies for the formulation of clinically relevant products with a microbiological origin, paying special attention to nanocarriers for advanced drug delivery. Through review of ongoing approaches, we have explored current academic and industrial interests toward the design of safer and better formulations. Besides some new emerging compounds, the current catalog of microbial drugs can alleviate most of the diseases for which they are described, but sometimes, at an excessive cost. Therefore, significant efforts have been paid for the development of new delivery systems, being among the most promising, the ones based on nanotechnology. These systems aim to improve some of the current drug limitations. Nanodevices maximize the surface by unit of mass, thus maximizing the possibilities for functionalization and interfacing with the biological environment, a characteristic that leads to unique properties as drug delivery carriers. In this way, new strategies attempt to enhance the bioavailability, minimize toxic effects, control the release of drugs, or broaden the range of treatable diseases with conventional drugs, among others. However, it is important to notice that nanomedicine is not a panacea since the properties of the materials drastically change at nanometric scale. On the one hand, new undesirable effects may emerge, even from

GRAS (generally recognized as safe) bulk materials at nanoscale, such as undesired accumulation in organs or even inside cells. On the other hand, the same formulation is not always universally applicable for different drugs; this means that every single compound requires a tremendous research effort in order to arise clinical market. It should be pointed out that there is a clear mismatch between the vast quantity of literature regarding this topic and the limited number of treatments approved so far. Notwithstanding, there is little doubt that after clinical approval, nanocarriers are safer and more efficacious than their traditional counterparts. Microbial drugs are a paradigm of variety and effectiveness, and if considered their synergic effect with a disruptive technology such as nanomedicine, each time more refined and accurate, we can boldly speculate that we are at the dawn of a new era that will utterly flourish in the next decades.

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The chemical structures were obtained from the PubChem Database (https://pubchem.ncbi.nlm.nih.gov/) and represented using the MarvinSketch software (ChemAxon Ltd, Budapest, Hungary).

Protein molecular models were obtained from the Protein Data Bank (PDB; http://www.rcsb.org/pdb; 1WCO). Molecular graphics and analyses were performed with the UCSF Chimera package (Pettersen et al. 2004). Chimera is developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco (supported by NIGMS P41-GM103311).

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