International Journal of Pharmaceutics 532 (2017) 139–148

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Broadening the spectrum of small-molecule antibacterials by metallic nanoparticles to overcome microbial resistance

Mahendra Rai[a,*], Avinash P. Ingle[a], Raksha Pandit[a], Priti Paralikar[a], Indarchand Gupta[a], Marco V. Chaud[b], Carolina Alves dos Santos[b]

[a] Nanobiotechnology Lab., Department of Biotechnology, SGB Amravati University, Amravati-444 602, Maharashtra, India
[b] LaBNUS – Biomaterials and Nanotechnology Laboratory, University of Sorocaba, Sorocaba/SP, Brazil

ARTICLE INFO

Keywords:
Nanoparticles
Drug resistance
Nanotechnology
Antimicrobials
Nanomedicine

ABSTRACT

Now-a-days development of microbial resistancce have become one of the most important global public health concerns. It is estimated that about 2 million people are infected in USA with multidrug resistant bacteria and out of these, about 23,000 die per year. In Europe, the number of deaths associated with infection caused by MDR bacteria is about 25,000 per year, However, the situation in Asia and other devloping countries is more critical. Considering the increasing rate of antibiotic resistance in various pathogens, it is estimated that MDR organisms can kill about 10 million people every year by 2050.

The use of antibiotics in excessive and irresponsible manner is the main reason towards its ineffectiveness. However, in this context, promising application of nanotechnology in our everyday life has generated a new avenue for the development of potent antimicrobial materials and compounds (nanoantimicrobials) capable of dealing with microbial resistance. The devlopement and safe incorporation of nanoantimicrobials will bring a new revolution in health sector. In this review, we have critically focused on current worldwide situation of antibiotic resistance. In addition, the role of various nanomaterials in the management of microbial resistance and the possible mechanisms for antibacterial action of nanoparticles alone and nanoparticle-antibiotics conjuagte are also discussed.

1. Introduction

The use of antimicrobials in therapeutics has increased considerably during the last few decades (Sandoval-Motta and Maximino, 2016). Moreover, new and emerging infections caused by microorganisms are also increased (Tanwar et al., 2014). The mechanism of action of antimicrobials is responsible for different range of action spectrum, as well as its application, from therapeutic use in humans, food additives/supplements, plants and animals (Nikaido, 2009). The antimicrobials available for the use are obtained by fermentation, synthetic and semisynthetic routes and cause the death of microorganisms, because they act on membrane of the microorganisms, affect nucleic acid synthesis and alter metabolism (Marinho et al., 2016).

The use of antimicrobials has generated a positive impact on the prolongation and improvement of the quality of life of the population. However, its excessive use has given rise to the emergence of antimicrobial resistance (AMR) to the compounds traditionally used, which is becoming a grave problem of world-wide public health (Fernadez et al., 2016). The bacterial strains, which acquired frequent emergence of resistance to antibiotics are referred to as “multi-drug resistant (MDR) bacteria”. Holmstrup and Klausen (2017) reported that in USA, AMR causes two million infections with 23,000 deaths annually and in Europe AMR is associated with about 25,000 deaths per year. However, the situation in Asia and other devloping countries is more critical. Moreover, considering the increasing rate of antibiotic resistance in various pathogens, it is estimated that MDR pathogens can kill about 10-million people every year by 2050, shockingly, this would surpass all other life threatening diseases including cancer (O’Neill, 2014).

Microbial resistance has caused a negative impact under the health system, increasing hospitalization time and treatment expenses (Holmstrup and Klausen, 2017). The mechanism of resistance is defined as the insensitivity of the microorganisms to a compound for which it was previously sensitive (Tanwar et al., 2014). Microbial resistance is classified as: (i) intrinsic resistance, (ii) incorporation of genetic material, and (iii) adaptive resistance. One of the major problems of microbial resistance is environmental dissemination and the absence of new compounds capable of reversing this scenario (Marinho et al., 2016). There is significant increase in infections caused by

* Corresponding author.
E-mail address: pmkrai@hotmail.com (M. Rai).

http://dx.doi.org/10.1016/j.ijpharm.2017.08.127
Received 15 June 2017; Received in revised form 31 August 2017; Accepted 31 August 2017
Available online 01 September 2017
0378-5173/

microorganisms which are resistant to many antimicrobials (Fernandez et al., 2016; Nikaido, 2009).

Nanotechnology represents a promising alternative for the development of new materials and compounds capable of being incorporated into everyday life, with applicability in health and other areas of science. According to Director General of the World Health Organization (WHO), Dr. Margaret Chan, use of nanomaterials as potential antimicrobial agents (nanomedicine) will be a post-antibiotic era, which has potential of overcoming the problem of AMR (http://www.nanowerk.com/spotlight/spotid=32188.php). Studies have demonstrated the ability of some organic and inorganic nanoparticles, which act as antimicrobial agents (Rudramurthy et al., 2016). The silver and gold nanoparticles, have the property to act on different parameters and functions of the microorganisms, which causes greater difficulty for the development of microbial resistance (Santos et al., 2014).

Hoseinzadeh et al. (2016) reported that some characteristics in nanomaterials are responsible for their antimicrobial effectiveness, which include nanomaterial load, type of material, shape, concentration, etc. Despite the advantages and potential applicability of nanomaterials in combating AMR, their toxicity and safety are barriers that limits their efficient and safe use (Wacker et al., 2016). The aim of this review is to focus on the current worldwide situation of AMR and role of various nanomaterials in overcoming the antibiotic resistance. In addition, possible antibacterial mechanisms of nanoparticles and nanoparticles-antibiotics conjugates against MDR bacteria and toxicity of nanomaterials is also discussed.

2. Role of metal nanoparticles in the management of AMR

The resistant bacteria include both Gram positive and Gram negative bacteria such as vancomycin-resistant *Enterococcus faecium* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug resistant (MDR) *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. It is well known that metal nanoparticles (MNPs) exhibit antimicrobial activity, which can efficiently deal with resistant strains of microorganisms. Table 1 summarizes the antibacterial efficacy of various nanoparticles against MDR bacteria.

2.1. Silver nanoparticles (AgNPs)

From the studies performed in the past it is evident that AgNPs possess strong antimicrobial potential against various microorganisms including MDR pathogens (Patra and Baek, 2017; Thapa et al., 2017). Percival et al. (2007) synthesized AgNPs and evaluated its antimicrobial activity against MDR Gram- positive and Gram- negative bacteria such as methicillin and vancomycin-resistant *Staphylococcus aureus* (MRSA and VRSA) and *Enterococcus faecium*. The study reported that AgNPs not only act as potential antimicrobial agent but also help in the inhibition of biofilm formation. Ingle et al. (2008) demonstrated the potential of AgNPs synthesized from *Fusarium acuminatum* against MDR *S.aureus*. Nanda and Saravanan (2009) evaluated the antimicrobial activity of AgNPs against MRSA, methicillin-resistant *Staphylococcus epidermidis* (MRSE). The authors suggested that AgNPs can be used as an alternative to combat the problem of drug resistant microorganisms.

The antimicrobial activity of AgNPs against MDR *P. aeruginosa*, ampicillin resistant *Escherichia coli* O157:H7 and erythromycin resistant *Streptococcus pyogenes* (ERSP) showed that AgNPs help in the reduction of the infections caused by MDR bacteria (Lara et al., 2010). Behera and Nayak (2013) agreed upon these findings and further presented the data supporting the use of AgNPs against MDR microbes. Rai et al. (2012) also reviewed that AgNPs can act as a powerful weapon against various MDR bacteria.

AgNPs synthesized from endophytic fungus *Penicillium* sp. possess antimicrobial activity against MDR *S. aureus* and *E. coli*. Both biologically and chemically synthesized AgNPs showed excellent antimicrobial activity against MDR pathogens (Singh et al., 2014). Chemically synthesized AgNPs inhibit 56% of biofilm formation by drug resistant strains of *P. aeruginosa* (Palanisamy et al., 2014). The antimicrobial activity of AgNPs depend on the stabilizing agent, charge and size of synthesized nanoparticles (Cavassin et al., 2015). Comparative antibacterial study of commercially available AgNPs and AgNPs stabilized with different compounds such as citrate, chitosan, polyvinyl alcohol against 54 drug resistant bacteria including oxacillin resistant *S. aureus*, carbapenem and polymyxin resistant *A. baumannii* (PRAB), carbapenem-resistant Enterobacteriaceae, vancomycin-resistant *Enterococcus* spp. demonstrated that citrate and chitosan AgNPs showed maximum antimicrobial activity. The antimicrobial activity of AgNPs was higher against Gram- negative microorganisms as compared to Gram- positive MDR resistant strains (Cavassin et al., 2015). Similarly, antibacterial efficacy of AgNPs was demonstrated against MDR *Enterobacter* sp., *P. aeruginosa*, *K. pneumoniae*, *E. coli* (Gopinath et al., 2015) and against MDR −Extended Spectrum Beta Lactamase producing *E. coli* (Kar et al., 2016).

2.2. Gold nanoparticles (AuNPs)

Compared to AgNPs, there are less reports available on the antimicrobial study of AuNPs. However, there are some reports which suggests that AuNPs do not have or possess very weak antimicrobial properties. The inconsistency in the antimicrobial activity of AuNPs may be due to improper purification of AuNPs (Shareena-Dasari et al., 2015). AuNPs did not show inherent activity against MDR bacteria. On the other hand, when AuNPs were functionalized with cationic group, antimicrobial activity against MDR microorganisms was demonstrated. *S. aureus* is considered as most deadly due to its resistance against various antibiotics. However, Li et al. (2014) demonstrated that AuNPs functionalized with thiol-group can be used as potential agent against MDR *S. aureus*. Vinoj et al. (2015) synthesized AuNPs and functionalized their surface with Acyl Homoserine Lactone Lactonase protein and the surface functionalized AuNPs were evaluated against MDR *Proteus* spp. *In vitro* effect of functionalized AuNPs was tested against biofilm of *Proteus* spp. Biofilm produced by *Proteus* spp. is the major cause of catheter-related urinary tract infections and the problems associated with it. Hence, synthesized AuNPs can act as a potential nanomaterial, which can be used against urinary tract infections caused by MDR bacteria such as *Proteus* spp. Zhao et al. (2013) reported the synthesis of AuNPs and coated its surface with dimethyl-biguanide. *In vitro* antimicrobial study of AuNPs alone and the coated nanoparticles against MDR *E. coli*, MRSA and *P. aeruginosa* showed that only coated AuNPs have antimicrobial activity against MDR microorganisms. Various antibiofilm agents with potential antimicrobial activity showed promising results in control of biofilm in medical sector. Combined use of antibiotics with antibiofilm agents like nanoparticles will upgrade action and prevent resistance problem (Abdel-Rahim and Mohamed, 2015).

2.3. Bismuth nanoparticles (BiNPs)

Bismuth is a crystalline, brittle metal and its compounds are used to treat gastrointestinal disorders (Tillman et al., 1996; Maev et al., 2008). Bismuth derivatives have been used in medicine to treat vomiting, diarrhea, nausea and stomach pain (Figueroa-Quintanilla et al., 1993). BiNPs in combination with chlorhexidine, nystatin, and terbinafine controls the growth and biofilm formation (Hernandez-Delgadillom et al., 2012). It was also reported that zerovalent BiNPs have potential to reduce cell growth of *Streptococcus mutans* in biofilm formation (Hernandez-Delgadillom et al., 2012). These nanoparticles prevent biofilm formation up to 69%. Bismuth-containing nanoparticles with X-ray irradiation treatment also have potential to kill MDR bacteria (Luo et al., 2013). The authors reported that the surface modified BiNPs showed up to 90% growth inhibition against MDR *P. aeruginosa*. Since, X-rays can easily penetrate human tissues, this bactericidal strategy has the potential to be used effectively in killing of MDR bacteria *in vivo*.