Morphological and physical - chemical issues of metal nanostructures used in medical field

L. D. Ducea, N. Velenciuc, E. C. Dobre

1 Apollonia University of Iasi, Romania.  
2 Academician Ioan Haulica Institute of Researches, Apollonia University of Iasi.  
3 Oncology Regional Institute of Iasi, Romania.

E-mail: vilinat2001@yahoo.com

Abstract. In recent years applications of nanotechnology integrated into nanomedicine and bio-nanotechnology have attracted the attention of many researchers from different fields. Processes from chemical engineering especially nanostructured materials play an important role in medical and pharmaceutical development. Fundamental researches focused on finding simple, easily accomplished synthesis methods, morphological aspects and physico-chemical advanced characterization of nanomaterials. Moreover, by controlling synthesis conditions textural characteristics and physicochemical properties such as particle size, shape, surface, porosity, aggregation degree and composition can be tailored. Low cytotoxicity and antimicrobial effects of these nanostructured materials makes them be applied in medicine field. The major advantage of metal based nanoparticles is the use either for their antimicrobial properties or as drug-carriers having the potential to be active at low concentrations against infectious agents.

1. Introduction

In our century, microbes type virulent strains of bacteria have developed resistance to antibiotics that lead to a tremendous health impact and need to deliver solutions to this worldwide problem. The use of nanotechnology in medicine field, particularly nanomedicine, has already proved its major action on the pharmaceutical industry, especially in the antimicrobial field [1]. Over the last century antibiotics and vaccines arguably reduced human morbidity and mortality being considered the most important medical discoveries against infectious diseases [2,3].

Antimicrobial agents development represent a necessary help for classic medicine considering high resistant of pathogen micro-organisms. Researchers identified several inorganic, organic, and hybrid materials with possible uses in prevention and treatment of infections reporting the current information on the action mechanism of nano/microparticles based antimicrobial agents [4].

2. Materials and methods

Nowadays, a well-established branch of science called micro/nanomedicine, manages with tailoring small size devices, i.e. micro/nanoparticles, possessing unique properties for human health. Figure 1
shows a schematic exemplification of nano/ microparticles frequently used for drug delivery and therapeutic systems. Their biological properties are correlated to structural and functional characteristics.

There are studies specifying the relationship between cells and micro/ nanoparticles correlated to their structural and textural characteristics like size, shape, charge and functional groups having a considerable impact on their internalization.

Figure 1. Exemple of nano/microsystems: a) antimicrobial polymers, b) polymer chains, c) inorganic nanoparticles, d) liposomes, e) polymeric nanoparticles, f) solid lipid nanoparticles loaded with antimicrobial drug, g) microbubbles loaded with nanoparticles.

Negative surface charge versus particles positive surface charge shows a significant reduction of particle association with cells [5].

3. Experimental part
Inorganic and hybrid materials were identified exhibiting antimicrobial activity depending on their physico-chemical and morpho-functional properties. Ionic form of metal based nanoparticles express antimicrobial ability compared to the metal, exhibiting an equivalent or superior antimicrobial effect [6-8]. Size, shape, porosity and surface properties are of great importance features inducing the antimicrobial efficacy of metal base nanoparticles. For example figure 2 shows TEM images of Ag nanoparticles revealing particles wide distribution ranging from 5 to 25 nm in diameter. Smaller particles are spherical in shape whereas the larger ones are in an elongated form and shape that could be the result of the aggregation degree of the two or more particles together. Silver size and shape nanoparticles are also influenced by the concentration silver salt solution [9]. A major increase in the surface area consists in a stronger interaction of nanoparticles with the surrounding materials. Disadvantages of these material synthesis methods are represented by the toxicity of the reagents and the agglomeration and precipitation of nanoparticles [10].

Figure 2. TEM and HRTEM images of silver nanoparticles on the GrO sheets at different salt concentrations: a) $8 \times 10^{-3}$ moldm$^{-3}$ AgNO$_3$, b) $1 \times 10^{-3}$ moldm$^{-3}$ AgNO$_3$, c) HRTEM with fringe spacing, d) enlarge image of fringe spacing.
Other uses of nanocomposite materials refer to coating medical devices and production of antimicrobial cotton textiles already being demonstrated to reduce postoperative infections [11]. Bionanotechnology use plants and micro-organisms such as bacteria, yeasts, fungi, and actinomycetes for fabrication of inorganic nanoparticles [12].

Multidisciplinary nano-scaled molecules used in diagnosis and treatment of different diseases are represented by metal oxide nanoparticles already applied as effective antimicrobial agents. Metal oxide nanoparticles are well known to target some cellular signaling pathways. Combination of metal oxides with other therapeutic agents enhances their bioavailability and efficacy. These remarkable nanomaterials have been used due to their various action mechanisms as antioxidant, anticancer, antimicrobial, and anti-inflammatory agents [13].

A serious threat to public health worldwide is considered to be the emergence of antibiotic-resistant microbial strains. Advanced nano-biotechnology enable the researchers to synthesize specific nanoparticulated metal oxide with well establish properties as antimicrobial activity. Zinc oxide nanoparticles were proven to inhibit the growth of wide spectrum bacterial strains such as gram-negative E. coli and Pseudomonas aeruginosa as well as gram-positive Staphylococcus aureus [14].

**Figure 3.** Test results of zinc oxides effect on P. aeruginosa in the oil-in-water emulsion, in the water-in-oil emulsion and in the dry powder.

Decreasing metal oxide nanoparticles size led to distortion and damage of bacterial cell membrane. Moreover, leakage of intracellular contents and possible death of bacteria demonstrate the antibacterial effects of these outstanding materials [15]. Different concentrations of ZnO nanoparticles in the anhydrous product were tested concerning P. aeruginosa as shown in figure 3.
4. Results and discussions

Results concerning P. aeruginosa bacterial strain revealed that bacterial population finally exceeded the control without zinc oxide nanoparticles at 28 days and decreased over 7 days, but then proliferated again during storage after 32 days [16].

Metal oxide nanoparticles known to possess a unique electronic structure provides a surface for direct free radical scavenging activity promising to act as an antioxidant therapeutic agent (Fig. 4).

Researchers found in a study of nerve cells (HT22), that CeO2/or Y2O3 nanoparticles, protect nerve cells suggesting that small size metal oxides could be the modulator of the oxidative stress in the biological systems [17].

Recent studies revealed that synthesized copper oxide nanoparticles using a thermal plasma technique have showed a minimum inhibitory concentration in the range 100 - 5000 μg/ml against drug resistant bacterial strains [18]. Other researches found that photo-activation of TiO2 nanoparticles using the ultra violet (UV) radiations, support the bactericidal effect which might be due to loss of respiratory activity caused by peroxidation of the polyunsaturated phospholipids of cell membrane [19].

![Figure 4. Brief representation of the direct free radical scavenging potential of metal oxide nanoparticles.](image)

Among aluminum, silicon, titanium and zinc oxide nanoparticles against bacterial strains of Bacillus subtilis, E. coli and Pseudomonas fluorescens, ZnO nanoparticles were found to be more potent with 100% motility followed by SiO2 and Al2O3 nanoaprticles [20].

![Figure 5. Representation of possible antibacterial mechanism of metal oxide nanoparticles activity.](image)
The mechanism of antimicrobial action of metal oxide nanoparticles is not completely understood, it may depend on chemical composition, surface changes and intrinsic properties of nanomaterials along with the preponderant bacterial species. Nanoparticles were proved to be assigned to the microbial cell with electrostatic interactions consisting of cell wall damage concomitant with the increase in permeability of the cell [21, 22]. Figure 5 shows electrostatic interactions of metal oxide nanoparticles followed by reactive oxygen species (ROS) generation and activation of oxidative stress genes and the inhibitory effect of these nanoparticulate materials on drug resistance mechanisms mediated by β-lactamases and antibiotic efflux pumps.

Mutagenic potential of ZnO, CuO, TiO₂, Al₂O₃, and Co₃O₄, and type metal oxides was investigated and reported significant colony inhibition activity of CuO nanoparticles. Generally, metal and metal oxide nanoparticles are known to destroy cell wall due to the interaction with the thiol (–SH) group of membrane proteins. Further more, metal oxide nanoparticles can deactivate the β-lactamases preventing the evolution of antibiotic resistance [23].

5. Conclusions
Remarkable morphology properties, physical-chemical characteristics, biological applications of metal nanoparticles significantly improve classic medicine. Metal and metal oxide nanoparticles incorporated into matrices act as active components in nanocomposites being biocompatible and suited for biomedical applications. In order to perform controlled release of drugs, by incorporating specific functional groups into matrices chemical engineering research has a major impact on nanomedicine research. Over the last few years nanosized materials have considerable evolved bringing to nanomedicine unprecedented advances in the diagnosis, imaging and treatment of a variety of hard to treat diseases. Nowadays, around 250 nanoproducts exist in various stages of development, including different compositions, nanostructures, physicochemical characteristics, surface functionality and morphology. Thus, nanomedicine researches will have to exceed chemical engineering and consider new medical aspects including in vivo studies and clinical trials.

References:

[1] Zhu X, Radovic-Moreno A F, Wu J, Langer R and Shi J 2014 Nanomedicine in the management of microbial infection—Overview and perspectives Nano Today 9 pp 478–498
[2] Cohen M L 2000 Changing patterns of infectious disease Nature 406 pp 762–767
[3] Armstrong G L, Conn L A and Pinner R W 1999 Trends in infectious disease mortality in the United States during the 20th century J. Am. Med. Assoc. 281 pp 61–66
[4] Cavalieri F, Tortora M, Stringaro A, Colone M, Baldassarri L 2014 Nanomedicines for antimicrobial interventions Journal of Hospital Infection 88 pp 183–190
[5] Gratton S E A, Ropp P A, Pohlhaus P D et al. 2008 The effect of particle design on cellular internalization pathways Proc. Natl. Acad. Sci. USA 105 pp 11613–11618
[6] Dallas P, Sharma V K and Zboril R 2011 Silver polymeric nanocomposites as advanced antimicrobial agents: classification, synthetic paths, applications, and perspectives Adv Colloid Interface Sci 166 pp 119–135
[7] Park H, Park S, Roh J et al. 2013 Biofilm-inactivating activity of silver nanoparticles: a comparison with silver ions J Ind Engng Chem 19 pp 614–619
[8] Nie M, Sun K, Meng D D 2009 Formation of metal nanoparticles by short distance sputter deposition in a reactive ion etching chamber J Appl Phys 2009 106 054314
[9] Das M R, Sarma R K, Saikia R, Kale V S, Shelke M V and Sengupta P 2011 Synthesis of silver nanoparticles in an aqueous suspension of graphene oxide Colloids and Surfaces B: Biointerfaces 83 pp 16–22
[10] Morones J R, Elechiguerra J L, Camacho A et al. 2005 The bactericidal effect of silver nanoparticles Nanotechnology 16 pp 2346-2353
[11] Seo S Y, Lee G H, Lee S G, Jung S Y, Lim J O, Choi J H 2012 Alginate-based composite sponge containing silver nanoparticles synthesized in situ Carbohydr Polym 90 pp 109-115
[12] Li X, Xu H, Chen Z and Chen G 2011 Biosynthesis of nanoparticles by microorganisms and their applications J Nanomat 3 pp 270974-270990
[13] Hardeep S T, Dharambir K, Simranjeet K B, Pardeep K, Gaurav K and Sardul S S 2015 Molecular aspects of metal oxide nanoparticle (MO-NPs) mediated pharmacological effects Life Sciences 143 pp 71–79
[14] Premanathan M, Karthikeyan K, Jeyasubramanian K and Manivannan G 2011 Selective toxicity of ZnO nanoparticles toward gram-positive bacteria and cancer cells by apoptosis through lipid peroxidation Nanomedicine 7 pp 184–192
[15] Sharma D, Rajput J, Kaith B S, Kaur M and Sharma S 2010 Synthesis of ZnO nanoparticles and study of their antibacterial and antifungal properties Thin Solid Films 519 pp 1224-1229
[16] Pasquet J, Chevalier Y, Couval E, Bouvier D and Bolzinger M A 2015 Zinc oxide as a new antimicrobial preservative of topical products: Interactions with common formulation ingredients International Journal of Pharmaceutics 479 pp 88–95
[17] Schubert D, Dargusch R, Raitano J and Chan S W 2006 Cerium and yttrium oxide nanoparticles are neuroprotective Biochem. Biophys. Res. Commun. 342 pp 86–91
[18] Rena G, Hub D, Cheng E W C, Reuse M A V, Reipd P, Allakerc R P 2009 Characterisation of copper oxide nanoparticles for antimicrobial applications Int. J. Antimicrob. Agents 33 pp 587–590
[19] Tsuang Y H, Sun J S, Huang Y C, Lu C H, Chang W H S and Wang C C 2008 Studies of photokilling of bacteria using titanium dioxide nanoparticles Artif. Organs 32 pp 167–174
[20] Jiang W, Mashayekhi H and Xing B 2009 Bacterial toxicity comparison between nano and micro scaled oxide particles Environ. Pollut. 157 pp 1619–1625
[21] Feris K, Otto C, Tinker J, Wingett D, Punnoose A, Thuberger A, Kongara M, Sabetian M, Quinn B, Hanna C and Pink D 2010 Electrostatic interactions affect nanoparticle mediated toxicity to gram-negative bacterium Pseudomonas aeruginosa PA01 Langmuir 26 pp 4429–4436
[22] Sinha R, Karan R, Sinha A, Khare S K 2011 Interaction and nanotoxic effect of ZnO and Ag nanoparticles on mesophilic and halophilic bacterial cells Bioresour. Technol. 102 pp 1516–1520
[23] Jayaraman R 2009 Antibiotic resistance: an overview of mechanism and a paradigm shift Curr. Sci. 96 pp 1475–1484