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Perspectives for the use of silver nanoparticles in dental practice

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Nanotechnology has been used for medical applications in several forms, including dental practice with the development of silver nanoparticles (Ag NPs) as a useful tool. The aim of this review was to identify the properties and appliances of Ag NPs in dental practice. Silver compounds and NPs have already been used as dental restorative material, endodontic retrofill cements, dental implants and caries inhibitory solution. Despite the effectiveness that Ag NPs has showed in dental practice, Ag NPs remain a controversial area of research with respect to their toxicity in biological and ecological systems. Therefore any application of Ag NPs in dentistry requires more studies. In order to avoided the toxicity of these materials Ag NPs can be temporarily used in dentistry.

Key words: *Silver nanoparticles, dental practice, applications of Ag NPs*

INTRODUCTION

Nanotechnology, which concerns structures at the nanometer scale (1–100 nm), is considered as a vital current technology of the 21st century based on its economic and scientific potential. In 2008, the public expenditure of nanotechnology was 430 mmd compared to 25 mmd in 1997[1,2]. Nanoparticles (NPs) have a greater surface-to-volume ratio (per unit mass) than non-nanoscale particles of the same material, and therefore are more reactive. Particles smaller than 50 nm are subject to the laws of quantum physics[3].

In 2008 and 2009, silver production was 21 300 and 21 400 tons, respectively, according to United States Geological Survey (USGS)[4]. Over the years, silver compounds and NPs (Figure 1) have exhibited antibacterial activity resulting in the widespread use of silver nanoparticles (Ag NPs) in bedding, washing machines, water purification, toothpaste, shampoo and rinse, nursing bottles, fabrics, deodorants, filters, kitchen utensils, toys and humidifiers[5]. Furthermore, silver compounds and NPs[6] have been studied for dental applications including dental restorative material[7], endodontic retrofill cement[8], dental implants[9], and caries inhibitory solution[10]. The aim of this brief review was to identify the properties and appliances of Ag NPs in dentistry practice.

ANTIMICROBIAL PROPERTIES

Most of the studies have indicated that silver interacts with sulfhydryl groups of proteins and with DNA, altering hydrogen bonding, respiratory processes, DNA unwinding, cell-wall synthesis and cell division[11,12]. At the macro level, these interactions effectively produce bacterial death[13].

It is recognized that Ag NPs have antimicrobial activity against Gram-negative bacteria performing 'pits' in the cell wall of the bacteria. Clearly, a membrane with such morphology exhibits a significant increase in permeability, resulting in death of the cell. Overall, silver mainly induces denaturation and oxidization for cell wall which lead to rupture of the internal cell organelles, resulting in bacterial death[14,15]. Although bacterial cell lysis could be one of the reasons for the observed antibacterial property, NPs also modulate the phosphotyrosine profile of putative bacterial peptides, which could affect bacterial signal transduction and inhibit the growth of the organisms[16].

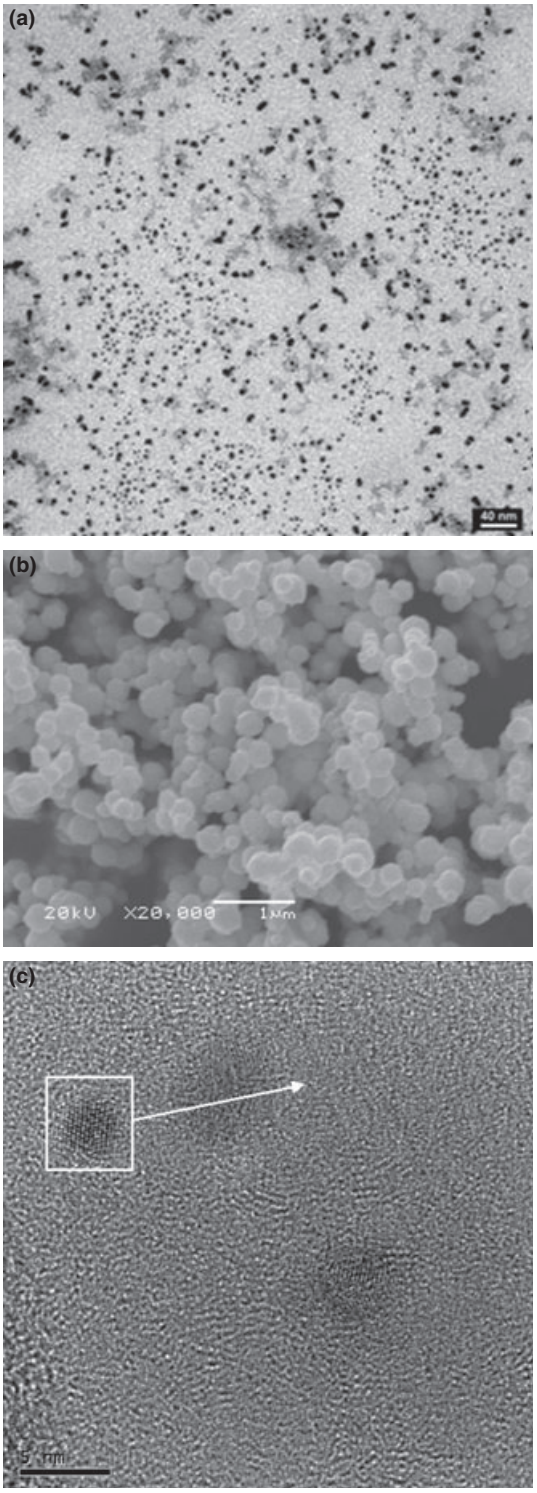

Figure 1. Scanning Electron Microscope views of Ag NPs. Illustration provided by Professor Raúl Alberto Morales Luckie, Faculty of Chemistry, UAEMex.

It is worth noting that the antibacterial activity of nanosilver is dominated by silver ions (Ag^+ ions) when fine Ag NPs (less than about 10 nm in average diameter) are employed that release high concentrations of these ions. In contrast, when relatively larger Ag NPs are used, the concentration of the released Ag^+ ions is lower[17]. Likewise, Ag NPs with average size 14 ± 6 nm and Ag^+ ions such as $AgNO_3$, inhibit the growth of *Escherichia coli* 55 ± 8% and 100%, respectively (Table 1 shows the antimicrobial effect of Ag NPs).

Table 1 Antimicrobial properties of Ag NPs

Gram-positive bacteria	*Streptococcus sanguis*[6]
	Bacillus subtilis[35]
	Enterococcus faecalis[35]
	Staphylococcus aureus[36]
Gram-negative bacteria	*Escherichia coli*[36]
	Salmonella typhimurium[35]
	Shigella dysenteriae type 1[38]
	Citrobacter sp[37]
	Pseudomona aeruginosa[37]
	Pseudomona fluorescens[38]
Fungi	*Candida albicans*[39]
	Fusarium oxysporum[37]
Virus	*Arenavirus*[40]
	Human immunodeficiency virus-1[42]
	Murine norovirus[41]
	Hepatitis B virus[42]

Furthermore, silver particles are also used as alternative radiopacifier to get the necessary radiopacity to calcium silicate cements (CSC) and assess the purity of the radiopacifying agents[18]. These nanomaterials, which can be prepared in a simple and cost-effective manner, may be suitable for the formulation of new types of bactericidal materials[13].

CARIES INHIBITORY PROPERTIES

The most common worldwide oral diseases are dental caries and periodontal diseases, 60–90%, according to the World Health Organization (WHO)[19]. In Mexico, some authors estimate that such diseases affect 90% and 70% of the population, respectively[20]. In this regard, the use of silver solution, specifically, silver diamine fluoride (Ag $[NH_3]$ 2F) has been used as caries inhibitor. In context, fluoride and silver interact synergistically to form fluorapatite. The first step is the formation of calcium fluoride (CaF_2) and silver phosphate (Ag_3PO_4) in a basic environment, the second reaction is the subsequent dissociation of calcium and fluoride[21].

Experimental composite adhesives (ECAs) showed slower bacterial growth than those containing conventional adhesives, suggesting that ECAs can help prevent enamel demineralization around their surfaces without compromising physical properties[22].

RESTORATIVE MATERIALS

Whereas restorative materials with a silver polymer compound have showed effective antimicrobial properties on implant components against *Streptococcus*

sanguis[6], silver has been incorporated into glass ionomer cements in order to improve the antibacterial properties, including also, compressive, tensile strength and creep resistance.

Biofilms are surface-adherent populations of microorganisms consisting of cells, water and extracellular matrix material. Nanotechnology is a promising field of science which can guide our understanding of the role of interspecies interaction in the development of biofilm. *Streptococcus mutans* with other species of bacteria has been known to form dental biofilm. The correlation between genetically modified bacteria *Streptococcus mutans* and nanoscale morphology has been assessed using atomic force microscopy (AFMi). Occasionally, silver nanofibers have been attached to the implant surfaces to reduce the need of using high doses of antibiotics during the healing period, giving self-cleaning against plaque biofilm[9].

THERAPEUTICS

Nanostructures of different sizes, shapes and material properties have many applications in biomedical imaging, clinical diagnostics and therapeutics. In spite of what has been achieved so far, a complete understanding of how cells interact with nanostructures of well-defined sizes, at the molecular level, remains poorly understood.

Gold and Ag NPs coated with antibodies can regulate the process of membrane receptor internalization. The binding and activation of membrane receptors and subsequent protein expression strongly depend on nanoparticle size. Although all NPs within the 2–100 nm size range alter signaling processes essential for basic cell functions (including cell death) 7, 40- and 50-nm NPs demonstrate the greatest effect. These results show that NPs should no longer be viewed as simple carriers for biomedical applications, but can also play an active role in mediating biological effects. These findings may assist in the design of nanoscale delivery and therapeutic systems and provide insights into nanotoxicity[23].

ADVERSE EFFECTS

Metal ions are released from casting alloys and cause damage to cell structures and local inflammation. $Ag(NH_3)2F$ in contact to Human Gingival Fibroblast (HGF) for only one hour induced irreversible necrosis cell death, whereas longer duration of contact with AgCl was necessary to induce this same effect. These data suggest the importance of cautious application of Ag $(NH_3)2F$ into the oral cavity[24]. $Ag(NH_3)2F$ shows much more sensibility at dose-dependent ion against three normal cells and three cancer line cells than AgCl (Figure 2a,b).

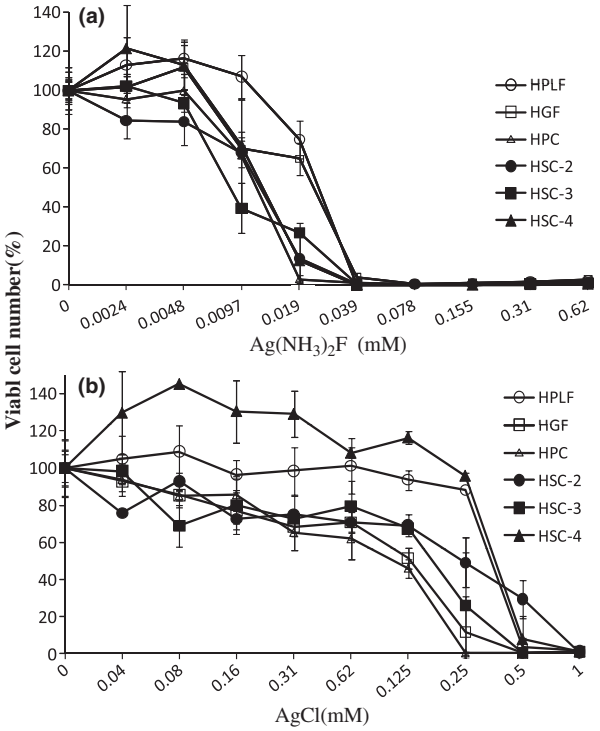

Figure 2. Cytotoxicity of $Ag(NH_3)F_2$ and AgCl against six cell lines, respectively. HPLF, human periodontal ligament fibroblast cells; HGF, human gingival fibroblast cells; HPC, human pulp cells and human oral squamous cells carcinoma obtained from different patients (HSC-2, 3, 4) were incubated for 24 h with the indicated concentrations of metal and then the relative viable cell number was determined by MTT method. Each value represents the mean ± S.D. of triplicate assays. Reproducible results were obtained in further two independent experiments.

Nanotoxicity is the toxicity imposed by nanomaterials[25]. The toxic effects of Ag NPs are proportional to the activity of free Ag^+ ions released by the NPs[26]. Although NPs have tremendous potential for a host of applications, their adverse effects on living cells have raised serious concerns for their use in the healthcare and consumer sectors. For example, NPs may be taken up directly into the brain by trans-synaptic transport and Ag NPs can enter via the blood-brain barrier and accumulate in different regions of the brain and this may be beneficial for drug delivery, increasing a risk to the patient. It has also been reported that nanoparticle exposure can induce impairments to normal neuron-microglia microenviroment and even aggravate the process of brain pathology[27].

In support of the damage notion, *in vitro* cell line studies have shown decreased mitochondrial function after exposure to Ag NPs in murine neuroblastoma cells[28], hepatic cells[29], germline stem cells[30], human skin carcinoma[31] and human epidermal keratinocytes and fibroblasts[32], while *in vivo* studies showed that exposure to NPs could result in an inflammation, oxidative stress, myocardial infarction and thrombosis[33].

As above mentioned, NPs could alter the permeability of blood brain barrier[34].

Exposure to Ag NPs has been associated with tissue damage especially in liver. In rats, it has been determined for Ag NPs a No Observable Adverse Effect Level (NOAEL) of 30 mg/kg and the Lowest Observable Adverse Effect Level (LOAEL) of 125 mg/kg[35].

NPs could also damage DNA causing deletions, mutations, single and double strand breakages, adduct formation, and cross linking with proteins. Some studies have confirmed DNA adducts and oxidation and induced DNA fragmentation following exposure to metal oxide NPs. In response to DNA insult, cells attempt to repair damage DNA but repair failure may lead to cell death (apoptosis) or cell transformation. In the case of severe damage to DNA, cells may die by either necrosis or apoptosis. In this regard, it has been published previously that exposure to certain metal oxide NPs induces apoptosis[36].

Corrosion and discoloration of dental materials in contact with Ag NPs may be a concern. On the other hand, antibacterial property carries with it a potential environmental risk once these NPs are discharged into the environment. Of particular concern, Ag^+ ions from $AgNO_3$ inhibit the algae's photosynthesis around 18 times more than Ag NPs. However, over a long period, the NPs are even more toxic than the ions alone[37]. These environmental concerns have led to a debate among advocacy groups and governments on whether special regulation of nanotechnology is warranted.

CONCLUSION

Despite the effectiveness that Ag NPs have showed in dental practice, Ag NPs remain a controversial area of research with respect to their toxicity in biological and ecological systems[38]. Therefore any applications of Ag NPs in dentistry requires more study. Initially, in order to avoide the toxicity of these materials we think Ag NPs can be used for temporary periods in the dental field.

REFERENCES

1. Harper TE, Holister P. *The Nanotechnology Opportunity Report*. 2nd edn, London: Cientifica; 2003.
2. Roco M. Nanoscale science and engineering: unifying and transforming tools. *AIChE J* 2004 50: 890–897.
3. Auffan M, Rose J, Bottero JY *et al.* Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective. *Nat Nanotechnol* 2009 4: 634–641.
4. Kelly TD, Matos GR. Historical statistics for mineral and material commodities in the United States. 2010. Available from: http://minerals.usgs.gov/ds/2005/140/. Accessed 31 May 2011, 18:04 PM.
5. Maynard AD. *Nanotechnology: A Research Strategy for Addressing Risk*. Washington: Woodrow Wilson International Center for Scholars; 2006. Available from: http://www.tinhoahoc.com/Nanotechnology/RiskRelatedReseach_Maynard_7-06-Final.pdf. Accessed 31 May 2011, 18:04 PM.
6. Slenters TV, Hauser-Gerspach I, Daniels AU *et al.* Silver coordination compounds as light-stable, nano-structured and antibacterial coatings for dental implant and restorative materials. *J Mater Chem* 2008 18: 5359–5362.
7. Jia H, Hou W, Wei L *et al.* The structures and antibacterial properties of nano-SiO2 supported silver/zinc-silver materials. *Dent Mater* 2008 24: 244–249.
8. Pissiotis E, Spangberg L. Reaction of bony tissue to implanted silver glass ionomer and a reinforced zinc oxide-eugenol cement. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000 89: 623–629.
9. Sheikh FA, Barakat NA, Kanjwal MA *et al.* Electrospun titanium dioxide nanofibers containing hydroxyapatite and silver nanoparticles as future implant materials. *J Mater Sci Mater Med* 2010 21: 2551–2559.
10. Swift EJ Jr. In vitro caries-inhibitory properties of a silver cermet. *J Dent Res* 1989 68: 1088–1093.
11. Lansdown AB. Silver in health care: antimicrobial effects and safety in use. *Curr Probl Dermatol* 2006 33: 17–34.
12. Oppermann RV, Johansen JR. Effect of fluoride and non-fluoride salts of copper, silver and tin on the acidogenicity of dental plaque in vivo. *Scand J Dent Res* 1980 88: 476–480.
13. Wu MY, Suryanarayanan K, van Ooij WJ *et al.* Using microbial genomics to evaluate the effectiveness of silver to prevent biofilm formation. *Water Sci Technol* 2007 55: 413–419.
14. Lara HH, Ixtepan-Turrent L, Garza-Trevino EN *et al.* PVP-coated silver nanoparticles block the transmission of cell-free and cell-associated HIV-1 in human cervical culture. *J Nanobiotechnology* 2010 8: 15.
15. Sondi I, Salopek-Sondi B. Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gram-negative bacteria. *J Colloid Interface Sci* 2004 275: 177–182.
16. Shrivastava S, Bera T, Singh SK *et al.* Characterization of antiplatelet properties of silver nanoparticles. *ACS Nano* 2009 3: 1357–1364.
17. Sotiriou GA, Pratsinis SE. Antibacterial activity of nanosilver ions and particles. *Environ Sci Technol* 2010 44: 5649–5654.
18. Camilleri J, Gandolfi MG. Evaluation of the radiopacity of calcium silicate cements containing different radiopacifiers. *Int Endod J* 2010 43: 21–30.
19. World Health Organization. 2011. Available from: http://www.who.int/mediacentre/factsheets/fs318/en/index.html. Accessed 31 May 2011, 18:04 PM.
20. de la Fuente-Hernández J, González de Cosío M, Ortega-Maldonado M *et al.* [Dental decay and tooth loss at the high school level in Mexican students]. *Salud Publica Mex* 2008 50: 235–240.
21. Rosenblatt A, Stamford TC, Niederman R. Silver diamine fluoride: a caries 'silver-fluoride bullet'. *J Dent Res* 2009 88: 116–125.
22. Ahn SJ, Lee SJ, Kook JK *et al.* Experimental antimicrobial orthodontic adhesives using nanofillers and silver nanoparticles. *Dent Mater* 2009 25: 206–213.
23. Jiang W, Kim BY, Rutka JT *et al.* Nanoparticle-mediated cellular response is size-dependent. *Nat Nanotechnol* 2008 3: 145–150.
24. Contreras RG, Sakagami H, Nakajima H *et al.* Type of cell death induced by various metal cations in cultured human gingival fibroblasts. *In Vivo* 2010 24: 513–517.
25. Fadeel B, Garcia-Bennett AE. Better safe than sorry: understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications. *Adv Drug Deliv Rev* 2010 62: 362–374.

26. Park EJ, Yi J, Kim Y *et al.* Silver nanoparticles induce cytotoxicity by a Trojan-horse type mechanism. *Toxicol In Vitro* 2010 24: 872–878.
27. Yang Z, Liu ZW, Allaker RP *et al.* A review of nanoparticle functionality and toxicity on the central nervous system. *J R Soc Interface* 2010 7(Suppl. 4): S411–S422.
28. Schrand AM, Braydich-Stolle LK, Schlager JJ *et al.* Can silver nanoparticles be useful as potential biological labels? *Nanotechnol* 2008 19: 104–119.
29. Hussain SM, Hess KL, Gearhart JM *et al.* In vitro toxicity of nanoparticles in BRL 3A rat liver cells. *Toxicol In Vitro* 2005 19: 975–983.
30. Braydich-Stolle L, Hussain S, Schlager JJ *et al.* In vitro cytotoxicity of nanoparticles in mammalian germline stem cells. *Toxicol Sci* 2005 88: 412–419.
31. Arora S, Jain J, Rajwade JM *et al.* Cellular responses induced by silver nanoparticles: in vitro studies. *Toxicol Lett* 2008 179: 93–100.
32. Burd A, Kwok CH, Hung SC *et al.* A comparative study of the cytotoxicity of silver-based dressings in monolayer cell, tissue explant, and animal models. *Wound Repair Regen* 2007 15: 94–104.
33. Kumar CSSR. Nanomaterials: toxicity, health and environmental issues. Wiley-VCH, LA, USA: 2006; p. 96, 306–308.
34. Zhao Y, Nalwa HS. *Nanotoxicology*. Stewenson Ranch, USA: American Scientific Publishers; 2006.
35. Kim YS, Song MY, Park JD *et al.* Subchronic oral toxicity of silver nanoparticles. *Part Fibre Toxicol* 2010 7: 20.
36. Huang YW, Wu C, Aronstam RS. Toxicity of Transition Metal Oxide Nanoparticles: recent Insights from in vitro Studies. *Materials* 2010 3: 4842–4859.
37. Navarro E, Piccapietra F, Wagner B *et al.* Toxicity of silver nanoparticles to Chlamydomonas reinhardtii. *Environ Sci Technol* 2008 42: 8959–8964.
38. Allaker RP. The use of nanoparticles to control oral biofilm formation. *J Dent Res* 2010 89: 1175–1186.
39. Sadhasivam S, Shanmugam P, Yun K. Biosynthesis of silver nanoparticles by Streptomyces hygroscopicus and antimicrobial activity against medically important pathogenic microorganisms. *Colloids Surf B Biointerfaces* 2010 81: 358–362.
40. Speshock JL, Murdock RC, Braydich-Stolle LK *et al.* Interaction of silver nanoparticles with Tacaribe virus. *J Nanobiotechnology* 2010 8: 19.
41. De GB, Sintubin L, Baert L *et al.* Biogenic silver for disinfection of water contaminated with viruses. *Appl Environ Microbiol* 2010 76: 1082–1087.
42. Lu L, Sun RW, Chen R *et al.* Silver nanoparticles inhibit hepatitis B virus replication. *Antivir Ther* 2008 13: 253–262.

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