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# Nano particles: An emerging tool in biomedicine

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ABSTRACT

Nanotechnology is an emerging scientific discipline with numerous applications in the field of biomedicine and manufacturing new materials. They hold potential to be applied in different biological fields and most strictly focused in medical applications, *e.g.*, tools for noninvasive imaging, diagnostic test assays for early disease detection, drug development and targeted drug delivery systems to reduce secondary systemic negative effects. Nanoparticles have contributed a lot to the advancement of the medical arena. To extract gold nanoparticles with different techniques, green biosynthesis is under exploration due to its cost-effective, eco-friendly preparations with controllable shape, size and disparity, great physical and chemical inertness, optical properties related with surface plasmon resonance, surface modification, surface bio-conjugation with molecular probes, excellent biocompatibility and less toxicity. A significant potential of nanoparticles in biomedical applications including imaging of tissues and cells, sensing of target molecules, drug delivery is among recent efforts in their synthesis and functionalization *e.g.*, Feridex (iron oxide nanoparticles) have been clinically administered as a contrast agent in MRI.

## 1. Introduction

Nanoparticles (NPs) are solid, spherical particles of size ~100 nm, prepared from polymers (natural or synthetic). Hydrophobic and hydrophilic drugs, vaccines and macromolecules can be delivered by using NPs which may also allow controlled drug delivery or a targeted administration to specific cell or organ[1,2]. Metallic NPs (*e.g.*, gold/silver NPs), among the variety of NPs, are the most prominent in biology and medicine[2]. During the last decade, noteworthy breakthrough was made in the field of biotechnology especially for application in biomedcine. Currently, dendrimers are investigated as pharmaceutical delivery systems owing to their abilities to facilitate drug delivery and release, improve the solubility of drugs, and target delivery to specific sites[3,4]. Silver NPs are widely used as a colloidal suspension for their biological activity reported to be associated with different components *e.g.*, carbon nanotubes and manganite[5,6]. Gold NPs are used enormously for a variety of applications such as ultrasensitive chemical, separation science, optoelectronic devices, biological sensors, catalysts, biomedical applications (nucleic acid analysis, drug delivery, antibacterial agent, cancer treatment and gene therapy)[7]. Interaction of NPs upon their uptake by cells is also influenced by their surface charges. Relatively higher extent of internalization by positively charged NPs seems apparently as a result of the ionic interactions established between negatively charged cell membranes and positively charged particles[8]. Numerous research groups have recently diverted their attention toward the synthesis of biofunctional NPs which result in constant evolve of this area.

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## 2. Application potential of NPs: A brief overview

Biosynthesized gold NPs have remarkable applications in different areas such as separation science, biological and chemical sensors, catalysts, heavy metal ion detection, electrical coatings, *etc.*[9]. Currently there are a number of synthetic techniques and materials that are being investigated for biomedical applications (Table 1).

Particles of nanosize have significantly different characteristics from macro particles which have often been applied in medical research[10]. During the last two decades, NPs have been extensively investigated and developed in imaging applications due to the superior narrow range of emission, photo stability, broad excitation wavelength, quantum dots and multiple possibilities of modification and have attracted the attention from scientists and engineers interested in drug targeting, biomarkers and sensors[11]. Recently techniques developed for conjugation of particle surface with biomolecules which allowed the targeting of cell with the help of quantum dots[12]. Using plant extract, the synthesis of gold NPs (AuNPs), is advantageous over the biological process by eliminating the sophisticated process to maintain cell culture and also suitable for large scale nanoparticle synthesis[13]. The NPs are capped by natural proteins and can be directly attached with multiple receptors such as luteinizing hormone releasing hormone, epidermal growth factor receptor and epithelial cell adhesion molecule without targeting agent involvement. These NPs can also bind with integrins and vascular endothelial growth factors for the development of novel anti-angiogenesis strategy for a wide range of tumor treatment[14]. Various surveys have shown that consumption of either antigens or adjuvants by antigen presenting cells could be enhanced by the delivery nanosystems and provide better immune responses as compared to systems which are obtained with the soluble counterparts[15]. The *in vitro* release of entrapped antigens can be made by poly(lactic-co-glycolic acid) NPs for long periods of time[16].

**Table 1**
Application(s) of some important NPs.

| Nanoparticles | Applications | Reference |
|---|---|---|
| Ag | Home appliance as antimicrobial agent | [6] |
| | Clothing for odor resistance | |
| $TiO_2$ | Paints and coating for antimicrobial property | [4] |
| | Cosmetics as a UV absorber | |
| Carbon nanotubes (CNT) | Consumer electronics | [6] |
| | Sports equipment for light weight and durability | |
| $Fe_2O_3$ | Contrast agent for targeted tumor imaging | [7] |
| Fullerenes | Drug delivery | [1] |
| Fe | Environmental remediation | [1] |
| Au | Medical diagnostics | [2] |

## 3. Types of NPs in biomedicine

Various types of NPs have been recognized with various biomedical applications as described below (Figure 1).

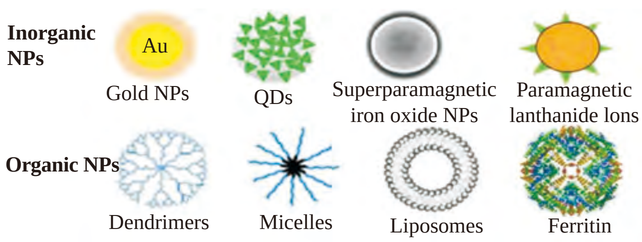



**Figure 1.** Different types of NPs used in biomedicine.
QDs: Quantum dots.

### *3.1. Composite (multimodal) NPs*

Composite or multimodal NPs have variety of combinational functionalities enabling them to be analyzed by number of techniques, thus broadening their domain of applications. The applications of these NPs in biomedicine have been reviewed[17].

### *3.2. Magnetic NPs*

The applications of magnetic NPs in biomedicine have been studied earlier[18]. The α-hydroxyacids such as tartaric or citric acid was received by high temperature hydrolysis of chelated iron(II) and (III) and diethylene glycol alkoxide complexes while ultra-small superparamagnetic iron oxide NPs by a post synthesis ligand exchange step enabling their high colloidal stability[19].

### *3.3. Noble metal NPs*

A broad scope of synthetic approaches have been applied to seek the synthesis of noble metal NPs. A general method has been developed for synthesis of NPs based on the diminution of the metal ions transferred by dodecylamine from an aqueous phase[20]. Monodispersed AuNPs (50–175 nm) were obtained by using reducing agent especially hydroxyquinone[21]. One of the recent researches reported the folic acid as reducing agent for synthesis of water soluble AuNPs (18 nm)[22]. The one-pot green synthesis in the presence of chitosan allowed AuNPs to be justifiable in morphology and size depending on the temperature of the reaction[23].

### *3.4. Semiconductor NPs*

Synthesis of semiconductor NPs and their applications in medicine have been reviewed[24]. Open air synthesis of 3-mercaptopropionic acid functionalized cadmium selenide QDs was reported by using a hydrazine hydrate-Se complex as a source of highly reactive selenium ions; subsequently, further reaction occurred in solution in the presence of cadmium. The resulting water soluble and air stable particles enabled quantum yield of 40%[25].

## 4. Uses of NPs in biomedicine

Nano particles have a number of uses in biomedicine (Figure 2).

### *4.1. Dendrimers*

During last decade, this NPs are extensively used as pharmaceutical delivery systems because of their ability to facilitate drug delivery and release of drugs, improvement in their solubility and target delivery to specific sites[3] (Figure 2).

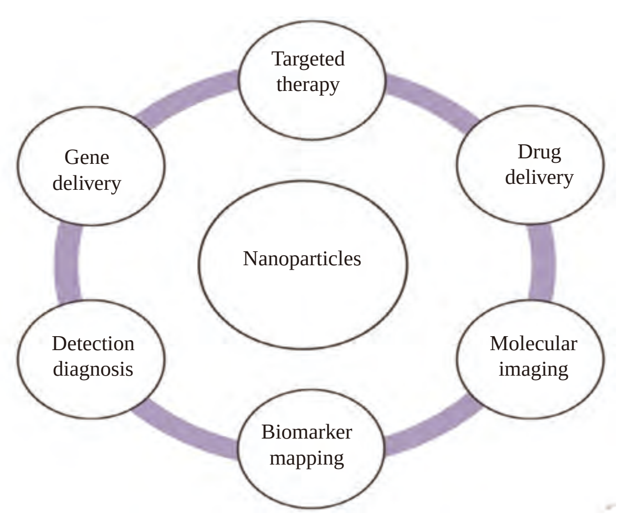



**Figure 2.** Application potential of NPs in biomedicines.

### 4.2. Gold nanoshells

Physicochemical and optical properties make nanoshells ideal for medical biosensing, cellular imaging and in cancer detection and treatment. In addition, photothermal cancer is possible by nanoshells tuned to absorb near-infrared radiation[26].

### 4.3. QDs

QDs are presently used for cytogenetics molecular diagnostics and multiplex diagnostics. They have extensively used in cancer diagnosis and diagnostics. A recent research reported that QDs covalently linked to antibodies against human epidermal growth factor receptor 2 to visualize tumorcells by immunofluorescence[27].

### 4.4. Mesoporous silica nanoparticles

Mesoporous silica nanoparticles are currently used for theranostic purposes. For example, they can be used as carriers for therapeutic agents and functionalized with different molecular or polymer moieties, which facilitate controlled drug delivery and release[28].

## 5. Function of NPs

### 5.1. NPs as vaccines

A strong immune response was created by treating it inside animal noses with a "nanoemulsion" (a suspension of alcohol, oil, soybean and surfactant) to create droplets of 200 to 300 nm in size. The oil particles can be used as key particle to react with protein and initialize an immune response which fights off infection. These particles bypass the use of needles as well as can be used where refrigeration is not available. The method of using anthrax vaccine may result in spreading of anthrax microbes by terrorist. Thus researches conclude that if nasal nanoemulsion proves to be an ideal vaccine in humans, it can be give to patients exposed to anthrax attack. Vaccines which are given after the exposure are used to boost the speed the immune response.

### 5.2. Role of silver nanoparticles as anti-microbial agent

Silver NP plays it role as anti-microbial as well as anti-bacterial agent. Particle size is very important because the smaller the particle size the greater the surface area which leads to higher inter-action with the bacteria. Microbes are found everywhere and they are dangerous to human body because of the existence of antibiotic resistant microbes. NPs are being used to restrain the effect of microbes. They are used in the prevention of bacterial colonization on surface of prostheses, catheters, dental materials and food processing surfaces such as stainless steel[29].

### 5.3. Role of pH-responsive NPs for targeted drug delivery

One application of NPs in medicine currently being developed involves employing NPs to deliver drugs, heat, tight or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells, which allow direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease. Nanotechnology offers another challenge to come to this goal a bit closer, to deliver the drug in the right place at right time[30].

### 5.4. Nanoparticles in stem cell therapy

Nanoparticles have been used successfully by chemical engineers to enhance stem cells ability to regenerate the damaged vascular tissue and reduce muscle degeneration in mice. This allows the use of NPs in gels, paints, polymers composites and high tech foams, living cells.

### 5.5. Gold NPs for the treatment of cancer

Cancer cells along with other organisms such as bacteria, viruses and DNA can be damaged by a technique like nanophotothermolysis with lasers and gold NPs. Gold NPs are probes for application in biomedical field because they can be easily prepared unlike other fluorescent probes. Cancer cell is invasive because one cell left over can lead to the regrow. The NPs will create bubbles in contact with cells due to extreme temperature change. These bubbles burst sending out the shockwaves which damage and cause them to lyse. This technique allows selecting only the cancer cells or abnormal cells. However, this technique has less efficiency in case of solid tumor, bones, and atherosclerotic plaques[31].

### 5.6. Role of respirocyte in human

Medical diagnosis with appropriate and effective delivery of pharmaceuticals is the medical areas where practical applications of nanosize particles have been found[32]. Nanodevices in medical sciences could function to replace defective or improperly functioning cells, such as the respirocyte proposed by Freitas[33].

### 5.7. Nanodiagnostics

Nanodiagnostics devices can be used for early disease identification at the cellular and molecular levels. Nanomedicine could increase the efficiency and reliability of *in vitro* diagnostics, through the use of selective nanodevices to collect human fluids or tissue samples and to make multiple analyses at the sub cellular level. From an *in vivo* perspective, nanodevices might be inserted into the body to identify the early presence of a disease, or to identify and quantify toxic molecules, tumor cells, and so forth[34].

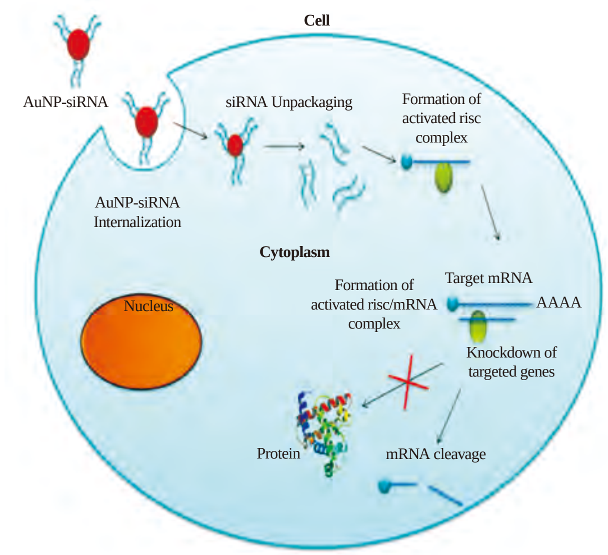
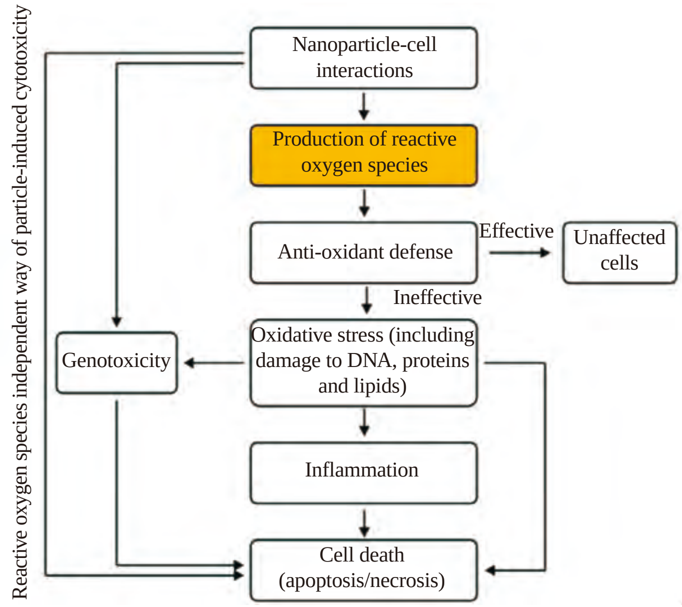



Figure 3. NP efficiency in cancer treatment.




### *5.8. Carbon nanotubes as NPs for orthopaedic implant*

NPs may prove effective tools for improving orthopaedic implants. In our day-to-day life orthopaedic implants are used in many surgical procedure to achieve better quality of life and to replace the damage bone or joint everything has a drawback likewise. Orthopaedic implant can result in loosening of the implant failures and complicated revision surgeries according to Spear and Cameron[35].

Give multifunctional capability–NPs with dual functionality can be used for diagnostic and therapeutic purposes (*e.g.*, $Fe_2O_3$-Pt NPs).

### *5.9. Cancer diagnosis and imaging*

Tumor imaging plays a key role in clinical oncology by helping to identify solid tumors, determine recurrence and monitor therapeutic responses. The development of non-invasive molecular imaging systems able to detect tumors at early stages would represent a significant improvement over the current available clinical diagnostic methods. The development of NPs for the delivery of contrast agents has emerged in recent years since the possibility of the production of multifunctional NPs which are able to specifically target the tumor[36]. It has been reported that nanomachines could administer drugs within a patient's body. Such nanoconstructions could deliver drugs to peculiar sites making treatment more accurate and precise[37]. The detail mechanism and efficiency of nanoparticle in cancer treatment is given in Figure 3.

NP concentration, culture conditions for *in vitro* studies, cell lines, introduction strategy of particles in *in vivo* studies, size and duration of exposure are key factors influencing the cytotoxicity of a nanomaterial[38]. Using a chemical and thermal constant protein extracted from *Populus tremula* as template, Pd NPs have been obtained. There was no effect reported for template after NPs deposition. Therefore further bio-functionalization for site-specific targeting can undergo[39].

## 6. Conclusion

NPs present highly attractive applications in the field of medicine. They have the potential to be used in various medical and biological applications *e.g.*, diagnostic tests assays for disease early detection, targeted drug delivery systems to minimize secondary systemic negative effects and tools for noninvasive imaging and drug development. For a given biomedical application, a wide range of chemical, physical, biological and physiological factors have to be established for successful preparation and bio-functionalization of NPs. Recently, in biomedical and material science, the toxicity of the nanoparticle is a critically important topic. Moreover, to increase colloidal stability in biological media, biomolecules incorporation into the synthesis of NPs have gained the attention that will also enable specific targeting in living tissues.

## Conflict of interest statement

We declare that we have no conflict of interest.

## References

[1] Hans ML, Lowman AM. Biodegradable nanoparticles for drug delivery and targeting. *Curr Opin Solid State Mater Sci* 2002; **6**: 319-27.

[2] Raghavendra R, Arunachalam KD, Annamalai SK, Arunachalam AM. Diagnostics and therapeutic application of gold nanoparticles. *Int J Pharm Pharmaceut Sci* 2014; **6**(Suppl): 74-87.

[3] Stieger N, Liebenberg W, Aucamp ME, De Villiers MM. The use of dendrimers to optimize the physicochemical and therapeutic properties of drugs. In: Cheng YY, editor. *Dendrimer-based drug delivery systems: from theory to practice.* Hoboken: John Wiley & Sons Inc; 2012, p. 93-137.

[4] Safarik I, Safarikova M. Magnetic nano- and microparticles in biotechnology. *Chem Papers* 2009; **63**: 497-505.

[5] Zhang WZ, Qiao XL, Chen JG. Synthesis of nanosilver colloidal particles in water/oil microemulsion. *Colloids Surf A Physicochem Eng Asp* 2007; **299**: 22-8.

[6] Wu CS, Lee CY, Chen JK, Kuo SW, Fan SK, Cheng CC, et al. Microwave-assisted electroless deposition of silver nanoparticles onto multiwalled carbon nanotubes. *Int J Electrochem Sci* 2012; **7**(5): 4133-42.

[7] Liao H, Nehl CL, Hafner JH. Biomedical applications of plasmon resonant metal nanoparticles. *Nanomedicine* (*Lond*) 2006; **1**(2): 201-8.

[8] Foged C, Brodin B, Frokjaer S, Sundblad A. Particle size and surface charge affect particle uptake by human dendritic cells in an *in vitro* model *Int J Pharm* 2005; **298**: 315-22.

[9] Armendariz V, Gardea-Torresdey JL, Jose-Yacaman M, Gonzalez J, Herrera I, Parsons JG. Gold nanoparticles formation by oat and wheat biomasses. 2002 Proceedings-Waste Research Technology; 2002 Jul 30-Aug 1; the Kansas City, USA. [Online] Available from: https://www.engg.ksu.edu/HSRC/ag/2002/proceed/k09.pdf [Accessed on 18th September, 2015]

[10] Bystrzejewski M, Cudzilo S, Huczko A, Lange H, Soucy G, Cota-Sanchez G, et al. Carbon encapsulated magnetic nanoparticles for biomedical applications: thermal stability studies. *Biomol Eng* 2007; **24**(5): 555-8.

[11] Ghaderi S, Ramesh B, Seifalian AM. Fluorescence nanoparticles "quantum dots" as drug delivery system and their toxicity: a review. *J Drug Target* 2011; **19**: 475-86.

[12] Hoshino A, Hanaki K, Suzuki K, Yamamoto K. Applications of T-lymphoma labeled with fluorescent quantum dots to cell tracing markers in mouse body. *Biochem Biophys Res Commun* 2004; **314**(1): 46-53.

[13] Kuamr V, Yadav SK. Plant-mediated synthesis of silver and gold nanoparticles and their applications. *J Chem Technol Biotechnol* 2009; **84**: 151-7.

[14] Syed A, Raja R, Kundu GC, Gambhir S, Ahmad A. Extracellular biosynthesis of monodispersed gold nanoparticles, their characterization, cytotoxicity assay, biodistribution and conjugation with the anticancer drug doxorubicin. *J Nanomed Nanotechol* 2013; **4**(1): 156-61.

[15] Beaudette TT, Bachelder EM, Cohen JA, Obermeyer AC, Broaders KE, Fréchet JM, et al. *In vivo* studies on the effect of co-encapsulation of CpG DNA and antigen in acid-degradable microparticle vaccines. *Mol Pharm* 2009; **6**: 1160-9.

[16] Thomas C, Rawat A, Hope-Weeks L, Ahsan F. Aerosolized PLA and PLGA nanoparticles enhance humoral, mucosal and cytokine responses to hepatitis B vaccine. *Mol Pharm* 2011; **8**: 405-15.

[17] Fang C, Zhang MQ. Multifunctional magnetic nanoparticles for medical imaging applications. *J Mater Chem* 2009; **19**: 6258-66.

[18] Pankhurst QA, Thanh NTK, Jones SK, Dobson J. Progress in applications of magnetic nanoparticles in biomedicine. *J Phys D Appl Phys* 2009; **42**(22): 3727-42.

[19] Goloverda G, Jackson B, Kidd C, Kolesnichenko V. Synthesis of ultrasmall magnetic iron oxide nanoparticles and study of their colloid and surface chemistry. *J Magn Magn Mater* 2009; **321**(10): 1372-6.

[20] Yang J, Sargent E, Kelley S, Ying JY. A general phase-transfer protocol for metal ions and its application in nanocrystal synthesis. *Nat Mater* 2009; **8**(8): 683-9.

[21] Perrault SD, Walkey C, Jennings T, Fischer HC, Chan WCW. Mediating tumor targeting efficiency of nanoparticles through design. *Nano Lett* 2009; **9**(5): 1909-15.

[22] Liu JY, Guo SJ, Han L, Wang TS, Hong W, Liu YQ, et al. Synthesis of phospholipid monolayer membrane functionalized graphene for drug delivery. *J Mater Chem* 2012; **22**: 20634-40.

[23] Potara M, Maniu D, Astilean S. The synthesis of biocompatible and SERS-active gold nanoparticles using chitosan. *Nanotechnology* 2009; **20**(31): 315602.

[24] Tomczak N, Jańczewski, D, Han M, Vancso GJ. Designer polymer-quantum dot architectures. *Prog Polym Sci* 2009; **34**(5): 393-430.

[25] Kalasad MN, Rabinal MK, Mulimani BG. Ambient synthesis and characterization of high-quality CdSe quantum dots by an aqueous route. *Langmuir* 2009; **25**(21): 12729-35.

[26] Hirsch LR, Stafford RJ, Bankson JA, Sershen SR, Rivera B, Price RE, et al. Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proc Natl Acad Sci USA* 2003; **100**(23): 13549-54.

[27] Tada H, Higuchi H, Wanatabe TM, Ohuchi N. *In vivo* real-time tracking of single quantum dots conjugated with monoclonal anti-HER2 antibody in tumors of mice. *Cancer Res* 2007; **67**: 1138-44.

[28] Li ZX, Barnes JC, Bosoy A, Stoddart JF, Zink JI. Mesoporous silica nanoparticles in biomedical applications. *Chem Soc Rev* 2012; **41**: 2590-605.

[29] Araújo EA, Andrade NJ, da Silva LH, Bernardes PC, de C Teixeira AV, de Sá JP et al. Antimicrobial effects of silver nanoparticles against bacterial cells adhered to stainless steel surfaces. *J Food Prot* 2012; **74**(4): 701-5.

[30] Gao W, Chan JM, Farokhzad OC. pH-responsive nanoparticles for drug delivery. *Mol Pharm* 2010; **7**(6): 1913-20.

[31] Letfullin RR, Joenathan C, George TF, Zharov VP. Laser-induced explosion of gold nanoparticles: potential role for nanophotothermolysis of cancer. *Nanomedicine (Lond)* 2006; **1**(4): 473-80.

[32] Kubik T, Bogunia-Kubik K, Sugisaka M. Nanotechnology on duty in medical applications. *Curr Pharm Biotechnol* 2005; **6**(1): 17-33.

[33] Freitas RA Jr. The future of computers. *Analog* 1996; **116**: 57-73.

[34] Freitas RA Jr. *Nanomedicine, Volume I: basic capabilities.* Georgetown: Landes Bioscience; 1999, p. 345-7.

[35] Spear RL, Cameron RE. Carbon nanotubes for orthopaedic implants. *Int J Mater Form* 2008; **1**: 127-33.

[36] Acharya S, Sahoo SK. PLGA nanoparticles containing various anticancer agents and tumour delivery by EPR effect. *Adv Drug Deliv Rev* 2011; **63**: 170-83.

[37] Triggle DJ. Rho Chi lecture. Pharmaceutical sciences in the next millennium. *Ann Pharmacother* 1999; **33**(2): 241-6.

[38] Pal A, Shah S, Devi S. Microwave-assisted synthesis of silver nanoparticles using ethanol as a reducing agent. *Mater Chem Phys* 2009; **114**: 530-32.

[39] Behrens S, Heyman A, Maul R, Essig S, Steigerwald S, Quintilla A, et al. Constrained synthesis and organization of catalytically active metal nanoparticles by self-Assembled protein templates. *Adv Mater* 2009; **21**: 3515-9.