

A REVIEW ON NANO DEVICES AND NANO BIO MEDICINE**Radha Gadela^{1*}, Ganapaty Seru² and Sravan Kumar Moka³**

Pharmaceutics Division, GITAM Institute of Pharmacy, GITAM University, Visakhapatnam-
530 045, Andhra Pradesh, India.

Article Received on
27 July 2016,

Revised on 16 August 2016,
Accepted on 05 Sept 2016

DOI: 10.20959/wjpr201610-6952

Corresponding Author*Dr. Radha Gadela**

Pharmaceutics Division,
GITAM Institute of
Pharmacy, GITAM
University,
Visakhapatnam- 530 045,
Andhra Pradesh, India.

ABSTRACT

A combination of both nanoparticles for drug delivery and self-assembling nanotechnology could be the building blocks for a future nano-robot device to act independently. Nano medicine is the process of diagnosing, treating and preventing disease and traumatic injury, relieving pain, and preserving and improving human health, using molecular tools and molecular knowledge of the human body. We can detect important medical problems by using nanoscale-structured materials and simple nanodevices that can be manufactured today, including the interaction of nano structured materials with biological systems. In the longer term, perhaps one to two decades from today, the earliest molecular machine systems and nano robots may join the medical armamentarium, finally giving physicians the most potent

tools imaginable to conquer human disease, ill-health, and aging. This article reviews the different nano devices, nanorobotics and newer advances in the field of nano technology.

KEYWORDS: Nanomaterials, Nanorobotics, Nanotechnology, Nanopores, Medical Nano Robots.

INTRODUCTION

Nano-devices today are still thought by many as science fiction but advances over the past 20 years have started becoming non-fiction. Many advances have been made into nanomedicine for application in the medical arena in particular nanoparticle and biomarkers for drug delivery as well as self-assembling nanotechnology. A combination of both nanoparticles for drug delivery and self- assembling nanotechnology could be the building blocks for a future nano-robot device to act independently by administering xenobiotics or other treatments to target specific health problems in the human body. Nanoparticles in drug delivery are

currently being developed with a promising role in medicine with improvements in localization and specificity of drugs. Furthermore, developments into passing drugs across the blood-brain barrier are being developed. Other promising developments in nanoparticles have been designed to deliver other payloads such as light or heat which can aid in diagnosis, treatment and applications in gene delivery. Research into self-assembling nanotechnology is becoming more popular but is still very much in the developing stages. There are currently two proposed approaches to carry out self-assembly which are the arrangements of independent atoms and molecules into a specific structure or self-assembly using biological molecules such as DNA and proteins

MEDICAL NANOMATERIALS AND NANODEVICES

NANOPORES

Simplest medical nanomaterials with surface perforated with holes are nanopores. In 1997 Desai and Ferrari created one of the earliest therapeutic nanomedical devices, employing bulk micromachining to fabricate tiny cell-containing chambers within single crystalline silicon wafers. The chambers interfere with the surrounding biological environment through polycrystalline silicon filter membranes which are micromachined to present a high density of uniform nanopores as small as 20 nanometers in diameter. These pores are large enough to allow small molecules such as oxygen, glucose, and insulin to pass, but are small enough to impede the passage of much larger immune system molecules such as immunoglobulins and graft-borne virus particles. The flow of materials through nanopores can also be externally regulated. The first artificial voltage-gated molecular nanosieve was fabricated by Martin and colleagues^[1] in 1995. Martin's membrane contains an array of cylindrical gold nanotubules with inside diameters as small as 1.6 nanometers. When the tubules are positively charged, positive ions are excluded and only negative ions are transported through the membrane. When the membrane receives a negative voltage, only positive ions can pass.

Artificial Binding Sites and Molecular Imprinting

Another early goal of nanomedicine is to study how biological molecular receptors work, and then to build artificial binding sites on a made-to-order basis to achieve specific medical results. Molecular imprinting^[2-3] is an existing technique in which a cocktail of functionalized monomers interacts reversibly with a target molecule using only noncovalent forces. The complex is then cross-linked and polymerized in a casting procedure, leaving behind a polymer with recognition sites complementary to the target molecule in both shape and

functionality. Each such site constitutes an induced molecular “memory,” capable of selectively binding the target species. Molecularly imprinted polymers could be medically useful in clinical applications such as controlled drug release, drug monitoring devices, quick biochemical separations and assays,^[5] recognition elements in biosensors and chemosensors and biological and receptor mimics including artificial antibodies (plastibodies) or biomimicking enzymes (plastizymes. But molecularly imprinted polymers have limitations, such as incomplete template removal, broad guest affinities and selectivities, and slow mass transfer. Imprinting inside dendrimers may allow quantitative template removal, nearly homogeneous binding sites, solubility in common organic solvents, and amenability to the incorporation of other functional groups.

Quantum Dots and Nanocrystals

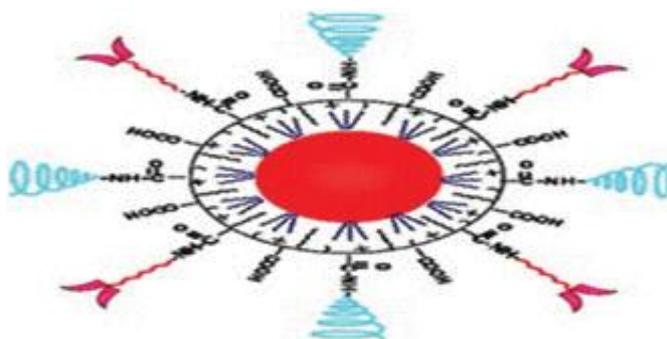


Fig 1: Antibody conjugated quantum dot

These are tiny crystals that glow when these are stimulated by ultraviolet light [Figure-1]. The latex beads filled with these crystals when stimulated by light, emit the color that lights up the sequence of interest. By combining different sized quantum dots within a single bead, probes can be created that release a distinct spectrum of various colors and intensities of lights, serving as sort of spectral bar code. Latex beads filled with crystals can be designed to bind to specific DNA sequences. When the crystals are stimulated by light, the colors they emit serve as dyes and light up the sequences of interest.^[6-8]

Fullerenes and Nanotubes

Nanotubes are smaller than nanopores. Nanotubes help to identify Dioxynucleic acid (DNA) changes associated with cancer cells. They are about half the diameter of a molecule of DNA. It helps to exactly pin point location of the changes. Mutated regions associated with cancer are first tagged with bulky molecules. The physical shape of the DNA Soluble derivatives of fullerenes such as C60 have shown great utility as pharmaceutical agents.

These derivatives, many already in clinical trials, have good biocompatibility and low toxicity even at relatively high dosages. carbon nanotubes are being investigated as biosensors, for example to detect glucose,^[9-11] ethanol, hydrogen peroxide,^[12] selected proteins such as immunoglobulins,^[13] and as an electrochemical DNA hybridization biosensor,

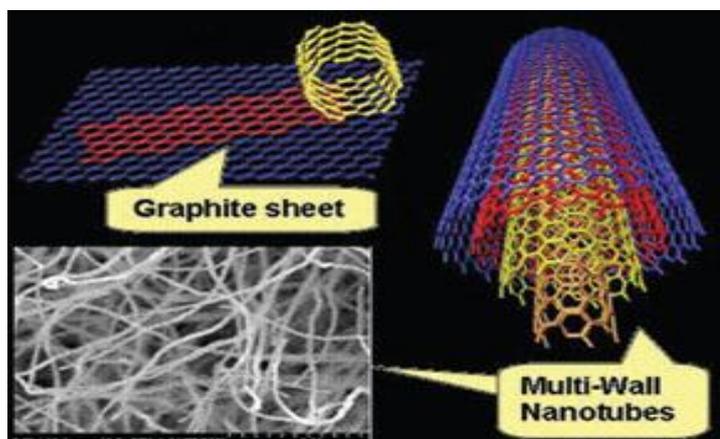


Figure 2: Nanotubes

Fullerene compounds may serve as antiviral agents, antibacterial agents, photodynamic antitumor and anticancer therapies, antioxidants and anti-apoptosis agents which may include treatments for amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) and Parkinson's disease.

Nanoshells and Magnetic Nanoprobes

Halas and West at Rice University in Houston have developed a platform for nanoscale drug delivery called the nanoshell. Unlike carbon fullerenes, the slightly larger nanoshells are dielectric-metal nanospheres with a core of silica and a gold coating, whose optical resonance is.

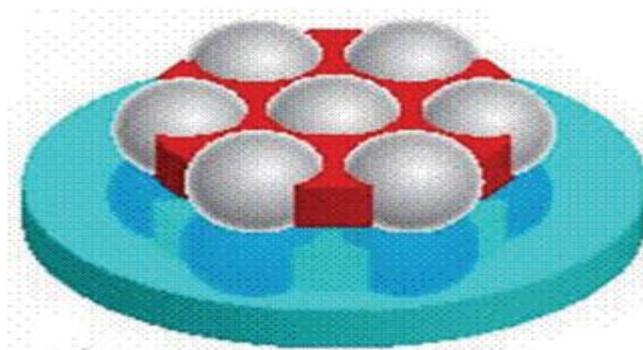


Figure 3: Nanoshells.

a function of the relative size of the constituent layers. The nanoshells are embedded in a drug-containing tumortargeted hydrogel polymer and injected into the body. The shells circulate through the body until they accumulate near tumor cells. When heated with an infrared laser, the nanoshells (each slightly larger than a polio virus) selectively absorb the IR frequencies, melt the polymer and release their drug payload at a specific site. Nanoshells offer advantages over traditional cancer treatments: earlier detection, more detailed imaging, fast noninvasive imaging, and integrated detection and treatment. This technique could also prove useful in treating diabetes. Instead of taking an injection of insulin, a patient would use a ballpoint-pen-size infrared laser to heat the skin where the nanoshell polymer had been injected. The heat from nanoshells would cause the polymer to release a pulse of insulin. Unlike injections, which are taken several times a day, the nanoshell-polymer system could remain in the body for months. The most useful NS are those that absorb near infrared light that can easily penetrate several centimeters in human tissues. Absorption of light by NS creates an intense heat that is lethal to cells. Metal NS which are intense near-infrared absorbers are effective both *in-vivo* and *in-vitro* on human breast carcinoma cells.

An alternative approach pursued by Triton BioSystems is to bond iron nanoparticles and monoclonal antibodies into nanobioprobes about 40 nanometers long. The chemically inert probes are injected and circulate inside the body, whereupon the antibodies selectively bind to tumor cell membranes. Once the tumor is covered with bioprobes after several hours, a magnetic field generated from a portable alternating magnetic field machine heats the iron particles to more than 170 degrees, killing the tumor cells in a few seconds^[14] Once the cells are destroyed, the body's excretion system removes cellular residue and nanoparticles alike. Test subjects feel no pain from the heat generated.

Cantilevers

Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer. These molecules may bind to altered DNA proteins that are present in certain types of cancer monitoring the bending of cantilevers; it would be possible to tell whether the cancer molecules are present and hence detect early molecular events in the development of cancer cells.^[15,16]

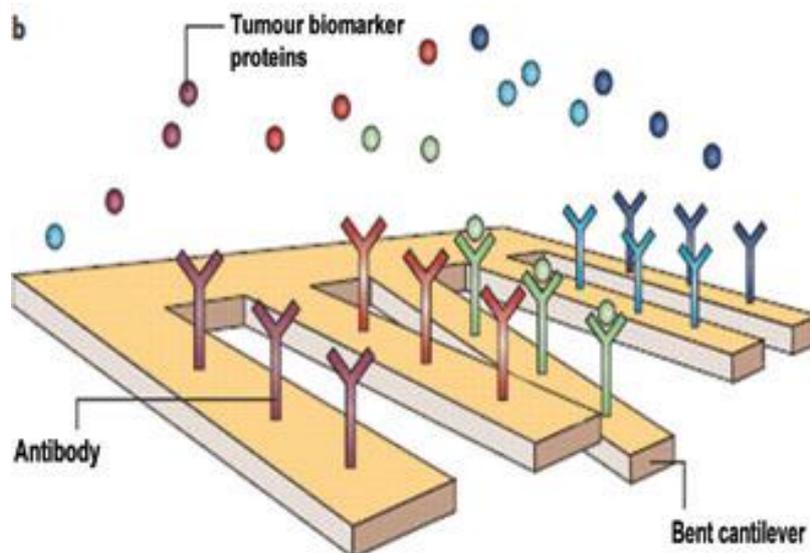


Fig 4: Nanocantilever array

Targeted Nanoparticles and Smart Drugs

Multisegment gold/nickel nanorods are being explored as tissue-targeted carriers for gene delivery into cells that can simultaneously bind compacted DNA plasmids and targeting ligands in a spatially defined manner and allow precise control of composition, size and multifunctionality of the gene-delivery system. The nanorods are electrodeposited into the cylindrical 100 nm diameter pores of an alumina membrane, joining a 100 nm length gold segment and a 100 nm length nickel segment. After the alumina template is etched away, the nanorods are functionalized by attaching DNA plasmids to the nickel segments and transferrin, a cell-targeting protein, to the gold segments, using molecular linkages that selectively bind to only one metal and thus impart biofunctionality to the nanorods in a spatially defined manner. For example to bind additional biofunctionalities such as an endosomolytic agent, or magnetic segments could be added to allow manipulating the nanorods with an external magnetic field. Targeted radioimmunotherapeutic agents include the FDA-approved “cancer smart bombs” that deliver tumorkilling radioactive yttrium (Zevalin) or iodine (Bexxar) attached to a lymphoma-targeted (anti-CD20) antibody. Other antibody-linked agents are being investigated such as the alpha-emitting actinium-based “nanogenerator” molecules that use internalizing monoclonal antibodies to penetrate the cell and have been shown, *in vitro*, to specifically kill leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells at becquerel (picocurie) levels^[17] with promising preliminary results against advanced ovarian cancer in mice.

Dendrimers and Dendrimer-Based Devices

Dendrimers^[18] represent yet another nanostructured material that may soon find its way into medical therapeutics. Dendrimers are tree-shaped synthetic molecules with a regular branching structure emanating outward from a core that form nanometer by nanometer, with the number of synthetic steps or “generations” dictating the exact size of the particles, typically a few nanometers in spheroidal diameter. The peripheral layer can be made to form a dense field of molecular groups that serve as hooks for attaching other useful molecules, such as DNA, which can enter cells while avoiding triggering an immune response, unlike viral vectors commonly employed today for transfection. Upon encountering a living cell, dendrimers of a certain size trigger a process called endocytosis in which the cell’s outermost membrane deforms into a tiny bubble, or vesicle. The vesicle encloses the dendrimer which is then admitted into the cell’s interior. Once inside, the DNA is released and migrates to the nucleus where it becomes part of the cell’s genome. Glycodendrimer “nanodecoys” have also been used to trap and deactivate some strains of influenza virus particles.^[19,20] The glycodendrimers present a surface that mimics the sialic acid groups normally found in the mammalian cell membrane, causing virus particles to adhere to the outer branches of the decoys instead of the natural cells.

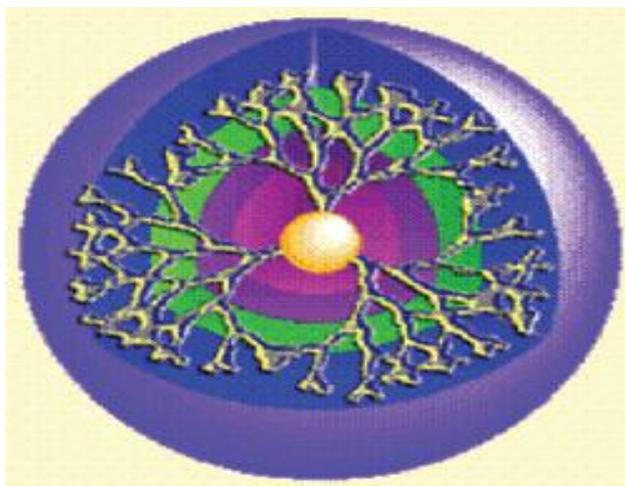


Fig 5: Dendrimer.

Radio-Controlled Biomolecules

Though there are already many examples of nanocrystals attached to biological systems for biosensing purposes, the same nanoparticles are now being investigated as a means for directly controlling biological processes they are called radio-controlled biomolecules. Jacobson and colleagues have attached tiny radio-frequency antennas-1.4 nanometer gold

nanocrystals of less than 100 atoms-to DNA. When a ~1 GHz radio-frequency magnetic field is transmitted into the tiny antennas, alternating eddy currents induced in the nanocrystals produce highly localized inductive heating, causing the doublestranded DNA to separate into two strands in a matter of seconds in a fully reversible dehybridization process that leaves neighboring molecules untouched. The long-term goal is to apply the antennas to living systems and control DNA via remote electronic switching. This requires attaching gold nanoparticles to specific oligonucleotides which, when added to a sample of DNA, would bind to complementary gene sequences, blocking the activity of those genes and effectively turning them off. Applying the magnetic field then heats the gold particles, causing their attached DNA fragments to detach, turning the genes back on. Such a tool could give pharmaceutical researchers a way to simulate the effects of potential drugs which also turn genes on and off.

MEDICAL NANO ROBOTICS

The third major development pathway of nanomedicine molecular nanotechnology (MNT) or nanorobotics takes as its purview the engineering of complex nanomechanical systems for medical applications. Just as biotechnology extends the range and efficacy of treatment options available from nanomaterials, the advent of molecular nanotechnology will again expand enormously the effectiveness, precision and speed of future medical treatments while at the same time significantly reducing their risk, cost, and invasiveness. MNT will allow doctors to perform direct *in vivo* surgery on individual human cells. The ability to design, construct, and deploy large numbers of microscopic medical nanorobots will make this possible.

Nanoparticles in drug delivery: Application of Nanotechnology in Medicine

Nanoparticles offer more advantages over common drugs by protecting premature degradation of drugs, releasing drugs to react in the localised area in the body, enhancing absorption therefore increase bioavailability and control of the pharmacokinetic profile. Development of nanoparticles has been designed for a variety of different medical conditions over the past few years where applications are proposed to cure HIV and many different types of cancers. A list below shows examples of different nanocarrier drugs on the market.

Table1: List of different Nano carrier drugs used commercially.

Compound	Commercial Name	Nanocarrier	Indications
PEG-L asparaginase	Oncaspar	Polymer-protein complex	Acute Lymphoblastic leukemia
IL-2 fused to diphtheria toxin	Ontak (Denilelukin diftiox)	Immunotoxin (fusion protein)	Cutaneous T-cell lymphoma
Anti-CD33 antibody conjugated to calicheamicin	Mylotarg	Chemo-immunoconjugate	Acute myelogenous leukemia
Daunorubicin	DaunoZome	Liposomes	Kaposi's sarcoma
Paclitaxel	Abraxane	Albumin-bound paclitaxel nanoparticle	Albumin-bound paclitaxel nanoparticle

A Biological Nanodevice for Drug Delivery

The nanobiological anticancer agent PK1 exploits the enhanced permeability and retention (EPR) effect associated with disease tissues with low integrity vasculature in order to deliver cytotoxin (doxorubicin) to tumors. The synthetic backbone of PK1 (N-2-(hydroxypropyl) methacrylimide or HPMA) gives the complex a size (diameter in the mid-nanometer range) that makes it unable to extravasate efficiently into healthy tissues with normal vasculature. Tumor vasculature is abnormally permeable, allowing preferential accumulation of PK1 in tumor tissue. HPMA-bound doxorubicin is non-toxic, limiting toxicity to healthy tissue, and active doxorubicin is released from the complex preferentially in tumor tissues. The labile peptidic linker tethering doxorubicin to HPMA was selected because it is the substrate for a protease known to be over-expressed in the target tumor types. PK1 increases the tolerated doxorubicin dose by more than an order of magnitude by virtue of EPR-based targeting and its engineered tumor-preferred doxorubicin release properties. It is in human clinical trial in Europe. Contemplated embellishments to this and similar polymer therapeutics include use of monodisperse nanoparticles (dendritic polymers) to enhance control of EPR properties, incorporation of protein docking domains that recognize tumor associated antigens to tether the complex following its delivery to the tumor, and incorporation of additional antitumor agents thought to have synergistic effects with cytotoxins, that is, angiostatic agents, among other.

Nucleic acid delivery

Lipid bilayer of the cell membrane poses the major barrier for the delivery of nucleic acids such as small interfering RNA or plasmid DNA. Several viral and polymeric nanocapsules, cationic liposomes, and non-viral vectors (lipoplexes, polyplexes, and inorganic nanoparticles) have been developed that can actively cross the lipid membrane and deliver nucleic acids with ease and reduced toxicity *in vitro*.

Inhibition of Neointimal Hyperplasia

Atherosclerosis affects many of whom require arterial intervention, treatment often fail due to the development of neointimal hyperplasia, necessitating reintervention. It is well understood that Nitric Oxide (NO) inhibits neointimal hyperplasia. Diazeniumdiolates {1-[N-(3-Aminopropyl)-N-(3-ammoniopropyl)]diazene-1,2-diolate [DPTA/NO] or disodium 1-[(2-Carboxylato)pyrrolidin-1-yl]diazene-1,2-diolate} are a class of NO donors that release NO spontaneously when placed in an aqueous environment. These diazeniumdiolates were formulated using nanofiber gels.^[21,22]

Management of Tuberculosis

The management of tuberculosis (TB) treatment is either preventive (i.e., vaccination) or therapeutic (i.e., chemotherapy). Liposomes and lipid nanoparticles are successfully used to deliver the anti-TB drugs with sustained release profiles for long-term therapy and also improved pharmacokinetic profile of the agent.^[23,24]

Nanotechnology in Pharmaceutical Aerosols

Most of the drugs are very poor candidates for developing aerosols, but with nanotechnological principles applied to prepare nanosuspensions for drugs insoluble in aqueous medium as well as in oily medium, gave improved pharmacokinetics which subsequently improved the bioavailability of drugs administered as aerosols. Furthermore, development of bioadhesive nanoparticles helped increased the mucosal residence time of the drugs which increased the absorption of the drugs and subsequently resulted in enhanced bioavailability.^[25-27]

Biochemical Sensors

One of the most important function of nanoparticles is catalysis, especially with noble metal nanoparticles which have high catalytic activity for many chemical reactions. Because nanomaterials also have good biocompatibility, they are used to immobilize biomolecules for the fabrication of biosensors. Glucose nanosensors are being used for the detection of glucose levels in diabetics. Nanosensors of triglycerides are extremely useful in detecting hyperlipidemia.^[28] Free gold colloid-based optical biosensors are available for qualitative and quantitative determination of biomolecular interactions and recent advances in the construction of gold colloid-based localized surface Plasmon resonance (LSPR) biosensors and their applications in immunosensing, nucleic acid detection, and quantification of toxins has added much value to this technology.^[29,30] Oligonucleotide-capped gold nanoparticles

have also been reported for polynucleotide or protein detection using various detection/characterization methods such as atomic force microscopy, gel electrophoresis, Raman spectroscopy, and surface plasmon resonance imaging.^[31-36]

CONCLUSION

Nanotechnology, from the very beginning, has been very successful in overcoming the hurdles offered by conventional therapy. Target specific nature of the delivery systems developed applying nanotechnology principles have been able to reduce the amount of drug that needs to be loaded and hence prevent many dose-related adverse reactions. Currently, not many products are available for clinical use, but looking at the amount of research activity happening in this field, the next few years will witness the outburst of nano-medical devices, therapeutic aids, and many products being launched in the market for clinical use. Though initially the cost of therapy may be presumed to be beyond the reach of common Indian population, but soon more and more economical devices and therapies shall be available. The field of nanotechnology yet remains to be explored to its fullest; as a result many more advanced products will be soon available.

REFERENCES

1. Muhlen AZ, Schwarz C, Mehnert W. Solid lipid nanoparticles for controlled drug delivery- drug release and release mechanisms. *Eur J Pharm Biopharm Res.*, 1998; 45(2): 149-55.
2. H.Shi and B.D.Ratner. Template recognition of protein imprinted polymer surfaces. *Journal of Biomed. Mater. Res.*, 2000; 49(1): 1- 11.
3. Jurgons, R. et al. Drug loaded magnetic nanoparticles for cancer therapy. *J. Phys. Condens. Matter.*, 2006; 18: 2893–2902.
4. O.Bruggemann, Molecularly imprinted materials – receptors more durable than nature can provide. *Adv. Biochem. Eng. Biotechnology.*, 2002; 76: 127-63.
5. M.Y oshikawa, Molecularly imprinted polymeric membranes. *Bioseparation.*, 2001; 10(6): 277-286.
6. Editorial. Nanomedicine: Grounds for Optimism, and a Call for Papers. *Lancet.*, 2003; 362.
7. Tiwari, S.B. & Amiji, M.M. Improved oral delivery of paclitaxel following administration in nanoemulsion formulations. *J. Nanosci. Nanotechnol.*, 2006; 6: 3215–3221.

8. D. Steinle, D.T. Mitchell, M.W. Irtz, S.B. Lee, V.Y. Young, and C.R. Martin. Ion channel mimetic micropore and nanotube membrane sensors. *Journal Anal. Chem.*, 2002; 74(10): 2416-2422.
9. S. Sotiropoulou and N.A. Chaniotakis. Carbon nanotube array based biosensor. *Journal Anal. Bioanal. Chem.*, 2003; 375: 103-105.
10. Kabanov, A.V. Batrakova, E.V. & Alakhov, V.Y. Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. *Journal Control. Release.*, 2002; 82: 189-212.
11. J. Wang and M. Musameh. Carbon nanotube/ Teflon composite electro chemical sensors and biosensors. *Journal of Anal. Chem.*, 2003; 75(9): 2075-2079.
12. R.J. Chen, S. Bangsaruntip, K.A. Drouvalakis, N.W. Kam, M. Shim, Y. Li, W. Kim, P.J. Utz, and H. Dai. Non covalent functionalization of carbon nanotubes for highly specific electronic biosensors. *Journal Proc. Natl. Acad. Sci.* 2003; 100(9): 4984-4989.
13. Dutta, T. et al. Poly (propyleneimine) dendrimer based nanocontainers for targeting of efavirenz to human monocytes/ macrophages in vitro. *J. Drug Target.*, 2007; 15: 89-98.
14. M. Kelly. Startups Seek Perfect Particles To Search And Destroy Cancer. *Small Times International Journal of Research in Pharmaceutical and Biomedical Sciences.*, 2003; 18.
15. J. Mongillo. Westport, Connecticut ABC-CLIO; *J. Nanotechnology.*, 2007; 101: 103-24.
16. Ferrari M. Cancer Nanotechnology: Opportunities and Challenges. *Nature Reviews. Cancer.*, 2005; 5: 161-171.
17. P.E. Borchardt, R.R. Yuan, M. Miederer, M.R. McDevitt, and D.A. Scheinberg, *Cancer Res. J. Polym. Sci.*, 2003; 63, 5084.
18. J.D. Eichman, A.U. Bielinska, J.F. Kulkowska-Latallo, and J.R. Baker, Jr. The use of PAMAM dendrimers in the efficient transfer of genetic material in to cell. *Pharm. Sci. Technol. Today.*, 2000; 3(7): 232-245.
19. J.D. Reuter, A. Myc, M.M. Hayes, Z. Gan, R. Roy, D. Qin, R. Yin, L.T. Piehler, R. Esfand, D.A. Tomalia, and J.R. Baker. *Bioconjug. Chem.* 1999; 10: 271.
20. J.J. Landers, Z. Cao, I. Lee, L.T. Piehler, P.P. Myc, A. Myc, T. Hamouda, A.T. Galecki, and J.R. Baker, Jr. *Journal of Infect. Dis.* 2002; 186: 1222-1230.
21. R.P. Feynman, Eng. Sci; Keefer LK. Progress toward clinical application of the nitric oxide releasing diazeniumdiolates. *Annu. Rev Pharmacol Toxicol.*, 2003; 43: 585.
22. Kapadia MR, Chow LW, Tshilis ND, Ahanchi SS, Eng JW, Murar J, et al. Nitric oxide and nanotechnology: A novel approach to inhibit neointimal hyperplasia. *Journal of Vasc Surg.*, 2008; 47: 173-82.

23. Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet. J. Am. Chem. Soc.*, 1995; 346: 1339-45.
24. Pandey R, Khuller GK. Nanotechnology Based Drug Delivery System(s) for the Management of Tuberculosis. *Indian J Exp Biol.*, 2006; 44: 357-66.
25. Fadi E, Hartwig S, Muller BW. *In vitro* evaluation of Cyclosporine A (CsA) inhalation nanosuspension. *Respir Drug Delivery IX.*, 2004; 2: 433.
26. Takeuchi H, Yamamoto H, Kawashima Y. Mucoadhesive nanoparticulate systems for peptide drug delivery. *Adv Drug Deliv Rev.*, 2001; 47: 39-54.
27. Patel AR, Vavia PR. Nanotechnology and pharmaceutical inhalation aerosols. *Indian J Exp Biol.*, 2007; 45: 166-74.
28. El-Ansary A, Faddah LM. Nanoparticles as biochemical sensors. *Nanotechnology, Science and Applications.*, 2010; 3: 65-76.
29. Mirkin CA, Letsinger RL, Mucic RC, Storhoff JJ. A DNA-based method for rationally assembling nanoparticles into macroscopic materials. *J. Drug Target.*, 1996; 382: 607-9.
30. Nam JM, Thaxton CS, Mirkin CA. Nanoparticle based bio-bar codes for the ultrasensitive detection of proteins. *Journal of Poly. Sci.*, 2003; 301: 1884-6.
31. Han S, Lin J, Zhou F, Vellanoweth RL. Oligonucleotide-capped gold nanoparticles for improved atomic force microscopic imaging and enhanced selectivity in polynucleotide detection. *Biochem Biophys Res Commun. Journal Am. Chem.*, 2000; 279: 265-9.
32. Jin R, He X, Wang K, Yang K, Li H, Jin Y, *et al.* Characterization of different sequences of DNA on si substrate by atomic force microscopy and gold nanoparticle labeling. *J Nanosci Nanotechnol.*, 2007; 7: 418-23.
33. Qin WJ, Yung LY. Nanoparticle-based detection and quantification of DNA with single nucleotide polymorphism (SNP) discrimination selectivity. *Nucleic Acids Res.*, 2007; 35: 111.
34. Li Y, Wark AW, Lee HJ, Corn RM. Single-nucleotide polymorphism genotyping by nanoparticle-enhanced surface plasmon resonance imaging measurements of surface ligation reactions. *Anal Chem J of pharma sci.*, 2006; 78: 3158-64.
35. A. M. Michaels, M. Nirmal, L. E. Brus, Surface enhanced raman spectroscopy of individual rhodamine 6G molecules on large Ag nanocrystals *J. Am. Chem. Soc.*, 1999; 121: 9932-939.
36. Shenoy, D, W. Fu, J. Li, C. Crasto, J. Graham, D. Charles, S. Srinivas and A. Mansoor., Surface-Functionalized Gold Nanoparticles. *International Journal of Nanomedicine.*, 2005; 1-4.