Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(6):257-264

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Nanotechnology: A smart drug delivery tool in modern healthcare

Tushar Madaan, Shweta Pandey and Sushama Talegaonkar*

Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard University, New Delhi

---

ABSTRACT

Nanotechnology can be described as the manipulation of matter at an atomic, molecular or supramolecular scale in the range of 1-100 nanometers. Nanotechnology is a modern science that is gaining immense popularity and applications in multiple scientific fields such as surface science, microfabrication, semiconductor, molecular biology, electronics, medicine, consumer products and many other industrial and military applications. Nanotechnology also raises various issues like the impact of nanoparticles on the environment, toxicity, regulation of nanotechnology and nanoparticles and the overall impact of nanotechnology on global economics. The present article focuses on the past, present and future of nanotechnology with a special focus on the application of nanotechnology in various fields of medicine.

Keywords: Nanotechnology, Nanomedicine, Devices based on Nanotechnology, Disease diagnosis, drug delivery and Marketed Nanoformulations.

INTRODUCTION

The possibility of fabrication of materials at the atomic level was first mentioned by the famous physicist Richard Feynman in 1959 [1].Two major innovations in the 1980s lead to the birth of modern nanotechnology, the invention of the Scanning Tunnel Microscope was one of the major breakthroughs in the history of nanotechnology. The Scanning Tunnel Microscope allowed us to view individual atoms and bonds in between atoms. It was later used to manipulate singular atoms. The discovery of Fullerenes was another major event. Buckminster fullerene (C_{60}) was employed along with carbon nanotubes which inspired further applications of fullerenes in Nanotechnology. In the 21st century, many countries are investing billions of dollars in the nanotechnology industry. The US government invested 3.7 billion dollars in various research and development projects in nanotechnology. The European Union and Japan have invested 1.2 billion dollars and 750 million dollars respectively in the nanotech industry [2].The use of nanotechnology in various sectors of therapeutics has revolutionized the field of medicine where nanoparticles of dimensions ranging between 1 and 100 nm are designed and used for diagnostics, therapeutics and as biomedical tools for research [3]. Nanotechnology based next generation techniques and rapidly developing subdivisions have many advantages including highly specific medical interventions for prevention, diagnosis, and treatment of diseases, with unique functions at the cellular, atomic and molecular levels [4]. On one hand nanotechnology is gaining immense popularity and applications in multiple scientific fields such as surface science, microfabrication, semiconductor, molecular biology, electronics, medicine, consumer products and many other industrial and military applications [5] while on another hand, nanotechnology also raises various issues like the impact of nanoparticles on the environment, toxicity and regulation of nanotechnology [6]. Over the past two decades, the rapid developments in nanotechnology have allowed the incorporation of multiple therapeutic, sensing, and targeting agents into nanoparticles, for detection, prevention, and treatment of diseases.

1. Applications of nanotechnology

Nanotechnology is helping to improve and revolutionize many technology and industry sectors. It has a multitude of applications as well as uncountable future applications in different areas. **(Fig 1).** This article is focused on the present developments and future prospects of nanotechnology in medicine. [7-11].

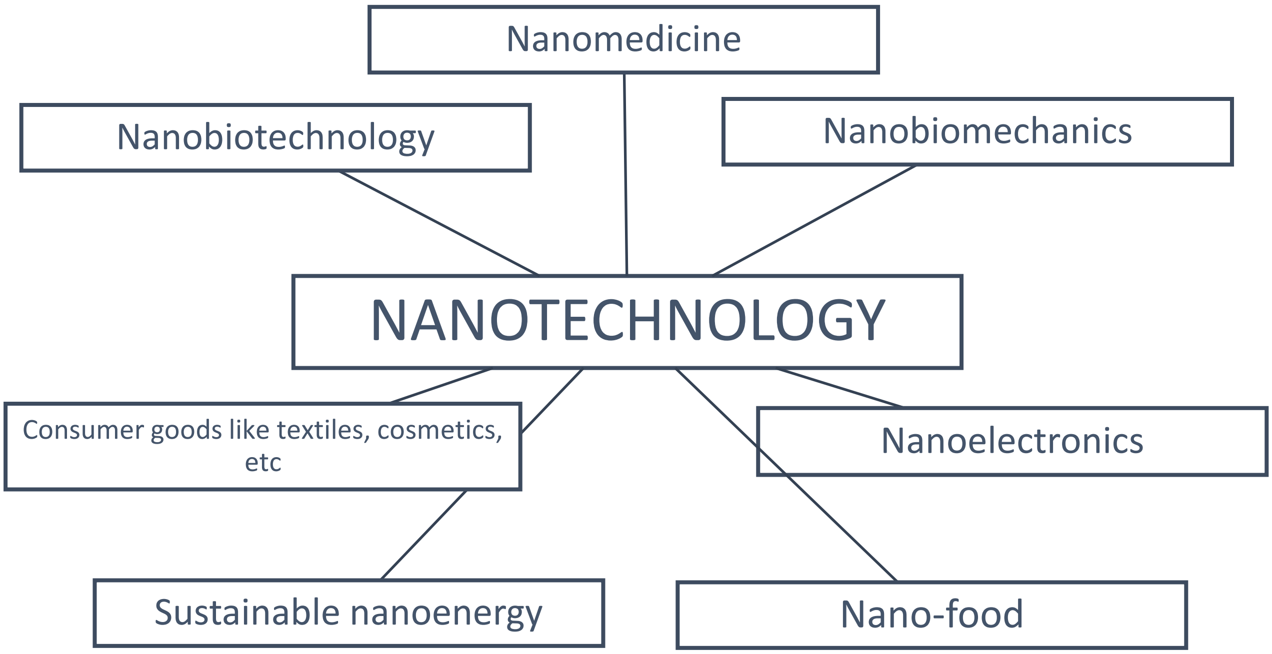

Fig 1. Applications of nanotechnology in various fields [7-11, 23-25]

2. Nanomedicine

Nanomedicine is a branch of nanotechnology that deals with the application of nanotechnology in medicine and healthcare. It is a steadily rising science which has a huge scope in future. According to the National Nanotechnology Initiative, nanotechnology will have numerous uses in pharmaceutical R&D as well as various commercial applications.

2.1 Nanomedicine in diagnosis

Nanoparticles have many applications in diagnosis and visualization of various abnormalities in the body, especially in cases of benign and malignant tumors due to their small size. Magnetic electro-chemiluminescent polyelectrolyte nanostructures of Cadmium Selenide-Cadmium Sulphide are used for the detection of carcinoembryonic antigen (CEA) which is used as a biomarker for many types of cancer [12]. These Cadmium Selenide nanoparticles enter the tumor cells and glow when exposed to ultraviolet light. This illumination of tumor cells aids the surgeon in better removal of tumor and tumor cells from the patient [13, 14].

2.2 Nanomedicine in therapeutic drug delivery

Nanomedicine can be used to design dosage forms for drugs that have poor bioavailability, especially those that undergo first pass metabolism. This can lead to less overall consumption of the drug as well as fewer chances of dose dumping, development of tolerance and less side effects. Nanoparticles made up of polymers, lipids and phospholipids [15] are being used to design dosage forms that counteract the problems faced by conventional drug dosage forms. Nanoparticles are often loaded in the drug reservoir of transdermal patches as they penetrate the skin more efficiently as compared to other relatively larger particles [16]. Nanoparticles can also be used in combination with other drugs in order to reduce antibiotic resistance. Nanostructured vectors including liposomes, micelles, nanoemulsions, nanogels, dendrimers, polymer-, lipid-, and ceramic-based nanoparticles, for drug delivery reduce the severity and incidence of side-effects by lowering the required drug dose and by increasing the interaction specificity between a drug and its target [17].

2.3 Cancer

Conventional cancer therapy has a lot of fallbacks which include drug resistance [18], less aqueous solubility and lack of selectivity [19]. Nanotechnology has the methods which can solve all the aforementioned problems associated with the conventional cancer therapy. Nanoparticles being extremely small in size, easily accumulate at the tumor sites in the body [20]. Nanoshells made up of gold coated silica have also been developed which are embedded in drug containing tumor target polymer [21]. These nanoshells when injected into the body reach the tumor site. These nanoshells are then heated with an IR laser, the laser melts the polymer and releases the drug at the tumor site [22-25]. A new microsphere composed of inorganic MSN (Mesoporous Silica Nanoparticles) and organic alginate was also synthesized [26]. These microspheres have the benefits of high surface area for increased drug loading as well as excellent biocompatibility [27]. The microspheres were successfully up took by liver cancer cells, hepatocellular carcinoma (HepG2) without apparent toxicity [28].

2.4 Neurology

Delivering therapeutic agents to the brain is a big challenge because most of the drugs are not able to cross blood brain barrier due to the presence of highly dense network of capillary endothelium cells [29]. Nanotechnology has significantly improvise the drug delivery strategy providing novel carriers for safe and effective brain targeting. Gelatin nanoparticles laced with medication can be used for delivering drugs to the brain in a noninvasive manner. Gelatin is biocompatible as well as biodegradable so the nanoparticles can be administered nasally and directly reach the brain. This allows the drug to surpass the blood-brain barrier and reach the brain. They can also be used to deliver drugs that have high toxicity or a short half-life [30].

2.5 Atherosclerosis

Of the cardiovascular syndromes, atherosclerosis has gained the most attention from nanomedicine researchers due to the number of potential targets within the lesions, including an abundance of specific cell types, like macrophages, and the overexpression of cell surface receptors, like vascular cell adhesion molecule-1[31]. Clinically, there exists a need to identify vulnerable lesions before the onset of symptoms. Nanoparticle agents, such as superparamagnetic nanoparticles and perfluorocarbon emulsions of nanoparticle, have been developed for noninvasive imaging [32]. Diazeniumdiolates nanofiber gels which released NO spontaneously when placed in an aqueous environment were formulated for Atherosclerotic patients with neointimal hyperplasia and require arterial intervention [33].

2.6 Tuberculosis

The management of tuberculosis (TB) treatment is either preventive (i.e., vaccination) or therapeutic (i.e., chemotherapy) [34]. Liposomes and lipid nanoparticles are successfully used to deliver the anti-TB drugs with sustained release profiles for long-term therapy and also improved the pharmacokinetic profile of the agent [35].

2.7 Gastrointestinal disorders

Gastrointestinal delivery of anti-inflammatory nanoparticles to treat inflammatory bowel disease is more efficient and less costly than systemic therapies [36]. In inflammatory bowel diseases, such as Crohn’s disease and ulcerative colitis and colon is the main targeted organ. A large number of drugs may potentially be loaded into nanoparticles (NPs) for specific targeting [37].

2.8 Diabetes

Nanotechnology offers some new solutions in treating diabetes mellitus [38]. Nanopores bearing boxes are being developed that protect transplanted beta cells from the immune system attack, nanospheres as biodegradable polymeric carriers for oral delivery of insulin, nanorobots as sensor of insulin level in blood are just some examples of the them [39].

2.9 Retinal diseases

The development of a drug delivery system (DDS) that can be used for the posterior segment of the eye that involves nanocarriers to overcome the issue of frequent intravitreal administration has received great attention [40]. Nanocarriers used in the field of retina is focused on liposomes, nanospheres, nanoemulsions and cyclodextrin nanoparticle suspension [41].

2.10 Nanodentistry
Subocclusal dwelling nanorobotic dentrifice delivered by mouthwash or tooth paste could patrol all supragingival and subgingival surfaces at least once a day [42], metabolize trapped organic matter into harmless and odorless vapors and perform continuous calculus debridement [43]. Orthodontic nanorobots could directly manipulate the periodontal tissues allowing straightening, rotating and vertical repositioning of rapid and painless tooth within minutes to hours [44].

2.11 Bone substitute
Biologically inspired rosette nanotubes, hydrogel nanocomposites and nanocrystalline hydroxyapatite can be used as bone substitute to improve bone [45]. Self- assembled Rosette nanotubes are formed by chemically immobilizing DNA base pairs that biomimics natural nanostructural component of bone [46].

2.12 Tissue Engineering
Nanotechnology may also be used to engineer tissues and repair damaged organs of the body. This evolution can replace conventional methods of treatment like organ transplants or artificial organ transplants [47]. Carbon nanotubes, graphene, tungsten disulphide [48-50] are some examples of nanoparticles that are currently being as strengthening agents to produce mechanically strong biodegradable polymers for bone tissue engineering [51]. The incorporation of the aforementioned nanoparticles at low concentration (about 0.2 weight %) has demonstrated significant amelioration in the compressive and flexural properties of polymeric nanocomposites [52].

2.13 Gene Therapy
Gene Therapy is a modern method of approach for the treatment of various genetic diseases like thalassemia, diabetes mellitus, cystic fibrosis, etc.[53-55]. The methods for gene therapy that are currently being used have a number of drawbacks like safety concerns with use of viral vectors as well as the inability of naked DNA to cross the cell membrane because of both of them being negatively charged [56]. Liposomes with dimensions of less than 100 nm, when incorporated with polyethylene glycol and glycol, target liver cells with great efficacy because of their rapid uptake by the Kupferr cells present in the liver. Significant decrease in fasting blood glucose levels and increase in plasma insulin levels was observed when human insulin gene incorporated in chitosan nanoparticles was transfected to streptozotocin diabetic rat via the GIT [57].

Table 1 summarizes some important marketed products based on nanotechnology.

Table 1: Marketed products based on nanotechnology

Product	Company name	Therapeutic agent	Nanotechnology	Therapeutic role	Route of Administration.
Pacliall	Panacea	Paclitaxel	Nanoparticles	Lung cancer	(i.v)
Myocet	ZeneusPharma, Sopherion	Doxorubicin	Liposome	breast cancer	(i.v)
LEP-ETU	Neopharm	Paclitaxel	Neolipid	Advanced Cancer	(i.v)
Clinical trial	-	SN38	PAMAM dendrimers	Hepatic colorectal cancer	Oral
Allovectin -7	VICAL	Plasmid DNA	Liposomal DNA/Lipidic complex	Melanoma	(i.v)
DepoCyt®	SkyePharma Enzon	Cytarabine	Liposome	Lymphomatousmeningitis	(i.v)
Avinza®	King Pharma, Elan	Morphine sulfate	NanoCrystal	psycho-stimulant	Oral
Tricor	Abbott Lab(USA)	Fenofibrate	Nanocrystal particles	Primary lipidemia	Oral
Clinical trial	AlphaRx	Streptomycin	Nanocapsule	tuberculosis	(i.m)
MiKasome	NeXstarPharmceutical	Amikacin	Liposome	tuberculosis	(i.v)
Clinical trial	-	Rifampicin + isoniazide	SLN Nebulization	tuberculosis	Inhalation
Emend	Merck, Elan	Aprepitan	DepoFoam,	antiemetic	Oral

			Nanocrystal		
Renagel	Genzyme	Sevelamer hydrochloride	Crosslinkedpolyallylamine resin	End-stage Renal failure	Oral
Clinical trial	-	Insulin	Protein liposome	Diabetes	
Restasis®	Allergan	Cyclosporine A	lipid nanoemulsion	dry eye	Ophthalmic
Durezol®	Siron Therapeutics	Difluprednate	lipid nanoemulsion	corticosteroid	Ophthalmic
Elyzol	Metronidazole	Camurus	Gel	ParodontisCamurus	Dental
Ceram X duo	Dentspley	Biomaterials	Nanoparticle composite	Dental filling material	Dental
Vitoss	Orthovita	hydroxyApetite	Nanoimplants	BoneGraft	Bone defects
Indaflex	AlphaRx	Indomethacin	Solid lipid nanoparticles	Osteoarthritis	Bone defects
AmBisome	Gilead	Amphoterecin B	Liposome	Mycotic infection	i.v
Emmelle	M-L Laboratories	dextrin 2 sulfate	vaginal gel	HIV/AIDS	Topical
Neoral®	Novartis	Cyclosporine A	Self micro emulsifying drug delivery system	Organ transplant	Oral
Elestrin®	BioSanté	Estradiol	estradiol gel +Ca_2PO_4 nanoparticles	menopause	Transdermal/Dermal
LMX®-4	Ferndale Laboratories	Lidocaine	liposomes	anesthesia	Transdermal/Dermal
Zincox	clinical trial	zinc	Nanopowders	Sun screen	Topical

3. Recent innovations and advances in nanotechnology

Various biocompatible nanotechnological carriers are currently being investigated by scientists for pharmacological and biomedical applications and now are also being explored as newer tools in nanomedicine and drug delivery.

3.1 Nanoshells

Nanoshells (NS) are gold coated miniscule beads. The wavelength of light absorbed by the beads is depended on to the coating thickness. Thus, designing of the beads with thickness manipulation will provide absorption of specific wavelength. The most useful NS are those that absorb near infrared light that can easily penetrate several centimeters in human tissues. Intense heat is produced by NS after absorption of light that is lethal to cells. Metal nanoshells which are intense near-infrared absorbers are effective both in-vivo and in-vitro on human breast carcinoma cells [58].

3.2 Nanotubes

Nanotubes are smaller than nanopores. Nanotubes help to identify Dioxyribonucleic acid (DNA) changes associated with cancer cells [59]. They are about half the diameter of DNA molecule. It helps exact pin pointing the location of the changes. Cancer associated mutated regions are tagged first with bulky molecules [60]. The physical shape of the DNA molecule can be traced with the help of the tip of nanotube. Disease related information is translated by computer into topographical map. The mutations affected regions are identified by bulky molecules on the map. These techniques are important in predicting disease as the location of mutations can influence the effects they have on a cell [61].

3.3 Nanowires

Nanowires are solid, crystalline rods with diameters in the nanometer range (10–100 nm) and typical lengths of around a few micrometers. These objects can be made from a wide range of inorganic materials and are occasionally termed nanorods or nanowhiskers. It has microchip containing nanowires and by placing antibodies on the wires, we can detect the biomolecules of our interest. The effect is a result of electrostatic attraction or repulsion of the electrical charges in the nanowire, and the consequent change in resistance, depending on the charge of the captured biomolecules. It has wide application in diagnosing disease, genetic screening and drug discovery. [62]

3.4 Quantum dots

These are tiny crystals that glow when stimulated by ultraviolet light and emit the color that lights up the sequence of interest. Probes can be created by combining different sized quantum dotes within a single bead, that release a distinct spectrum of various colors and intensities of lights. Light stimulated crystals emit colors act as dyes and light up the sequences of interest in tumor detection. [63]

3.5 Nanorobotics

Nano-robots that can function as tiny surgeons could be introduced into the body through the vascular system or at the ends of catheters into various vessels and other cavities in the body.[64] Such a device could perform various functions such as searching for pathology and then diagnosing and correcting lesion by nanomanipulation [65] coordinated by an onboard computer while maintaining contact with the supervising surgeon *via* coded ultrasound signals [66].

3.6 Cantilevers

Tiny bars are engineered and anchored at one end which can be bound to associated cancer molecules. These molecules may bind to altered DNA proteins that are present in certain types of cancer. It would be possible to tell whether the cancer molecules are present by monitoring the bending of cantilevers and hence it can detect early molecular events in the development of cancer cells [67].

3.7 Respirocytes

Respirocytes are hypothetical artificially engineered red blood corpuscles which might hold the capacity to hold several times the amount of oxygen than a normal human RBC. In the near future, respirocytes could be infused into the body in cases which require blood transfusion. There would be nanosensors on the surface of these respirocytes and a nanocomputer would regulate the intake and output of the oxygen and carbon dioxide molecules. An infusion of one liter dose of 50% respirocytes saline suspension in a human can theoretically keep the patient oxygenated up to four hours following cardiac arrest [68]. This would reduce the need for transfusion of human blood and hence would successfully be able to combat several problems associated with blood transfusion viz. infections, shortage of blood in blood banks, etc.

3.8 Microbivores

Microbivores are hypothetical artificially engineered white blood corpuscles which could be infused into the blood stream and trap microbes present in the circulation. They are expected to show greater efficacy than cellular blood cells in phagocytosis. The microbivores surface is arranged with processes which can extend in length and secure the microbe which gets in contact with it. The microbe will move skilfully to the ingestion port and undergoes the process of morcellization and enzymatic degradation. The end products are released as amino acids, nucleotides, fatty acids, and sugars. Application of the microbivores in human circulation could theoretically clear the blood stream in septicaemia at a much greater rate than the natural defence mechanism with antibiotics [69]. Microbivores would also have a lot of applications, especially in case of diseases in which the immune system of the body gets compromised viz. AIDS.

4. Challenges in nanotechnology

The current challenges that are faced by the development of nanomedicine are the various detrimental effects of nano-sized particles on health and environment [70]. Nanotechnology is fast-growing new wave of science that deals with nanoparticles engineered from many materials such as carbon, zinc and gold, which are inhaled by factory welders, followed a rapid and efficient pathway from the nasal cavity to several regions of the brain and lungs.58Regulatory issues play a major role in the development of nanoformulation drugs. Regulatory capacity, information asymmetry, inter-agency coordination, overlapping roles and mandates are the ones which likely to make the task of regulating nanotechnology difficult [67]. A nanoformulation of a drug which is based on a previously approved drug in microformulation can undergo a shorter approval pathway by means of abbreviated new drug application if bioequivalence can be demonstrated to its microformulation drug.[12] However, if bioequivalence cannot be demonstrated, it would necessitate approval of all the stages of new drug application. Further, when a nanodrug is designed as a new chemical entity, the evaluation procedure becomes more rigorous [23]. There is an increasing concern over the safety of nanodrugs since knowledge of the toxic effects of nanodrugs is limited but is rapidly growing. Nanoformulations are expected to be able to diminish the toxicity of chemotherapeutic drugs or other drugs with a narrow therapeutic index, however, a number of studies have shown that some nanoparticles demonstrated toxicity in biological systems, causing cytotoxicity, allergy, or inflammatory response [71].

CONCLUSION

The field of nanomedicine has a bright future with the emergence of several promising approaches for delivery of therapeutic agents and imaging using the advantages of the nanoscale carriers. Various initiatives from both the federal agencies as well as industry support the continual research into the application of nanotechnology to improve drug delivery and molecular imaging. Nanostructures and nanotechnology-based devices are under active development towards the design of diagnostic and therapeutic tools and devices. Nanomaterials are increasingly used in diagnosis, imaging, and targeted drug delivery applications. Nanotechnology promises to facilitate the development of personalized medicine called pharmacogenomics, in which patient therapy is tailored by the patient's individual genetic and disease profile. The coupling of nanotechnology strategies and telecommunication will improve the precision of diagnostics and therapeutics and promise to impact the care and management of diseases such as intestinal diseases and cancer. In the near future, medical approach and diagnostics will certainly change dramatically.

REFERENCES

[1] KE Drexler. Nanosystems: Molecular Machinery, Manufacturing, and Computation, 1stedition, John Wiley & Sons, New Delhi, **1992**; 1-3.
[2] RRHCoombs, DW Robinson. Nanotechnology in Medicine and the Biosciences:Developments in Nanotechnology, 0th edition, Gordon & Breach, **1996**.
[3] R Saini; S Saini; S Sharma, *Journal of Cutaneous and Aesthetic Surgery*.**2010**, 3, 32-33.
[4] C Buzea; IIP Blandino; K Robbie. *Biointerphases*. **2007**, 2(4), 17–71.
[5] S Rao; A Tan; N Thomas; C Prestidge. *Journal of Controlled Release*. **2014**, 193, 174-187.
[6] AG Cattaneo; R Gornati; E Sabbioni; M Chiriva; E Cobos; MR Jenkins; G Bernardini. *Journal of Applied Toxicology*. **2010**, 30(8), 730-744.
[7] NA Melosh; A Boukai; F Diana;B Gerardot; A Badolato; PM Petroff; JR *Heath. Science*.**2003**, 300(5616), 112–115.
[8] E Serrano; G Rus; J Garcia-Martinez. *Renewable and Sustainable Energy Reviews*. 2009, 13, 2373–2384.
[9] JK Patra; S Gouda. *Journal of Engineering and Technology Research*. **2013**, 5(5), 104 – 111.
[10] M Fitzgerald, Nanobiomechanics. *MITTechnology Review*.**2011**.
[11] L Yu-Te; L Chia-Hung; Y Jilashing; W Kevin. *International Journal of Nanomedicine*. **2014**, 9(1), 2767-2778.
[12] S Onoue; S Yamada; H Chan. *International Journal of Nanomedicine*. **2014**, 9, 1025-1037.
[13] I Lynch;IL Feitshans; M Kendall. *Phil. Trans. R. Soc*.**2015**, 370.
[14] HA Santos.*Advances in Delivery Science and Technol*ogy **2015**, 571-613.
[15] V Poonam; K Pathak. *Journal of Advanced Pharmaceutical Technology & Research*.**2010**; 3, 274–282.
[16] M Banoee, S Seif, ZE Nazari, PJafari-Fesharaki.*J Biomed Mater Res B ApplBiomater*.**2010**, 93 (2), 557–61.
[17] YA Luqmani. *Med PrincPract.* **2005**, 14, 35-48.
[18] M Chidambaram; R Manavalan; K Kathiresan. *Journal of Pharmacy & Pharmaceutical Sciences.* **2011**, 14(1), 67–77.
[19] N Shuming; Y Xing; GJ Kim; J.W. Simmons. *Annual Review of Biomedical Engineering*. **2007**, 9, 257–88.
[20] R Freitas Jr. Nanomedicine. *Nanotechnology, Biology, and Medicine*.**2005**, 1(1), 2-9.
[21] G Jie; L Wang; S Zhang. *European Journal*. **2011**, 17(2): 641–648.
[22] G. Lalwani; MH Allan; F Behzad; L Liangjun; KF Kurtis; X Yi- Qin, GM Antonios; S Balaji. *Biomacromolecules*. **2013**, 14 (3), 900–909.
[23] A Surendiran; S Sandhiya;S Pradhan;C Adithan. *Indian Journal of Medical Research*. **2009**, 130, 689-701.
[24] SChokaouychai, DFei, Y Ge. Nanomedicine, 1st Edition, Springer, New York, **2014**, 321-340.
[25] U Agarwal; R Sharma; M Gupta; SP Vyas. *Drug Discovery Today*. **2014**, 19(10), 1531-1546.
[26] A Alok; S Panat; A Aggarwal; N Upadhyay; N Agarwal; M Kishore. *Journal of Research in Dental Sciences*. **2013**, 4 (4), 154-160.
[27] G Calixto; JBernegossi; B Fonseca-Santos; M Chorilli. *International Journal of Nanomedicine*. **2014**, 9, 3719-3735.
[28] C Dianzani; GP Zara; GMaina. *BioMed Research International*.**2014**, 1-13.
[29] MFakhouri; R Takechi; HAl-Salami.*British Journal of Medicine and Medical Research*. **2015**, 6(6), 547-556.
[30] XWang; XYu; W Vaughan; M Liu; YGuan. *Neuroscience Bulletin*. **2015**, 9, 1-9.
[31] D Deshpande; AJamal-Allial; K Sankhe; M Amiji. Advances in Delivery Science and Technology Part-II, 1st Edition, Springer United States, **2014**, 359-385.

[32] AC Anselmo; SMitragotri. *Journal of Controlled Release*. **2014**, 190, 531–541.
[33] K Jain; NK Mehra; NK Jain. *Current Opinion in Pharmacology*.**2014**, 15, 97-106.
[34] G Chinnasamy; VJ Reddy; S Subramanian; S Radhakrishnan; S Dinesh. *Journal of Nanoscience and Nanotechnology.* **2015**, 15, 2591-2604.
[35] RTSadikot. *Advanced Drug Delivery Reviews*. **2014**, 77, 27-31.
[36] B Sun; Y Fang; Z Li; Z Chen; J Xiang. *Molecular and Clinical Oncology*. **2015**, 3, 274-280.
[37] H Laroui; P Rakhya; B Xiao; E Viennois; D Merlin. Elsevier: *Digestive and Liver Disease*. **2013**, 45, 995-1002.
[38] VPKinesh; DP Neelam; BP Punit; SB Bhavesh; KS Pragna. *International Journal of Pharmaceutical Sciences and N*anotechnology. **2010**, 3(3), 1057-1064.
[39] O Veiseh; BC Tang. *Nature Reviews Drug Discovery*. **2015**, 14, 45–57.
[40] SKSahoo; F Dilnawaz; S Krishnakumar, *Drug Discovery Today*. **2008**, 13(3-4), 144-151.
[41] AM Al-Halafi, *Saudi Journal of Ophthalmology*. **2014**, 28, 304–309.
[42] Z Khurshid; M Zafar; S Qasim; S Shahab; M Naseem, *Materials*. **2015**, 8(2), 717-731.
[43] RS Gambhir;GM Sogi; A Nirola; R Brar; T Sekhon; H Kakar, *Journal of Orofacial Sciences*. **2013**, 5, 9-14.
[44] TSV Satyanarayana; R Rai, *Journal of Interdisciplinary Dentistry*. **2011**, 1, 95-100.
[45] ANiakan; S Ramesh; P Ganesan; CY Tan; JPurbolaksono.*Ceramics International.* **2015**, 41(2), 3024–3029.
[46] CGanz; T Gerber,*Key Engineering Materials*. **2014**, 26, 321-325.
[47] S. Kunjalukkal; L Salvatore, F Gervaso; M Catalanol A Taurino; ASannino, *Journal of Nanoscience and Nanotechnology.* **2015**, 15,504-509.
[48] MG Wacker, *Journal of Pharmaceutical Sciences*. **2014**, 103, 777–784.
[49] J Wright. *Nature Drug Delivery*. **2014**, 509, 59.
[50] X Zhou; AL Porter; DKR Robinson; MK Shim; Y Guo, *Nanomedicine: Nanotechnology, Biology, and Medicine.* **2014**, 10, 889–896.
[51] PD Marcato; NDurán. *Journal of Nanoscience and Nanotechnology*.**2008**, 8, 1-14.
[52] HM Mansour; CW Park; RBawa. Handbook of Clinical Nanomedicine, Pan Stanford, **2015**, 1-33.
[53] MZH Saad; R Jahan; U Bagul, *Asian Journal of Biomedical & Pharmaceutical Sciences*, **2012**, 2(14), 11-20
[54] LNiu; YC Xu; Z Dai; HQ Tang, *World Journal of Gastroenterology*, **2008**, 14, 4209-4215.
[55] PB Davis; MJ Cooper,*AAPS Journal*. **2007**, 9(1), E11–E17.
[56] A Pathak; SP Vyas; KC Gupta, *International Journal ofNanomedicine*.**2008**, 3, 31-49.
[57] M Jadupati; G Amitava; B Aalok; NA Kumar. *International Research Journal of Pharmacy* **2012**, 3(2), 36-40
[58] CC Anajwala; GK Jani; SMV Swamy, *International Journal of Pharmaceutical Sciences and Nanotechnology*. **2010**, 3, 1043-1056.
[59] L Lacerda; J Russier; G Pastorin; MA Herrero; E Venturelli; Hélène Dumortier, KTAl-Jamal; M Prato; K Kostarelos; B Alberto, *Biomaterials*. **2012**, 33, 3334-3343.
[60] MT Kartel; LV Ivanov; SN Kovalenko; VPTereschenko. *Advanced Materials and Methods for Health Protection*. **2011**, 11-22.
[61] Z Liu; S Tabakman; K Welsher; H Dai, *Nano Research*. **2009,** 2(2), 85-120.
[62] F.Patolsky; G. Zheng; CM Lieber, *Nanomedicine*.**2006**, 1(1), 51-56.
[63] OM Koo; M Rubinstein; H Onyuksel, *Nanomedicine: Nanotechnology, Biology, and Medicine*. **2005**, 1, 193 – 212.
[64] S Singh; A Singh, Anesthesia: Essays and Researches. **2013**, 7(2), 237-242.
[65] J Mishra; AK Dash; R Kumar, *Int. Res. J. of Pharmaceuticals*. **2012**, 2, 112-119.
[66] RAFreitasJr, *J ComputTheorNanosci*. **2005**, 2, 1-25.
[67] EA Martis;RR Badwe; MD Degwekar, *Chronicles of Young Scientists*. **2012**, 3. 68-73.
[68] AR Jaiswal, *Innovare Journal of Life Sciences*. **2013**, 1, 1-2.
[69] RA FreitasJr, *J EvolTechnol.* **2005**, 14, 1-52.
[70] K Park, *ACS Nano*. **2013**, 7(9), 7442-7447.
[71] KH Basavaraj, *Indian Journal of Dermatology*. **2012**, 57(3), 169-174.