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Nanomedicine and its applications

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ABSTRACT

Innovations and discoveries are constantly being made in the medical field. Nanoparticles have contributed to many of these advances. One of the most promising applications of nanotechnology is in the field of medicine. Applications of nanotechnology for treatment, diagnosis, monitoring and control of biological systems is referred to as nanomedicine. It is a relatively newer technology based on the uses of engineered nanomaterials like liposomes, carbon nanotubes, fullerences, polymeric micelles, quantum dots. Engineered nanomaterials are medical materials available in nanometer (one-millionth of a millimeter) scale. Because of nanoscale, the molecules acquire changes in their physicochemical properties which are utilized for easier and more thorough penetration in cells. Nanomedicine has shown promising results both in diagnostics as well as therapeutics. The most striking use can be repairs at a molecular level. Like other modalities of treatment, nanomedicine also has disadvantages, however currently the benefits outweigh the risks.

Keywords: Liposomes, Nanotubes, Bucky ball, Gold nanoshells, Micelles

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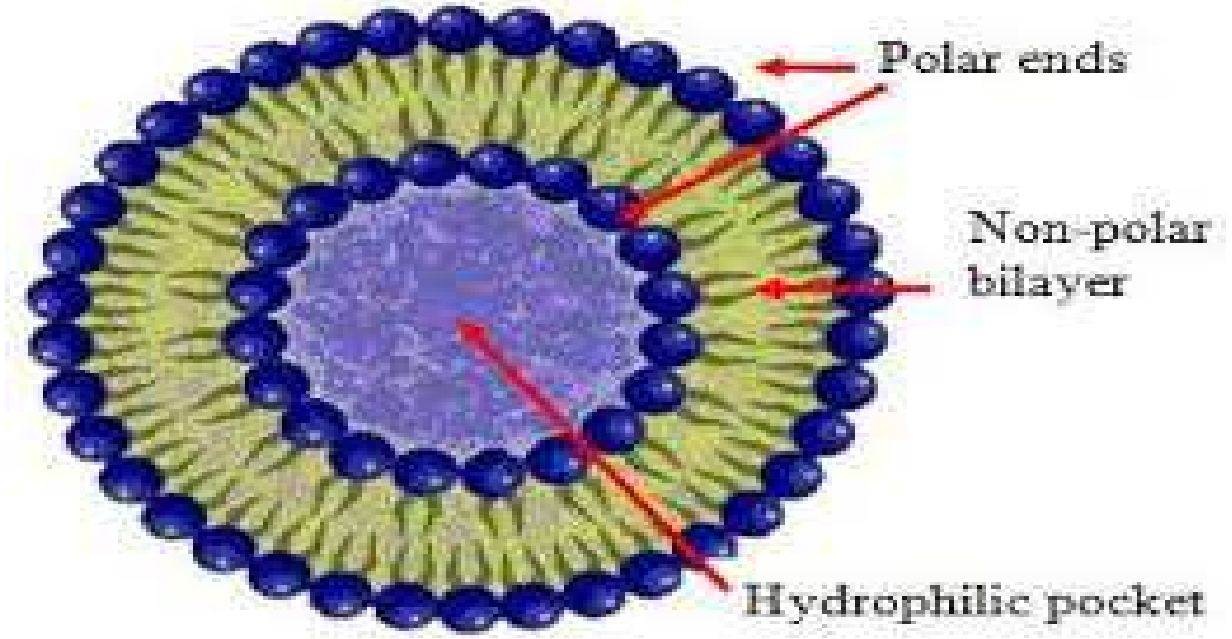
INTRODUCTION

Nanotechnology is design, characterization, production and application of structures, devices and systems by controlling shape and scale. A nanometer is one billionth of a meter or 1/75,000$^{th\ the}$ size of a human hair or about the width of six carbon atoms. A human hair is approximately 80,000 nm wide and a red blood cell approximately 7000 nm wide. Nanoscience studies the phenomena, properties and responses of materials at atomic, molecular and macromolecular scales, and in general at sizes between 1-100nm. Applications of nanotechnology for treatment, diagnosis, monitoring and control of biological systems is referred to as nanomedicine. It is derived from Greek word, nanos means dwarf and meros means meter**[**1]. On Dec 29, 1959 physicist Richard Feynman gave a lecture at American Physical Society meeting at Caltech titled there is plenty of room in the bottom. Feynman proposed employing machine tools to make smaller machine tools, these are to be used in turn to make still smaller machine tools, and so on all the way down to the atomic level. This lecture was the birth of idea and study of nanotechnology **[**2]. Norio Taniguchi at Tokyo Science University in 1974 coined the term nanotechnology to describe the precision manufacture of materials with nanometers tolerances and was unknowingly appropriated by Drexler in his 1986 book Engines of creation: The Coming Era of Nanotechnology**.** Twenty years from now, nanotechnology will have given us specially engineered drugs that specifically target just the mutant cancer cells in the human body, and leave everything else blissfully alone. There are different kinds of nanoparticles which are suitable to be applicable in drug and gene delivery and are categorized as liposomes, quantum dots, polymer nanoparticles, solid lipid nanoparticles, nanocrystals, dendrimers, fullerenes, inorganic nanoparticles (e.g. gold and magnetic nanoparticles) and nonobubbles [3]. There are various methods of entry of nanoparticles into cell that includes endocytosis, diffusion and through ion channels or transport proteins. Advantages of these drugs over conventional drugs are eenhanced solubility of the drug, reduction in the number of doses given to the patient and protection of drug from degradation before it reaches the target and effective drug targeting.

Liposomes

Figure 1: Structure of liposome



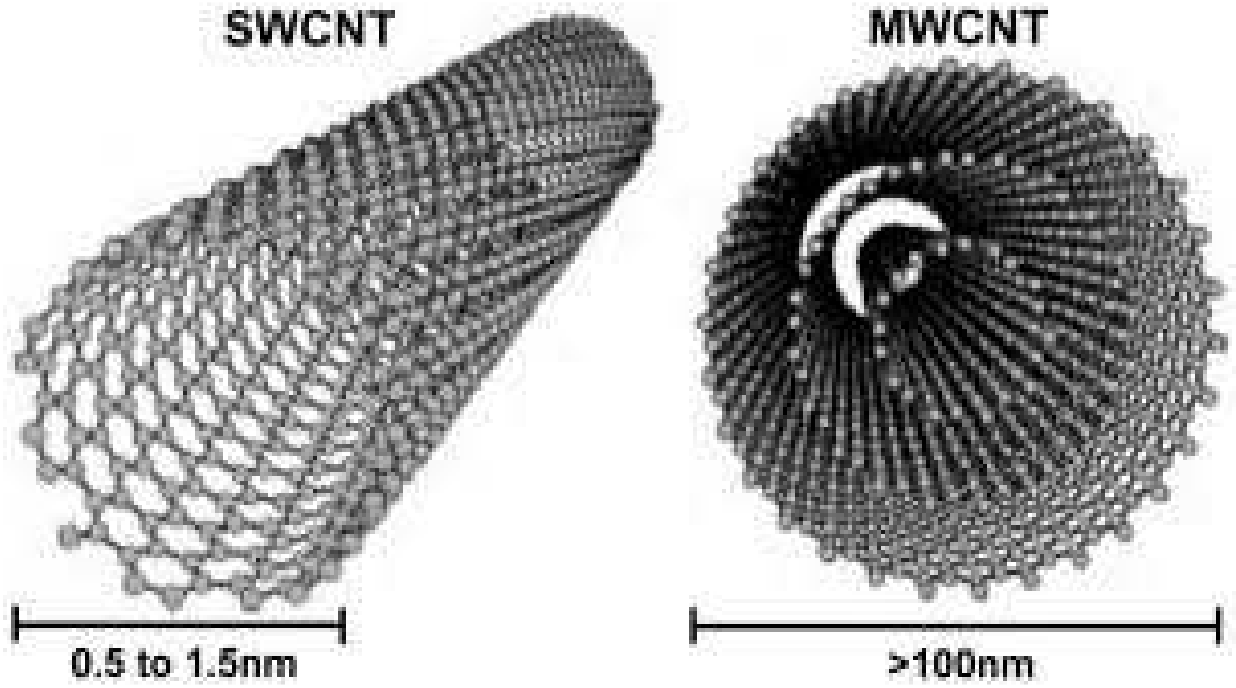
These are simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecule. The name liposome is derived from two Greek words, 'lipos' meaning fat and 'soma' meaning body.There are various types of liposomes like unilamellar, bilamellar liposomes, cationic liposomes, virosomes, immunoliposomes, gene based liposomes, pH sensitive liposome, long circulatory liposome, fusogenic liposome [4]. The advantages of using liposomes in drug delivery are decreased toxicity of encapsulated drug, both hydrophilic and hydrophobic drugs can be encapsulated within liposomes, they are biologically inert, biodegradable, non toxic, non antigenic, non pyrogenic and can be used as effectively for drug targeting and they transport their load across biological membranes and even across BBB. The disadvantages of liposomes are high cost of production, their uptake by RES, allergic reactions may occur to liposomal constituents, problem to targeting to various tissues due to their large size, less stability and low solubility [5]. Stealth liposomes are a type of liposomes where the liposomes are coated with materials like polyoxyethylene which prevents opsonisation of the liposome and their uptake by macrophages. The circulation time of liposomes can be prolonged by incorporation of substances like cholesterol, polyvinylpyrollidone polyacrylamide lipids. The unique ability of liposomes to entrap drugs both in an aqueous and a lipid phase make such delivery systems attractive for hydrophilic and hydrophobic drugs. Usually water soluble drugs are loaded in aqueous compartment and lipid soluble drugs are incorporated in the liposomal membrane. Liposomes can be made from several different types of lipids however; phospholipids are most commonly used to generate liposomes as drug carriers. Additives like cholesterol or sphingomyelin may be added to the liposomal mixture in order to help stabilize the liposomal structure [6]. Virosome is a type of liposome in which liposome surface is modified with fusogenic viral envelope proteins. Influenza vaccine is developed by using virosomes containing the spike proteins of influenza virus and elicits high titres of influenza specific antibodies. Trials of virosome influenza vaccine in children showed that it is highly immunogenic and well tolerated. Similar type vaccines are under development for Hepatitis A [7]. Liposomal Hemoglobin also called as haemasomes are found to be useful in preventing reperfusion arrhythmias and in post myocardial infarction patients. The major disadvantages of haemasomes are they are easily phagocytosed by macrophages and cause compliment activation. Liposomal ATP is investigated for their role in wound healing and preserves mechanical properties of the heart under ischemic conditions in an isolated rat heart model **[**8**].**

Table 1. Liposomal preparations

Liposomal drug	Indication	
Liposomal preparation of Amphotericin B	Fungal infections	Marketed
Pegylated Liposomal Doxorubicin	HIV-related Kaposi's Sarcoma Metastatic Ovarian and Breast cancer	Marketed
Liposomal Estradiol	Menopausal therapy	Marketed
Liposomal Cytarabine	Malignant Lymphmatous meningitis	Marketed
Liposomal Morphine	Post surgical neuralgesia	Marketed
Liposomal Verteporfin	Age Related Macular Degeneration	Marketed
Lipo-ATR (All Trans retinoic acid)	Acute Pro Myelocytic Leukemia(APML), Renal cell cancer	Marketed
Liposomal Vincristine	Acute Lymphocytic Leukemia, Melanoma	Marketed
Liposomal Cisplatin	Pancreatic cancer	Marketed

Carbon nanotubes

Figure 2: Structure of Carbon nanotubes



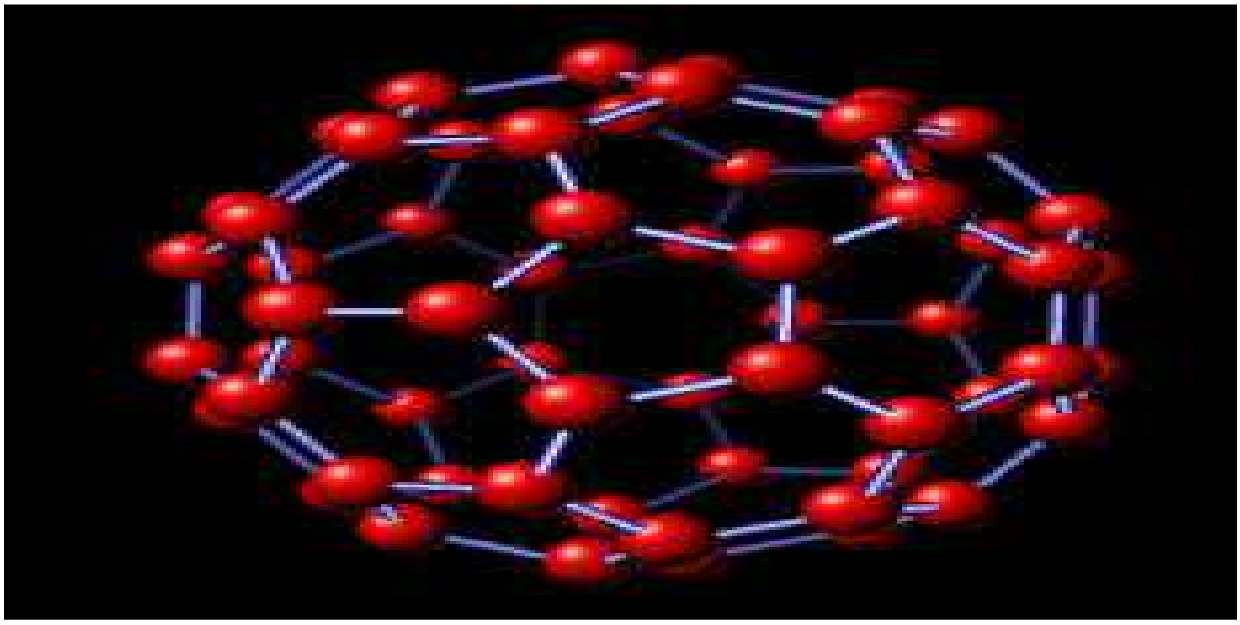
Carbon nanotubes (CNTs) are cylinders of one or more layers of graphene. There are various types of nanotubes like Single Walled Nano Tube (SWNT) characterized by the presence of a single graphene sheet of size 0.8 to 2 nm and Multi Walled Nano Tube (MWNT) formed from several concentric graphene sheets of size of 5 to 20 nm. Carbon nanotubes can be made water soluble by surface functionalization. These nanotubes can be made more soluble by incorporation of carboxylic or ammonium groups to their structure and can be used for the transport of peptides, nucleic acids and other drug molecules.The carbon nanotubes are loaded with drugs and their surface coated with tumor targeting ligands. Anticancer drug Cisplatin is loaded into MWCNTs and functionalized with folic acid. With external magnet, CNTs are targeted to lymph nodes and the drug is released and thus inhibiting the tumor growth. Other anticancer drugs like Gemcitabine, Epirubicin and Camphothecin are also incorporated into nanotubes for effective tumor targeting.

These nanotubes bind to specific receptors on surface of tumor and thus can be used for effective target specific drug delivery. CNTs itself has anti microbial effect which adsorbs the micro organism into its surface. Nanotube induced oxidation of intercellular antioxidant glutathione, resulting in increased oxidative stress on bacterial cell and thus bacterial cell lysis [9].

Amphoterecin B nanotubes are under development to treat serious fungal infections and visceral leishmaniasis [10]**.** CNTs enclosed Amphotercin B had less toxicity when compared to the free drug. Vaccine delivery can be achieved by linking an antigen to CNT without losing its confirmation and by inducing antibody response with right specificity. It is found that CNTs protein complex enhances the immune response when attached to the antigen which strengths the possibility of incorporating CNTs in vaccine [9].

Fullerences

Figure 3: Structure of Fullerence



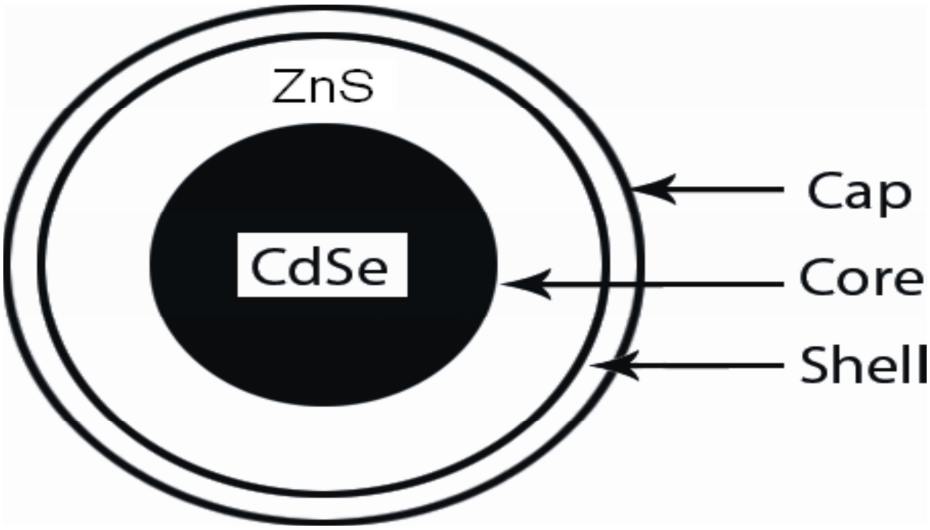
It was discovered by Harry Kart, Richard Smalle, Robert Curl. They are also called as buckyballs. "Buckyball" is the common name for a molecule called Buckminsterfullerene, which is made of 60 carbon atoms formed in the shape of a hollow ball. The arrangement of the atoms resembled the shape of the geodesic domes invented by architect Buckminster Fuller, hence the name. It resembles a soccer ball with 20 hexagons and 12 pentagons and is highly symmetrical.These are spherical molecules of size 0.7nm [11]. They are found to have aantiviral activity against HIV and Hepatitis C virus. Fullerenes deactivate both the HIV-1 and HIV-2 types of virus and don't seem to harm normal cells or organs, which is a major problem with some other HIV inhibitors.They also cause membrane disruption of bacteria and so possess antibacterial action against E. coli, Streptococcus, Mycobacterium tuberculosis. A new variant of Vancomycin that contains fullerene tiny cage-shaped molecules of pure carbon could become the worlds first targeted antibiotic, creating a new line of defence against disease like anthrax [12]. Fullerences also act as scavenger of free radicals along with anti-inflammatory actions. Fullerences have antioxidants action and anti-apoptosis properties which might be useful in the treatment for Amyotrophic lateral sclerosis and Parkinson's disease. Fullerenes can also generate reactive oxygen species during photosensitization. This property can be used in cancer therapy [13]. These are able to interrupt the allergic reaction by inhibiting a basic process in the cell that leads to release of an allergic mediator. Essentially, the fullerenes are able to prevent mast cells from releasing histamine [14]. These findings open a new emerging field of medicine, which is known as nanoimmunology. Degree of purification of fullerene determines its cost and highly purified fullerenes are expensive, restricting its application in medical field.

Quantum dots

Are nanocrystals measuring about 2-10 nm, which can be made fluorescence when stimulated by light. Quantum dots can be made to emit light at any wavelength in the visible and infrared ranges, and can be inserted almost anywhere, including liquid solution. Quantum dots absorb white light and then reemit it a couple of nanoseconds later at a specific wavelength. By varying the size and composition of quantum dots, the emission wavelength can be tuned from blue to near infrared. For example, 2nm quantum dots luminance bright green, while 5nm quantum dots luminance red [15]. Quantum dots can be attached to a variety of surface ligands and inserted into a variety of organisms for in-vivo research.The structure consists of a core which is made up of semiconductor material mainly CdSe (Cadmium Selenide) that emits light, surrounding it is a shell made up of insulator material ZnS (Zinc Sulphide). Outside to shell is a biocompatible layer of Polyethylene glycol and lastly a synthetic coating layer. Quantum dots can be coated with antibodies which are targeted to Prostate Specific Antigen and thus can be used for imaging of sentinel nodes in prostate cancer patients for tumour staging and planning of therapy. The same technique can be applied to detect sentinel nodes in melanoma, breast, lung and gastrointestinal tumours. By combining a quantum dot with a gadolinium, a nanoparticle that can spot apoptosis, cell death can be detected. Imaging programmed cell death in the body by MRI, could provide an early indication that an antitumor therapy is indeed killing cancer cells. MRI experiments showed that the nanoparticles produced an imaging signal that was approximately 40 times stronger than that produced by the gadolinium carrier alone. In active targeting by quantum

dots in order to treat cancerous cells, they can be conjugated with tumour specific active binding sites so as to attach themselves to tumour cells. In passive targeting, the quantum dot probes do not have the tumour specific active binding sites. The enhanced permeability and retention factor of the tumour enables the absorption of nanocrystalline quantum dots and thus killing cancer cells [16]. Rapid and sensitive diagnosis of Respiratory Syncytial Virus (RSV) can be done by using quantum dots. RSV virus infects lung cells it leaves part of its coat containing F and G proteins on the cell's surface. Quantum dots have been linked to antibodies keyed to structures unique to the RSV coat. As a result, when Quantum dots come in contact with either viral particles or infected cells they stick to their surface and they illuminate bright fluorescence and thus antibody- conjugated Quantum dots rapidly and sensitively detects RSV. Cryptosporidium parvum, Giardia lamblia, Escherichia coli and Salmonella Typhi can also be detected by quantum dots. Due to their extremely small size and optical resolution, they are also well suited for tracking the molecular dynamics of intracellular and intercellular molecular processes like small size of the synaptic cleft or between an astrocyte process and a neuron. Quantum dots can be considered as an alternative for organic dyes in the imaging of biological systems, due to their excellent fluorescent properties, good chemical stability, broad excitation ranges and high photo bleaching thresholds. Quantum dots are being investigated as chemical sensors for cancer cell detection, gene expression studies, gene mapping and DNA microarray analysis, immunocytochemicalprobes, intracellular organelle markers, live cell labelling, medical diagnostics and drug screening, Single Nucleotide Polymorphism genotyping and vascular imaging. The main shortcoming of quantum dots is their toxicity and therefore their application is problematic. Quantum dot complexes, including their capping materials may be immunogenic, which could result in immune reactions in subjects. The heavy metals contained in the core and the materials used for capping may be toxic to the host. Scientists have been using gelatin during the production of CdSe quantum dots thereby reducing the toxicity of the particles. The size of quantum dot complexes precludes renal excretion, making clearance from the bloodstream unlikely [17].

Figure 4: Structure of quantum dot



Nanoshells

Nanoshells consist of nanoparticles with a core of silica and a coating of thin metallic shell. Gold nanoshells are spherical particles with diameters typically ranging in size from 10 to 200nm. They are composed of a dielectric core covered by a thin gold shell. The nanoshells are embedded in a drug containing tumour targeted hydrogel polymer and injected into the body. These shells circulate through in the body until they accumulate near tumour cells. When heated with an infrared laser, the nanoshells selectively absorb the IR frequencies, melt the polymer and release their drug payload at a specific site. The surface of gold nanoparticles is now routinely functionalized with PEG (PEGylation) to stealth the nanoparticles from immune surveillance and this has led to a dramatic increase in its circulation time [18]. Nanoshells offer advantages over traditional cancer treatments like earlier detection, more detailed imaging, fast non invasive imaging and integrated detection and treatment. Nanoshells facilitate the detection of cancer in its earliest stages, before any significant pathogenesis, tumour formation and metastasis. Conjugating nanoshells to antibodies that target epithelial cell surface receptors (e.g., EGFR and HER2) which are commonly over expressed in cancer cells. The resultant high concentrations of nanoshells found on the surface of targeted cancer cells, greatly facilitates imaging on the cellular level. Nanoshells 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 fromnanoshells 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 [19].

Table 2: Nanoshell preparation

Nanoshell	Indications	
AuroLase™-Gold nanoshell	Head and neck cancer	Phase 1

Figure 5: Structure of gold nanoshell

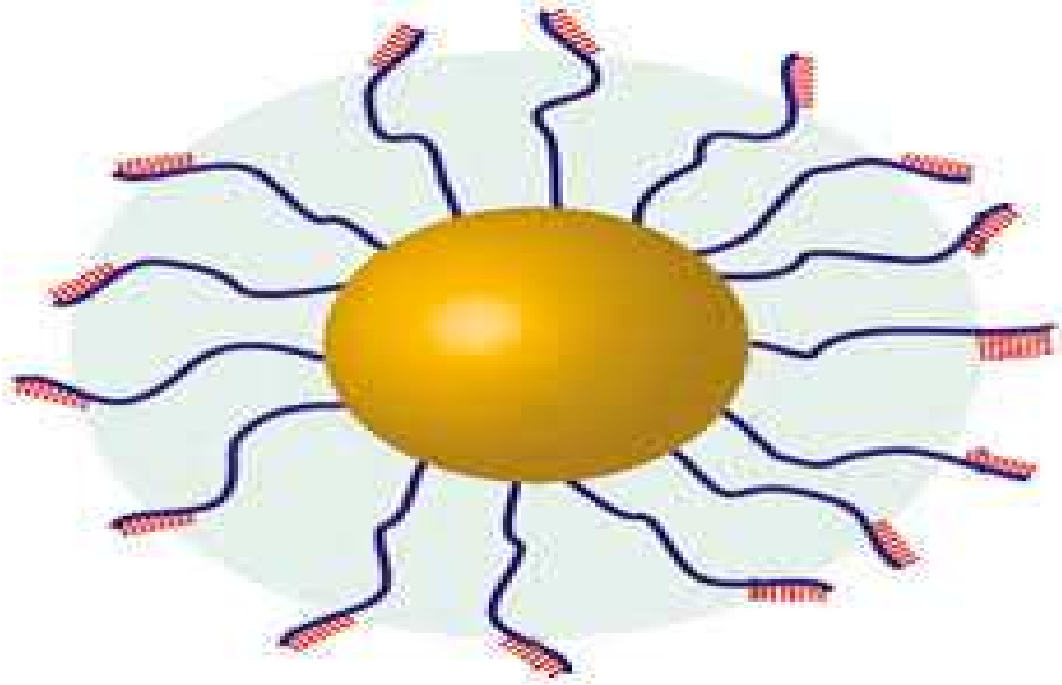
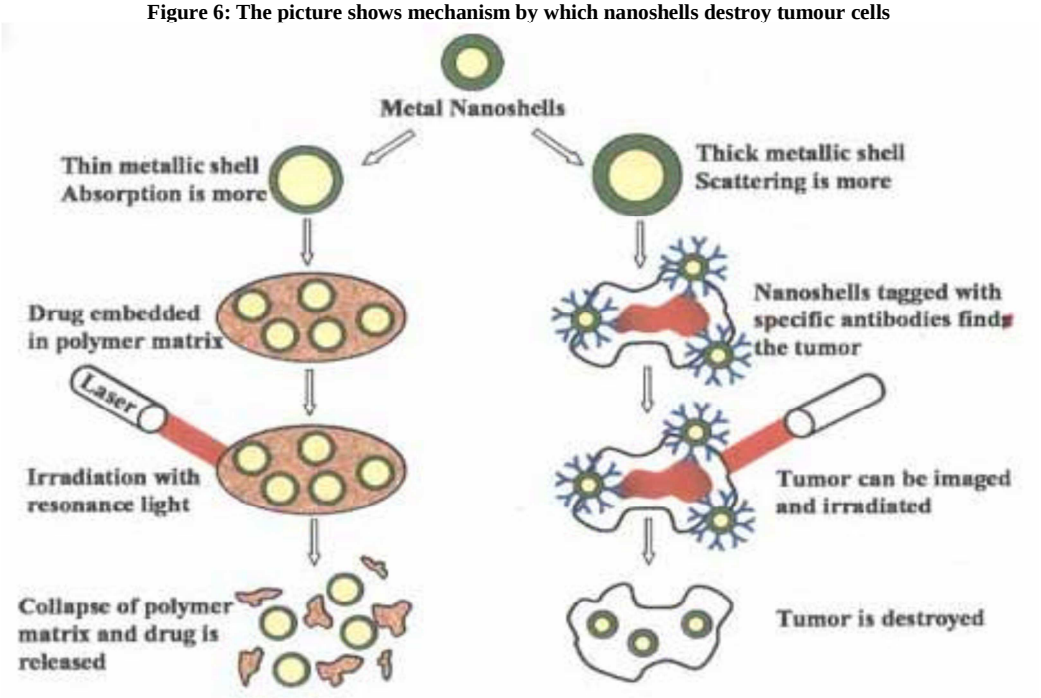


Figure 6: The picture shows mechanism by which nanoshells destroy tumour cells



Nanobubbles

Nanobubbles remain stable at room temperature and when heated to physiological temperature within the body, they coalesce to form microbubbles. These have the advantages of targeting the tumour tissue and delivering the drug selectively under the influence of ultrasound exposure. This results in increased intracellular uptake of the drug by the tumor cells. It also provides an additional advantage of enabling visualisation of the tumour. Nanobubble loaded doxorubicin, when injected, reach the tumour tissue through leaky vasculature and get accumulated at the site of tumour. This is followed by formation of microbubbles by coalescing of nanobubbles which can be visualised by

ultrasound techniques. When the site is focused with high intensity focused ultrasound (HIFU), it causes disruption of the microbubbles resulting in release of the drug. The microbubbles retained the drug in a stable state until stimulated by HIFU. This results in attainment of higher levels of drug in the target cells and hence reduced toxicity and increased efficacy [21]. Nanobubbles are also being tried as a therapeutic measure for removal of clot in vascular system in combination with ultrasound, a process called as sonothrombolysis. This method has advantages of being non invasive and causing less damage to endothelium [22].

Polymeric nanoparticles

Polymeric nanoparticles are either nanosized solid particles or capsules which consist of natural or synthetic polymers, to which the drug is attached. Their size is between 10-100nm. The most commonly used polymer is polyethylene glycol because it is inexpensive and is less toxic. Though it is not biodegradable, it is easily removed from body by excretion pathways. Other polymers used in research are poly (propylene oxide), poly (caprolactone), and poly (L-lactic acid) [23].

Figure 7: Structure of polymeric nanoparticle

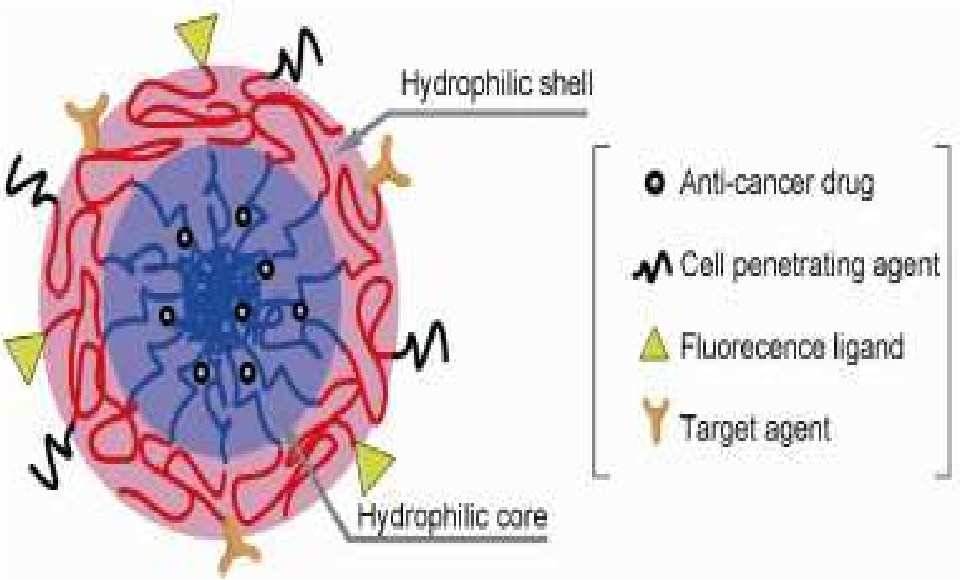


Table 3: Polymeric nanoparticle preparations

Polymeric nanoparticle	Indications	
L-Leucine, L-glutamate Copolymer and Insulin	Type 1 diabetes	Phase 2
PEG-anti TNF-antibody fragment	Rheumatoid arthritis and Crohn's disease	Phase 3
Polymer Protein Conjugate-Neulasta	Febrile neutropenia	Marketed
Polyglutamate Paclitaxel	Non-small-cell lung cancer, Ovarian cancer	Phase 3
PEG -Uricase	Hyperuricemia from gout	Marketed
Polymer Protein Conjugate-Pegasys	Hepatitis C	Marketed
Polymeric Drug-Copaxone	Multiple Sclerosis	Marketed
Pegaptanib Sodium	Neovascular agerelated Macular degeneration	Marketed

Micelle

Micelles are formed when amphiphilic surfactant or polymeric molecules spontaneously associate in aqueous medium to form core-shell structures or vesicles. Polymeric micelles are formed from amphiphilic block copolymers, such as poly(ethylene oxide), poly(benzyl-Laspartate) and poly(N-isopropylacrylamide), polystyrene. Their diameter is around 5-199nm. Micelles are formed in solution as aggregates in which the component molecules are generally arranged in a spheroidal structure with hydrophobic cores shielded from the water by a mantle of hydrophilic groups. The inner core of a micelle is hydrophobic which is surrounded by a shell of hydrophilic polymers such as poly (ethylene glycol). Their hydrophobic core enables incorporation of poorly water soluble and amphiphilic drugs while their hydrophilic shell prolong their circulation time in the blood and increase accumulation in tumour tissues [24]. Drugs or contrast agents may be trapped physically within the hydrophobic cores or can be linked covalently to component molecules of the micelle. Polymeric micelles can be employed to administer chemotherapeutics in a controlled and targeted manner with high concentration in the cancer cells and reduced side effects [25].

Figure 8: Structure of a micelle

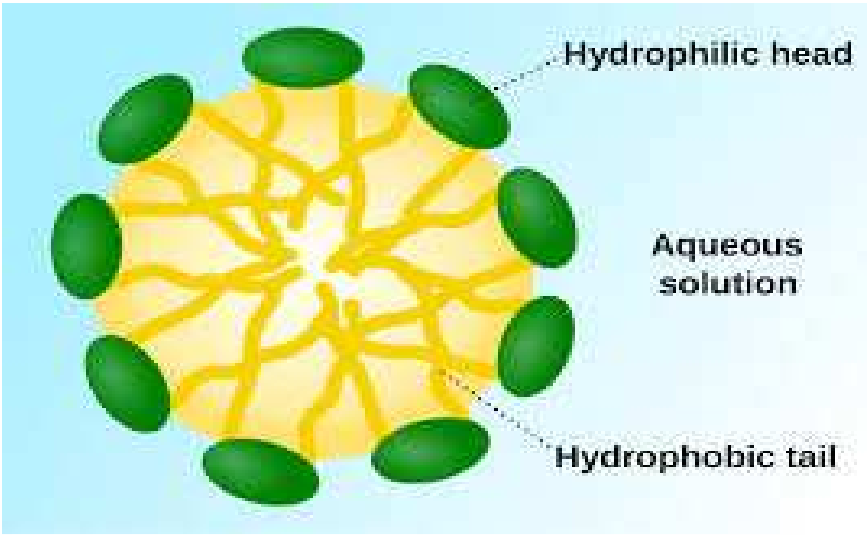


Table 4: Micelle preparations

Micelle	Indications	
Estradiol hemihydrate Micellar nanoparticles	Reduction of vasomotor Symptoms	Marketed
Paclitaxel	Ovarian, lung, breast cancer	Marketed

Nanocrystal

These are crystalline nanoparticle of size <1µm.The small size of these nanoparticles offer the advantage of increased surface area and increase in the solubility of drugs [26].

Table 5: Nanocrystal preparations

Nanocrystal	Indications	
Nanocrystal Sirolimus	Transplant rejection	Marketed
Nanocrystal Fenofibrate	Primary Hypercholesterolemia, hypertriglyceridemia	Marketed
Nanocrystal Palperidone	Psychosis	Marketed
Nanocrystal Aprepitant	Vomiting in chemotherapy patients	Marketed

Dendrimers

Dendrimers are nanoparticles with regular branching structures. They are called Polymers of 21st century. The word dendrimer is derived from Greek word, *dendron* meaning tree and *meros* meaning part. The chemistry of dendrimers was introduced in 1978 by Fritz Vogtle and co-workers. Dendrimers have a tree-like structure with many branches where a variety of molecules, includingdrugs can be attached. Cavities in the core structure and folding of the branches create cages and channels. The surface groups of dendrimers are amenable to modification and can be tailored for specific applications. Therapeutic and diagnostic agents are usually attached to surface groups on dendrimers by chemical modification. With size less than 5 nm in diameter, dendrimers are small enough to slip through tiny openings in cell membranes and to pass vascular pores and tissues in a more efficient way than bigger polymer particles.The structure of dendrimer has 3 parts a core, interior layers which is composed of repeating units and an exterior that is attached to the outer most interior generations. 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. Dendrimers are also used as Magnetic resonance imaging (MRI) contrast agent. The advantages of using gadolinium chelates based on polylysine dendrimers are optimal circulation time within the body, reduced risk of accumulations of gadolinium compounds and good quality of imaging [27]. There are various types of dendrimer like PAMAM (Polyamidoamine) dendrimer, hybrid dendrimer, peptide dendrimer, chiral dendrimer, amphiphilic dendrimer, tecto dendrimer, multilingual dendrimer, micellar dendrimer. PAMAM dendrimers, the best known molecules belonging to this group of compound. Tecto-dendrimers have a single core dendrimer surrounded by additional dendrimer modules of different types, each type designed to perform a function necessary to a smart therapeutic nanodevice. Dendrimers have nanoscopic particle size range from 1-100 nm, which makes them less susceptible for reticulum endothelium uptake. Multiple functional groups are present on outer surface of dendrimers, which can be used to attach vector devices for targeting to particular site in the body. Dendrimers can be modified as stimuli responsive to release drug [28].

Figure 9: Structure of Dendrimer

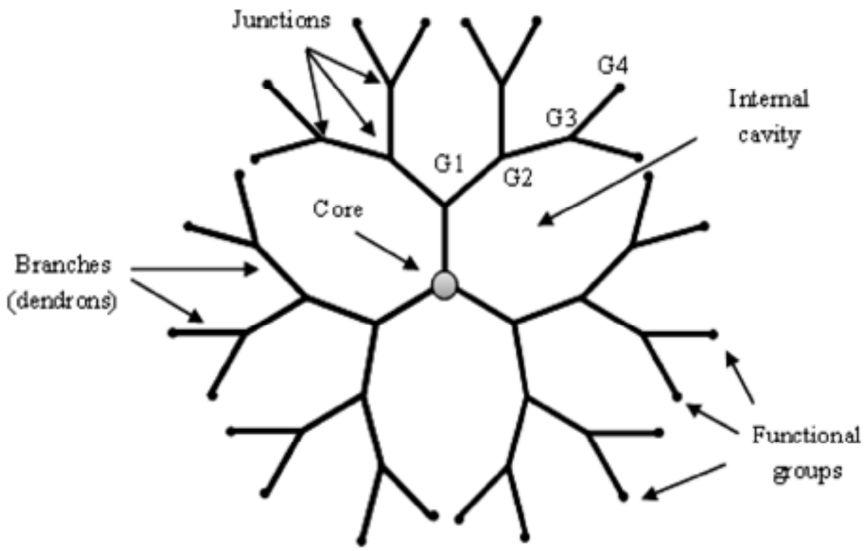


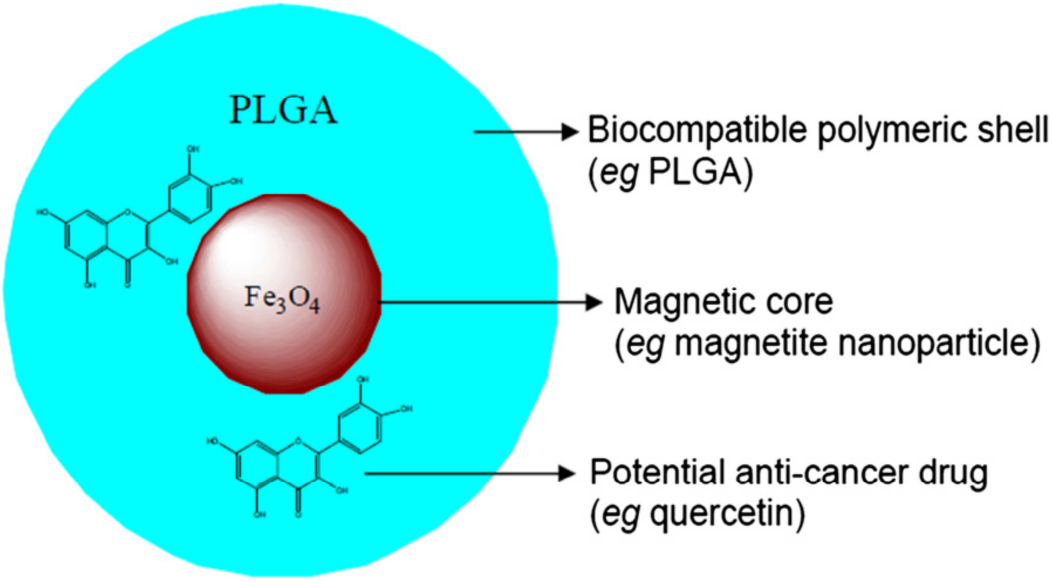
Table 6: Dendrimer preparations

Dendrimer	Indications	
Viva Gel	Microbicide	Phase 3
Folic acid PAMAM dendrimers –Methotrexate	Epithelial cancer	Preclinical
Efaverenz	HIV infection	Preclinical

Magnetic nanoparticles

Magnetic nanoparticles (MNPs) exhibit a wide variety of attributes, which make them highly promising carriers for drug delivery. Due to their unique physicochemical properties and ability to function at the cellular and molecular level of biological systems, MNPs are being actively investigated as the next generation of targeted drug delivery vehicle. In particular, these are easy handling with the aid of an external magnetic field, the possibility of using passive and active drug delivery strategies, the ability of visualization as they are used in MRI and enhanced uptake by the target tissue resulting in effective treatment at the therapeutically optimal doses [29]. Magnetic nanoparticles are divided into pure metals such as cobalt, nickel, manganese and iron, their alloys and oxides. Iron oxide nanoparticles, are the only type of MNPs approved for clinical use by FDA. Binding of drug with MNP may be achieved by covalent binding, electrostatic interactions, adsorption or encapsulation process. Targeting a drug with MNPs, is carried out by passive or active mechanism. Passive targeting is a result of enhanced vascular permeability and retention of tumour tissues. Active strategy relies on the attraction of magnetic nanoparticle to the affected site by using recognition ligands (e.g. antibodies) attached to the surface of MNPs and by handling of an external magnetic field. Drugs which are conjugated with magnetic nanoparticles are Doxorubicin, Daunorubicin, Dopamine, 5 Flurouracil, Cisplatin, Paclitaxel. Magnetic hyperthermia involves the delivery of magnetic nanoparticles to target sites. Once the particles have been taken up by a tumour, an alternating field is applied that couples to the particles, resulting in efficient heating. If the tumour cell is heated to 40–42^{0}C for 30 min., apoptosis may be induced thus effectively killing the tumour. In order to retain the magnetic nanoparticle-drug complex at a particular location, the externally applied field must have a relatively strong gradient. Additionally, once the drug is released from the magnetic complex, it no longer responds to the applied magnetic field. It is then free to resume its normal distribution patterns in the body. Therefore, if the drug or gene is released while the carrier particles are still within the vasculature, even if they are held at the target site, there will still be some degree of systemic distribution. Another problem with these systems is the potential for embolization as the particles accumulate within the bloodstream, blocking blood flow. The particles also can become concentrated in the liver where cytotoxicity may be an unwelcome side effect. However, both of these problems potentially may be turned to good advantage as it may be possible to enhance targeting of tumours in the liver and block the blood supply to the tumour mass [30].

Figure 10: Structure of a magnetic nanoparticle



Ethics and nanomedicine

Debates also exist over whether nanomedicine has any unique ethical issues or the ethical issues of past technologies apply to nanoscience. Several nanoethicists have lately identified the need for 'better' ethics of emerging technologies and believed that researchers should consider ethical reflection as part and parcel of the research and development processes and should be transferred to nanomedicine. Therefore, it is essential to proactively address the ethical, social and regulatory aspects of nanomedicine in order to diminish its side effects on the environment and public health and also to avoid a public reaction. Ethical issues involving nanomedicine is helpful to decision makers, particularly employers, workers, investors, and health authorities. The ethical considerations involved in nanomedicine are related to risk assessment in general, somatic-cell versus germline-cell therapy, the enhancement of human capabilities, risk management of engineered nanomaterials, research into human embryonic stem cells [31]. For instance, recently, the identification of cytotoxicity of nanoparticles toward mammalian gremline stems cells has aroused great concern over the bio safety of nanomaterials. Ethical issues is a major concern in nanomedicine. If a computer chip is implanted in humans and this chip can diagnose diseases from which the person is suffering currently, it can also analyze our DNA to determine the diseases to which one may be susceptible to in future. Ethical issues concerning a patient's right-toknow, right-not-to-know and the duty-to-know arises. The safety of nanomedicine has to be thoroughly examined due to their unpredictable nature, before coming to the trials in human [32].

Advantages of Nanoparticles

Due to their small size nanoparticles penetrate small capillaries and are taken up by the cell which allows for efficient drug accumulation at the target sites in the body. The surface of the nanoparticles are modified with ligands like antibodies for drug targeting and delivery.

They can be coated to avoid opsonisation and also protection of the encapsulated drug before they reach the target site. Nanoparticles have longer clearance time and increased bioavailability with good therapeutic efficacy. Due to their small size they have increased surface area results in a faster dissolution of active agents in an aqueous environment [33].

Disadvantages with Nanomedicine

Nanotoxicology is the study of the toxicity of nanomaterials. Nanomaterials can enter human tissues through several ports via the lungs after inhalation, through the digestive system and possibly through the skin. Systemic distribution of nanoparticles has been demonstrated after inhalation and oral uptake and nanoparticles have been found to cross the blood brain barrier, reaching the olfactory bulb and the cerebellum. Many of the artificially manufactured nanoparticlesare made of non-biodegradable pollutants, such as carbon black and metals and the long-term behaviour of such substances is not known. Carbon nanotubes are found to cause asbestos like effects on the mesothelium following intracavitary injection of high doses in rodents. They also release reactive oxygen species which can cause necrosis or apoptosis of macrophage cell lines and changes in cell morphology. Carbon nanotubes also causes aggregation of platelets. Cadmium is a recognized toxicant that has been classified as a probable human carcinogen. It is a heavy metal that has the potential to cause lysosomal damage and DNA breakage in mammalian

hepatocytes and many other cells and tissues. Cadmium also disrupts mitochondrial function both in vivo and in vitro. In humans, male infertility is strongly linked to cadmium exposure vitro. Cadmium is a considered a human carcinogen [34]. It is proved to cause lysosomal damage and DNA breakage in mammalian hepatocytes. Cadmium also disrupts mitochondrial function and promotes apoptosis. In the testis, cadmium induces lysosomal damage in testicular Sertoli cells, but its main toxic effects appears in germ cells but not in somatic cells. Exposure of human keratinocytes to insoluble single-wall carbon nanotubes is associated with oxidative stress and apoptosis. Extensive use of polyvinyl alcohol as a detergent with nanoparticles can cause toxicity. These particles are found to cause pulmonary, alveolar inflammation and pulmonary carcinogenicity. They cause disturbance in the autonomic system and have a direct effect on heart and vascular function. Silver nanoparticles cause intensive toxic effects on the proliferation and cytokine expression by peripheral blood mononuclear cells. They are proved to cause severe toxic effects on the male reproductive system as they cross blood-testes barrier and are deposited in the testes and that there is potential for adverse effects on sperm cells. Magnetic nanoparticles can naturally be broken down resulting in the release of ferric iron which can then participate in the normal iron metabolism. It has, however, been recognized that the small size of MNPs might pose an additional hazard as the particles can reach high local concentrations within the cells and are generally more difficult to be efficiently cleared from the body. Furthermore, free iron has been associated with the formation of free radicals, which would be particularly harmful to neural tissues already weakened by pathological processes [35]. Presently, nanotechnology is very expensive and developing it can cost a lot of money. It is also pretty difficult to manufacture, which is probably why products made with nanotechnology are more expensive. Patients from the low income groups would be deprived of these novel therapeutics and the developing nations would be affected most. The products would be manufactured in developing nations because of the cheap labour, it would be difficult to afford medication for them. This will create not only socio-economic barrier but could also promote radical feelings in the individuals.

Obstacles of Nanoparticles

There are various hindrance for nanoparticles within the human body. These particles must be small enough to avoid ingestion by macrophages in the reticuloendothelial system and should possess property to avoid recognition as foreign particle within the body. Nanoparticles have to selectively enter tumor cells and cause cell lysis without damaging normal cells [35].

CONCLUSION

With the conventional methods of treatment, it is not possible to repair the defect at a molecular level. Nanoparticles represents promising drug carrier for various drug delivery systems. Nanotechnology is breakthrough technology pervading all fields, newer applications of this field are being explored worldwide. Nanoparticles represents a technology to overcome solubilities and bioavailability problems of drugs which can be generally applied to all poorly soluble drugs. Nanomedicine will have an impact on many medical applications. The usefulness is not only therapeutic but also diagnostic. At its best it is hoped that nanomedical machines will cover up the deficiencies by replacing or improving the DNA molecules of body. A real therapeutic breakthrough can be achieved solely by carrying out painstaking studies in the field of nano-therapy. Nanomedicine will be coming up with some ground breaking advances in medical sciences but the current knowledge on the safety profile is very limited. As there are no specific regulatory guidelines for the approval of the nanomedicinal product, it is suggested that individual applications should undergo risk based. What nanomedicine will be able to achieve in the future is beyond current imagination. However, it will be a tough task to handle the ethical issues which will be arising with the same pace.

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