AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Nanotechnology Drug Delivery System - An Unconventional Approach In Conventional Form

Nitesh Kumar[*1], Digvijay Patil[1], Adil Rasid Bhat[1]

1. Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Rewa – 486 001 (M. P.), India.

ABSTRACT

Nanotechnology received a lot of attention with the never-seen-before enthusiasm because of its future potential that can literally revolutionize each field in which it is being exploited. In drug delivery, nanotechnology is just beginning to make an impact. The multidisciplinary approach of nanotechnology has opened new vistas for the development of nanoscale drug delivery systems to meet the requirements for new drug moieties. These drug moieties can either be integrated into the matrix or attached to the surface of drug delivery particles. The importance of nanotechnology in drug delivery is in the concept and ability to manipulate molecules and supramolecular structures for producing devices with programmed functions. Nanostructures like micelles, liposomes, dendrimers etc. and nanoparticles like solid lipid nanoparticles, polymeric/pegylated nanostructures, metallic nanoparticles etc. have been used to deliver drug at specific sites and reduce side effects on non target organs.

Keywords: Nanotechnology, Drug delivery system, Nanostructures, Nanoparticles, Nanosystems

*Corresponding Author Email: niteshprof@gmail.com

Received 9 August 2012, Accepted 17 August 2012

Please cite this article in press as: Niteshkumar *et al.*, Nanotechnology Drug Delivery System-An Unconventional Approach In Conventional Form. American Journal of PharmTech Research 2012.

INTRODUCTION

Nanotechnology is enabling technology that deals with nano-meter sized objects[1]. The nanomaterials level is the most advanced at present, both in scientific knowledge and in commercial applications. A decade ago, nanoparticles were studied because of their size-dependent physical and chemical properties[2]. Now they have entered a commercial exploration period[3].

Living organisms are built of cells that are typically 10 μm across. However, the cell parts are much smaller and are in the sub-micron size domain. Even smaller are the proteins with a typical size of just 5 nm, which is comparable with the dimensions of smallest man, made nanoparticles. This simple size comparison gives an idea of using nanoparticles as very small probes that would allow us to spy at the cellular machinery without introducing too much interference[4]. Understanding of biological processes on the nanoscale level is a strong driving force behind development of nanotechnology[5].

History:

The **"Magic Bullet"** concept, first theorized by Paul Ehrlich in 1891, represents the first early description of the drug-targeting paradigm [6]. The aim of drug targeting is to deliver drugs to the right place, at the right concentration, for the right period of time.

The roots of nanotechnology go back to the 1959 talk presented by Nobel Prize winning physicist, Richard Feynman at a meeting of the American Physical Society titled, "There's plenty of room at the bottom''. Simply put, Feynman's message was that in the future scientists and engineers would be able to build structures from atoms and molecules, from the bottom up [7].

Eric Drexler is credited as being the first person to use the word nanotechnology to describe engineering on the billionth of a meter scale. Peter Paul Speiser and his research group in the late 1960s developed the first nanoparticles for drug delivery purposes and for vaccines[8]. A later and important development was the discoveries of Fullerenes, better known as "Buckyballs'' by a group including Nobel Prize winning Richard Smalley. This led to the discovery of tube-like structures of carbon atoms which is basically a rolled up sheet of carbon that has outstanding properties[7].

The first commercial nanoparticle product containing a drug (Abraxane™, human serum albumin nanoparticles containing paclitaxel) appeared on the market at the beginning of 2005. A second product based on poly (isohexyl cyanoacrylate) nanoparticles (Doxorubicin-Transdrug®) loaded with doxorubicin is presently being developed by the company Bio Alliance in Paris for

the treatment of resistant hepatocellular carcinomas and a Phase I/II clinical trial has been conducted[8].

Scale of Nanotechnology:

A simple definition of nanotechnology is the art of manipulating matter, atom by atom. The most widely use definition of nanotechnology is provided by the United States Government's National Nanotechnology Initiative. According to them nanotechnology is defined as: "Research and technology development at the atomic, molecular and macromolecular levels at the scale of approximately 1 - 100 nm range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small size" [9].

The term nano is derived from the Greek word “dwarf” and is usually combined with a noun to form words such as nanometer, nanobot and nanotechnology. A nanometer is defined as one-billionth of a meter. For comparison, the wavelength of visible light is between 400 and 700 nm [7]. To get a perspective of the scale used in nanotechnology, representative structures and materials found in nature are typically referenced to have the following dimensions:

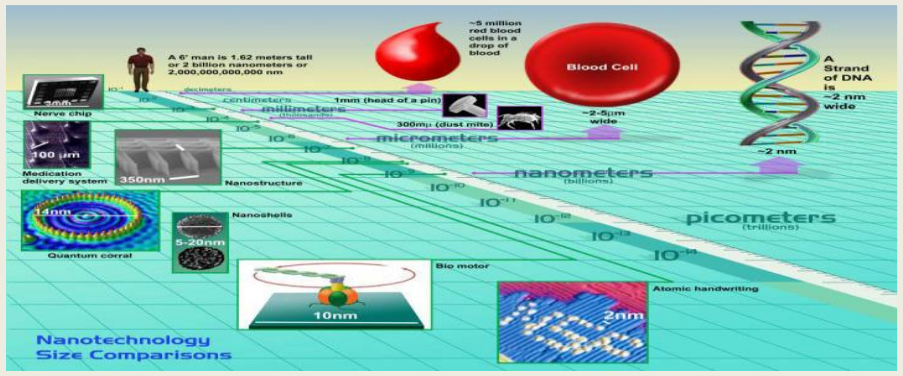

Figure 1: Schematic Representation of Scale of Nanotechnology

It is expected that nanotechnology will be developed at several levels: materials, devices and tools [9].

Nanotechnology tools include microscopy techniques and equipment that permit the visualization and manipulation of items at the nanoscale level such as cells, bacteria, viruses and single molecules. The range of tools includes the atomic force microscope, scanning tunneling microscope, molecular modeling software and other technologies.

Nanotechnology materials can be grouped into three main areas: raw materials, nanostructured materials and the group composed by nanotubes and fullerenes. The raw material includes nanoparticles and nanocrystalline materials that are readily manufactured and substitute for less

performing bulk materials. Nanostructured materials are typically processed forms of raw material that provide special shapes and functionality. Examples of nanostructured materials include the quantum dots and the dendrimers. Nanotubes and fullerenes can produce materials that are 100 times stronger than steel, more conductive than copper and can be safely used in some medical applications.

Two classes of devices are commonly associated with nanotechnology. These are the micro devices and nano devices. Examples of micro devices are micro-electromechanical systems better know as MEMS, microfluidics and microarrays. Even thought they are not considered part of nanotechnology, these microtechnologies have diverse medical applications. Nano devices are those device technologies that are dimensioned at the nanoscale level. Nano devices are difficult to produce at this moment, but they are expected to have a brilliant future in the medical and veterinary fields.

Drug targeting:

The aim of drug targeting is to deliver drugs to the right place, at the right concentration, for the right period of time. An important and long-term goal of the pharmaceutical industry is to develop therapeutic agents that can be selectively delivered to specific areas in the body to maximize the therapeutic index. Drugs, given systemically, provide a profound beneficial effect but can also exhibit adverse reactions. Historically, cancer chemotherapy agents have been well-known examples of achieving balance between efficacy and toxicity. Cytotoxic compounds can be highly effective in destroying cancer cells but may also damage normal cells resulting in possible adverse and potentially life-threatening effects[6].

Many promising new compounds are compromised by poor physiochemical properties that lead to poor solubility and biodistribution and therefore the drug does not interact with the site of action[10]. Poor oral absorption (i.e., proteins and peptides), low solubility at physiological pH[11], insufficient cellular uptake[12] and rapid drug elimination[13] are impediments for drug development. New drug candidates must provide evidence that they reach the site of action and have an effect. The field of drug delivery designs carriers, excipients, and solubilizers to transport drugs to the site of action.

An answer to poor drug physiochemical properties is to associate the drug with a pharmaceutical carrier {i.e., a drug delivery system (DDS)}[14]. A DDS can enhance a drug pharmacokinetics and cellular penetration. Moreover, obstacles arising from low drug solubility, degradation, fast clearance rates, nonspecific toxicity and inability to cross biological barriers may also be addressed by a DDS. To be useful, a DDS is required to be biocompatible with processes in the

body as well as with the drug to be delivered. Overall, the challenge of increasing a drug's therapeutic effect, with a concurrent minimization of side effects, can be optimized through proper design and DDS engineering[15].

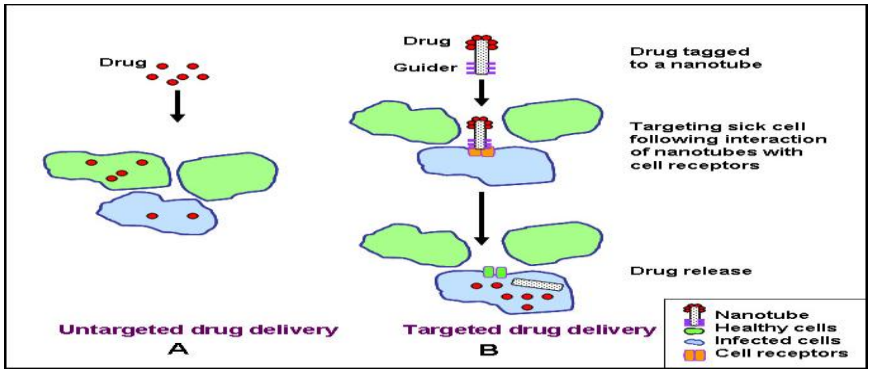

Figure 2: Schematic Representation of Untargeted and Targeted Drug Delivery Hurdles or Barriers to drug targeting:

Targeting of drugs offers enormous advantages but is equally challenging. A better understanding of the physiological barriers which a drug needs to overcome should enable the pharmaceutical scientists to develop successful design of targeted drug delivery systems. Main hurdles to drug targeting include physiological barriers, biochemical challenges to identify and validate the molecular targets and the pharmaceutical challenges to devise appropriate techniques of conjugating targeting ligands to the nanosystems[16].

The challenge in drug targeting is not only the targeting of drug to a specific site but also retaining it for the desired duration to elicit pharmacological action. For a nanosystem administered intravenously, the first and foremost barrier is that of the vascular endothelium and the basement membrane. Also, plasma proteins have the ability to affect the biodistribution of drug carrier systems introduced in the blood stream. The *in vivo* biodistribution and opsonization of nanosystems in blood circulation is governed by their size and surface characteristics. For the nanosystems to remain in blood circulation for a long time, the major problem is to avoid its opsonization and subsequent uptake by the phagocytic cells. Another barrier is that of the extracellular matrix, which should be crossed to access the target cells in a tissue. If the whole tissue constitutes a target then the uniform distribution of drug throughout the tissue is another problem. For drugs whose targets are located in the cytoplasm/nucleus of a cell, further barrier needs to be crossed to allow internalization of nanosystems into specific cells[17]. Drugs/nanosystems need to diffuse through the viscous cytosol to access the particular cytoplasmic targets where site of action is located. Nuclear membrane poses another formidable

barrier for drugs such as oligonucleotides, plasmid DNA and other low molecular weight drugs whose site of action is located in the nucleus of a cell.

Thus, to harness the potential of new targets in imaging and therapy, one would need to develop targeted systems which can successfully overcome the physiological barriers and for drug therapy, deliver the pharmacological agent to its site of action at therapeutically relevant drug levels for a time sufficient to allow therapeutic action. Conjugation of targeting ligands to drugs or drug carrier nanosystems is the most popular way of directing them to their target sites [16].

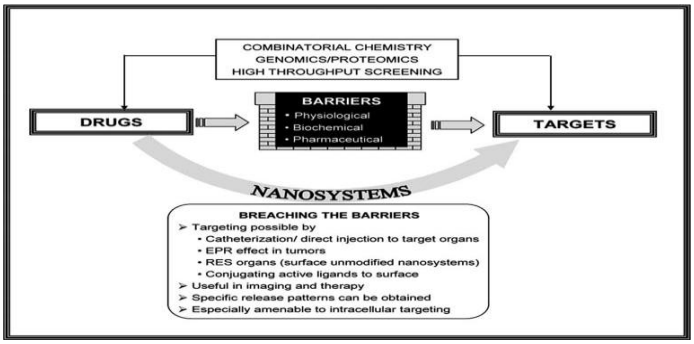

Figure 3: Schematically describing the barriers to drug targeting and the role of nanosystems in overcoming these barriers.

APPROACHES TO DRUG TARGETING:

An ideal targeted drug delivery approach would not only increase therapeutic efficacy of drugs but also decrease the toxicity associated with drug to allow lower doses of the drug to be used in therapy. A vast array of methods, which can further be classified into two key approaches – active and passive have been explored for targeting drugs by means of designing innovative nanosystems. Following is a description of such approaches to drug targeting.

Passive Targeting Approaches:

Passive targeting refers to the accumulation of drug or drug-carrier system at a particular site due to physicochemical or pharmacological factors. Drug or drug carrier nanosystems can be passively targeted making use of the pathophysiological and anatomical opportunities.

1. Pathophysiological Opportunities:

The physiology of diseased tissues may be altered in a variety of pathological conditions and can be exploited for passively targeting drugs. Release of various chemotactic factors from the infected/inflamed tissues results in vascular remodeling to enable leukocyte extravasation and hence also increases permeability for particulate drug carriers. Such pathophysiological opportunities include increased vascular permeability in various inflammatory conditions which allows extravasation of the nanosystems and their selective localization in the inflamed tissue[18].

Rapidly growing or metastasizing tumors recruit new blood vessels through the process of angiogenesis to meet the nutritional demands of increasing number of cells. Unlike the tight endothelium of normal blood vessels, the vascular endothelium of angiogenic blood vessels has large gaps (600-800 nm) in between the adjacent endothelial cells. This increased vascular permeability coupled with the impaired lymphatic drainage in tumors allows an enhanced permeability and retention effect of the nanosystems in the tumor[18].

2. Physicochemical Factors:

The clearance kinetics and *in vivo* biodistribution of nanosystems depend on the physicochemical factors like size, surface charge and surface hydrophobicity and can be manipulated to enable passive targeting. A major part (~90%) of the nanosystems injected intravenously generally is lost to the reticulo-endothelial system (RES), mainly fixed macrophages in the liver and spleen after opsonization by proteins present in the blood stream. Particles < 100 nm can pass through the fenestrations in the liver endothelium and the sieve plates of sinusoids to localize in the spleen and bone marrow. This natural tendency of nanosystems to localize in the RES presents an excellent opportunity for passive targeting of drugs to the macrophages present in the liver and the spleen. It has been utilized for targeting antibiotics and antiviral agents for intracellular infections[18].

3. Anatomical Opportunities:

Drugs may be introduced into "discrete anatomical compartments" for example: lungs, knee joints, respiratory tract, and eye by means of minimally invasive procedures, using catheters or direct injections at local sites. These methods of site-specific localized drug delivery prevent unwanted systemic exposure of the drug and thus avoid adverse effects of drugs in the non target tissues. This not only minimizes the dose but also the cost of therapy[16].

4. Chemical Approaches:

Chemical approaches towards drug targeting include the well-known prodrug approach and the emerging chemical delivery systems. Two prodrug technologies for targeting cytotoxic compounds selectively to tumor cells are undergoing evaluation at present. These include the antibody directed enzyme prodrug therapy (ADEPT) and the gene directed enzyme prodrug therapy (GDEPT). ADEPT involves antibody targeted against tumor antigen to deliver a non endogenous enzyme specifically to tumor cells. The prodrug is administered subsequently and gets converted into an active drug by the enzymatic action only in the desired cell population. GDEPT approach is similar to ADEPT however, here inspite of using enzyme, the cells are transfected with the gene responsible for expression of the non endogenous enzyme. The gene is

targeted to specific cells and expressed intracellularly so that the prodrug gets converted into its active form only in selected tissues. One such example is that of suicide gene therapy based on the metabolism of prodrug – ganciclovir by the transgene herpes simplex thymidine kinase[19].

Active Targeting Approaches:

Active targeting employs specific modification of a drug/drug carrier nanosystem with "active" agents having selective affinity for recognizing and interacting with a specific cell, tissue or organ in the body[6].

1. Biochemical Targets:

Drug targeting to specific cells has been explored utilizing the presence of various receptors, antigens/proteins on the plasma membrane of cells and also by virtue of the lipid components of the cell membranes. The receptors such as folic acid receptor, low density lipo-protein receptor, peptide receptor and surface bound protein antigens may be uniquely expressed in diseased cells only or may exhibit differentially higher expression in diseased cells as compared to the normal cells. Active agents, such as ligands (folic acid, sugars, lectins, modified albumin and peptides) for the receptors and antibodies to the surface proteins have been used extensively to target specific cells[16]

2. Physical or External Stimuli:

In addition to the aforementioned active targeting methods, targeting and release from a drug delivery system can be achieved by applying external stimuli such as ultrasound or magnetic fields[20].

3. Pretargeting or Sandwich Targeting:

It involves pretargeting of specific cells with a ligand followed by treatment with a drug linked to another molecule having high affinity for the ligand used for pretargeting. Avidinbiotin is one of the biological pairs employed for pretargeting[21]. The proteins of target cells (endothelial cells) were biotinylated by accessing the tissue using a catheter. The active drug or drug carrier system bound to avidin was then injected intravenously. *In vivo* experiments demonstrated that drugs bind to biotinylated endothelial cells through avidin, without getting cleared by blood flow in the artery. This novel approach for targeted drug delivery has implications in targeting drugs for intravascular diseases which need continuous presence of drug at the target site for a long period of time, for example angiogenesis in tumors.

4. Promoter or Transcriptional Targeting:

It's a novel approach towards targeted gene therapy which involves the use of specific tissue, tumor, or induced promoters that can limit gene expression to target cells which express a

specific transcription factor[22]. This specifically restricts the transgene expression in the target tissue. An ideal tumor specific promoter is the one highly active in tumor cells with little or no activity in normal cells. Promoter for telomerase gene can be genuinely classified as tumor specific and is being used to drive transgene expression in a variety of cancer cells[23].

DIFFERENT NANOMATERIAL USED AS PHARMACEUTICAL CARRIER:

Numerous nanoparticle-based drug delivery and drug targeting systems are currently developed or under development. Several varieties of nanoparticles are available: different polymeric and metal nanoparticles, liposomes, micelles, quantum dots, dendrimers, microcapsules, lipoproteins and many different nanoassemblies. Among particulate drug carriers, liposomes, micelles and polymeric nanoparticles are the most extensively studied and possess the most suitable characteristics for encapsulation of many drugs and diagnostic (imaging) agents.

1. Micelles:

Micelles represent so-called colloidal dispersions (with particle size normally within the 5–100-nm range) that belong to a large family of dispersed systems consisting of particulate matter or dispersed phase, distributed within a continuous phase or dispersion medium. They belong to a group of association or amphiphilic colloids. Such colloids are spontaneously formed under certain concentration and temperature by amphiphilic or surface-active agents (surfactants), molecules of which consist of two clearly distinct regions with opposite affinities toward a given solvent[24]. At low concentrations in aqueous medium, these amphiphilic molecules exist separately; however, as their concentration is increased, aggregation takes place within a rather narrow concentration interval. Those aggregates, known as micelles, include several dozens of amphiphilic molecules and usually have a shape close to spherical. The concentration of a monomeric amphiphile at which micelles appear is called the critical micelle concentration, while the temperature below which an amphiphilic molecule exist as unimers and above as aggregates is called the critical micellization temperature. Hydrophobic fragments of amphiphilic molecules form the core of a micelle, which can solubilize poorly soluble pharmaceuticals, while hydrophilic fragments form the micelle's corona [25]. In aqueous systems, nonpolar molecules are solubilized within the micelle core, polar molecules will be adsorbed on the micelle surface and substances with intermediate polarity will be distributed along surfactant molecules in intermediate positions.

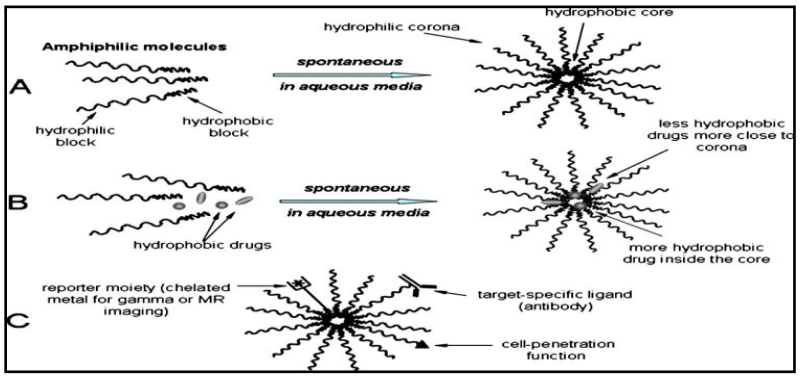

Figure 4: Principal scheme of micelle formation from an amphiphilic molecule

Polymeric micelles represent a class of micelles and are formed from block copolymers consisting of hydrophilic and hydrophobic monomer units. In the majority of cases the structure of amphiphilic unimers follows a few simple rules: poly (ethylene glycol) (PEG) blocks with a molecular weight from 1 to 15 kDa are usual corona-forming blocks, and the length of a hydrophobic core-forming block is close or somewhat lower than that of a hydrophilic block [26]. Though other hydrophilic polymers may be used to make corona blocks [27], PEG still remains the hydrophilic block of choice. At the same time, a variety of polymers may be used to build hydrophobic core-forming blocks: propylene oxide, L-lysine, aspartic acid, *b*-benzoyl-L-aspartate, *g*-benzyl-L-glutamate, caprolactone, D, L-lactic acid and spermine [24].

2. Dendrimers:

Dendrimers, a unique class of polymers, are highly branched macromolecules whose size and shape can be precisely controlled [28]. Dendrimers are synthetic, three-dimensional macromolecules formed using a nanoscale fabrication process. A dendrimer is built up from a monomer, with new branches added in steps until a tree-like structure is created. A dendrimer is technically a polymer. They consist of a central core, branching units and terminal functional groups. The core chemistry determines the solubilizing properties of the cavity within the core, whereas external chemical groups determine the solubility and chemical behavior of the dendrimer itself. Targeting is achieved by attaching specific linkers to the external surface of the dendrimer which enable it to bind to a disease site, while its stability and protection from phagocytes is achieved by 'decorating' the dendrimers with polyethylene glycol chains. Dendrimers used in drug delivery studies typically incorporate one or more of the following polymers: polyamidoamine (PAMAM), melamine, poly (L-glutamic acid) (PG), polyethyleneimine (PEI), poly (propylene imine) (PPI), and poly (ethylene glycol) (PEG) [29].

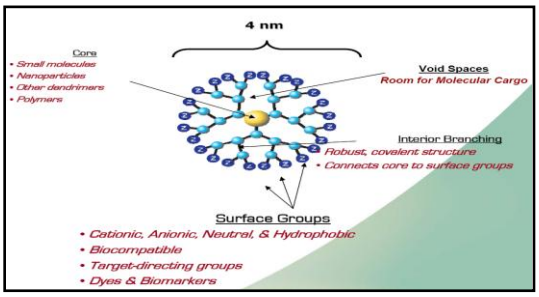

Figure 5: Dedrimers

Synthesis:

Dendrimers are generally prepared using either a divergent method or a convergent one. There is a fundamental difference between these two construction concepts. In the divergent methods**,** dendrimer grows outwards from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated for several generations and a dendrimer is built layer after layer. The convergent methods were developed as a response to the weaknesses of the divergent synthesis. In the convergent approach, the dendrimer is constructed stepwise, starting from the end groups and progressing inwards. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule[30].

Drug delivery properties:

Dendrimers, which are capable of interacting specifically with cancerous tumor tissue, are an excellent option as a drug transporter within the body. Various polymers and other highly branched structures lack consistency of functional groups, monodispersive nature, and uniform molecular weight distribution. Dendrimers also have an exceptionally high drug loading capacity, which provides a greater accumulation of drug at the tumor site. Considering that dendrimers can be prepared with a predetermined, specific number of monomers and polymer branches, as well as peripheral functional group specific, they are the ideal macromolecule to enter the highly permeable vasculature of tumor sites and remain localized at the site to deliver an immense amount (within cytotoxic levels) of drug to the specific tissue. The surface of dendrimers can be modified with functional groups so that drugs will be physically entrapped, encapsulated, or conjugated by covalent bonds, ionic interactions, or hydrogen bonds. With the increase of molecular weight of the drug, due to the dendrimer-drug interaction, the hydrodynamic volume increases causing longer circulation time and slower elimination of drug so cytotoxicity levels are lowered and dosage can be decreased. Lastly, dendrimers have the

ability to solubilize some insoluble anti-cancer drugs. Increased solubility results in higher loading efficiency, which prevents nonspecific interactions and negative side effects of the drug[31].

3. Nanoparticles:

Nanoparticles are sub-micron sized polymeric colloidal particles with a therapeutic agent of interest encapsulated within their polymeric matrix or adsorbed or conjugated onto the surface. Polymeric nanoparticles constitute a versatile drug delivery system, which can potentially overcome physiological barriers, and guide the drugs to specific cells or intracellular compartments; either by passive or ligand mediated targeting approaches. It also allows controlling the release pattern of drug and sustaining drug levels for a long time by appropriately selecting the polymeric carriers[16].

4. Carbon structures:

Carbon, the common element in organic compounds, is known to exist in two allotropic forms, *viz*, diamond and graphite. In 1985, a third form of carbon called fullerenes was discovered. The scientists named the newly found molecule after the architect Richard Buckminster Fuller, who created the dome in 1967 with the same shape as the carbon cluster. Fullerenes generated so much interest and excitement among research scientists that the three scientists who discovered fullerenes received Nobel Prize in Chemistry in 1996[32]. Two nanostructures that have received much attention in recent years are hollow, carbon-based, cage-like architectures: nanotubes and fullerenes, also known as buckyballs because of their spherical structure resembling the geodesic domes of Buckminster Fuller.

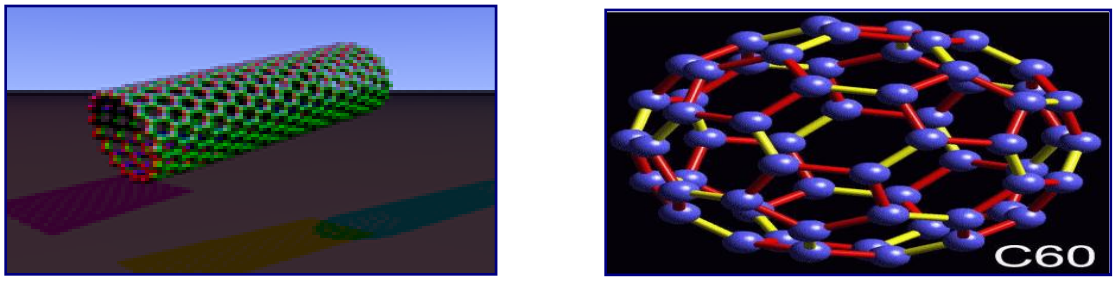

Figure 6: Shows nanotubes and fullerenes, respectively

A. Nanotube:

Carbon nanotubes (CNT) consist exclusively of carbon atoms arranged in a series of condensed benzene rings rolled-up into a tubular structure. CNT can be classified in two general categories, based on their structure: single- walled (SWNT), which consist of one layer of cylinder graphene and multi-walled (MWNT), which contain several concentric graphene sheets. CNT have

nanometric dimensions: SWNT have diameters from 0.4 to 2.0 nm and lengths in the range of 20–1000 nm, while MWNT are bigger objects with diameters in the range of 1.4–100 nm and lengths from 1 to several μm [33].

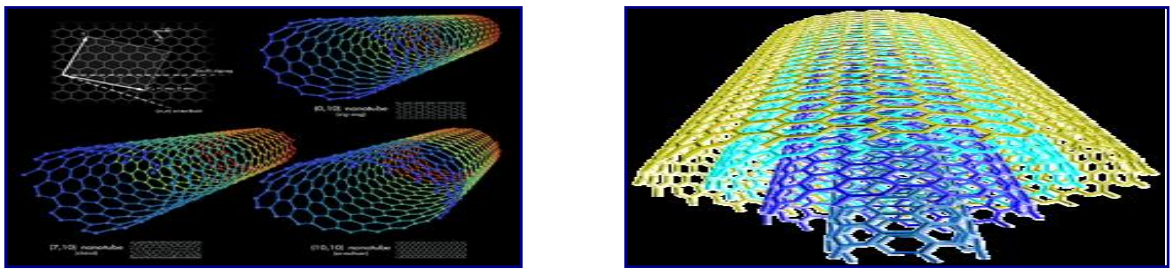

Figure 7: Shows single wall and multi wall nanotubes, respectively

CNT have very interesting physicochemical properties such as: ordered structure with high aspect ratio, ultralight weight, high mechanical strength, high electrical conductivity, high thermal conductivity, metallic or semi-metallic behaviour and high surface area. The combination of these characteristics makes CNT a unique material with the potential for diverse applications, including biomedical [33].

B. Fullerenes:

Fullerenes are large carbon cage molecules considered to be three-dimensional analogues of benzene. The most abundant form of fullerenes is Buckminster fullerene (C60) with 60 carbon atoms arranged in a spherical structure. The shape of the molecule, known as truncated icosahedron, resembles that of a soccer ball, which contains 12 pentagons and 20 hexagons [32].

Fullerenes are inert, hollow and indefinitely modifiable. When administered orally in the water-soluble form, they are not absorbed; while on i.v. injection, they get rapidly distributed to various body tissues. They are excreted unchanged by kidney. Acute toxicity of water-soluble fullerenes was found to be quite low. All these interesting properties offer possibilities of utilizing fullerenes in biology and medicinal chemistry and promise a bright future for fullerenes as medicinal agents. However, this possibility faces a significant problem, i.e., natural repulsion of fullerenes to water. To overcome this limitation, a number of methodologies are being developed. These include synthesis of fullerene derivatives having modified solubility profile, encapsulation of C60 in cyclodextrins or in calixarenes or water suspension preparations [32].

5. Liposome:

Liposomes have been receiving a lot of interest as a carrier for advanced drug delivery. Liposomes were first produced in England in 1961 by Alec D. Bangham, who has studying phospholipids and blood clotting. It was found that phospholipids combined with water

immediately formed a sphere because one end of each molecule is water soluble, while the opposite end is water insoluble. Water soluble medications added to the water were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated in to the phospholipids bilayer. A liposome is a spherical vesicle with a membrane composed of a phospholipid bilayer used to deliver drugs or genetic material in to a cell. Liposomes can be composed of naturally-derived phospholipids with mixed lipid chains (like egg phosphatidyl ethanolamine) or of pure components like DOPE (dioleolylphosphatidylethanolamine) [34, 35].

Types of liposomes: Depending up on the structure there are two types of liposomes [34]:

a. **Unilamellar liposomes:** Unilamellar vesicle has a single phospholipids bilayer sphere enclosing aqueous solution.

b. **Multilamellar liposomes:** Multilamellar vesicles have onion structure. Typically, several unilamellar vesicles will form one inside the other in diminishing size, creating a multilamellar structure of concentric phospholipids spheres separated by layers of water.

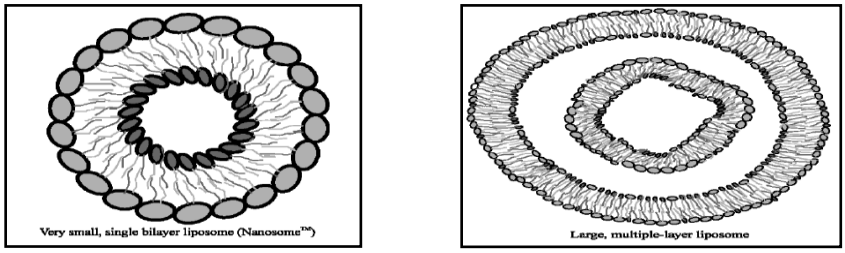

Figure 8: Shows unilamellar and multilamellar liposomes, respectively

c. **Conventional liposomes:** Stabilized natural lecithin (PC) mixtures, Synthetic identical-chain phospholipids, Glycolipid containing liposomes.

d. **Specialized liposomes:** Bipolar fatty acids, Antibody directed, Methyl/methylene X-linked, Lipoprotein coated, Carbohydrate coated, Multiple encapsulated, Emulsion compatible

There are another special type of liposomes getting popularity now a days namely stealth liposome and liposome with homing device.

Stealth liposome:

For conventional liposomes removal from the circulation is too fast to benefit from this escape mechanism. Thus, long circulation times of liposomes were required to take full advantage of this ‘leaky endothelium’ effect. Coating liposomes with polyethylene glycol (PEG) reduces the rate of uptake by macrophages (stealth effect) and leads to prolonged presence of liposomes in the circulation [36].

Vincristine, an anticancer agent having been used as a folk remedy for centuries although, it causes certain toxicities like peripheral neuropathy, hyponatremia, constipation etc. In vivo study

shows that, C-VINC (conventional vincristine) was rapidly eliminated from the plasma and had AUC, half-life, MRT, and *C*max values that were significantly lower, as well as Vss values that were significantly higher than those for liposomal vincristine formulations. Also, the plasma concentrations of free vincristine following injection of liposomal drug were significantly lower than those observed following C-VINC administration at equivalent doses. This may explain the reduced toxicity observed for liposomal vincristine formulations compared with C-VINC in several previous rodent studies [37].

6. Niosomes:

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells.

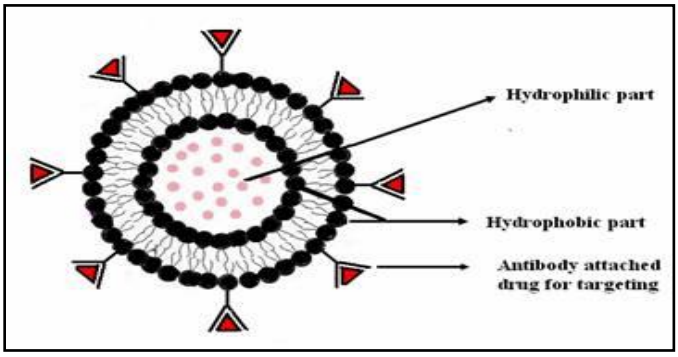

Figure 9: Niosomes

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media [38]. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate. These vesicles appear to be similar to liposomes in terms of their physical properties. They are also prepared in the same way and under a variety of conditions, from unilamellar or multilamellar structures. Niosomes alleviate the disadvantages associated with liposomes, such as chemical instability, variable purity of phospholipids and high cost [38].

7. Magnetic nanoparticles:

Magnetic nanoparticles offer some attractive possibilities in biomedicine. First, they have controllable sizes ranging from a few nanometres up to tens of nanometres. Second, the

nanoparticles are magnetic, which means that they obey Coulomb's law and can be manipulated by an external magnetic field gradient. This 'action at a distance', combined with the intrinsic penetrability of magnetic fields into human tissue, opens up many applications involving the transport and/or immobilization of magnetic nanoparticles, or of magnetically tagged biological entities. Third, the magnetic nanoparticles can be made to resonantly respond to a time-varying magnetic field, with advantageous results related to the transfer of energy from the exciting field to the nanoparticle. For example, the particle can be made to heat up, which leads to their use as hyperthermia agents, delivering toxic amounts of thermal energy to targeted bodies such as tumours; or as chemotherapy and radiotherapy enhancement agents, where a moderate degree of tissue warming results in more effective malignant cell destruction. These, and many other potential applications, are made available in biomedicine as a result of the special physical properties of magnetic nanoparticles [39].

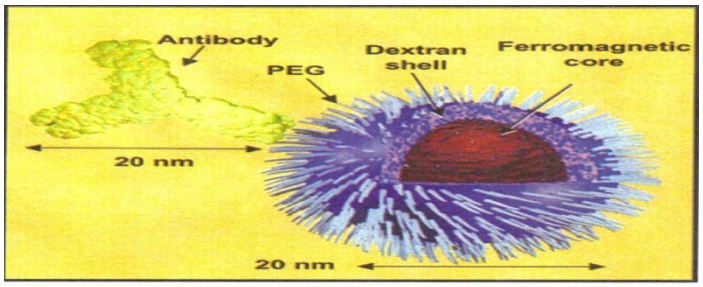

Figure 10: Magnetic nanoparticles

The carriers typically have one of two structural configurations:(i) a magnetic particle core (usually magnetite, Fe_3O_4, or maghemite, γ -Fe_2O_3) coated with a biocompatible polymer or (ii) a porous biocompatible polymer in which magnetic nanoparticles are precipitated inside the pores[39].

8. Silicon based structures:

Among all the materials that have been investigated, silica based materials with well defined structures and surface properties appear to be promising candidates as a DDS material. Silica is a very appealing material for a DDS because it is relatively inexpensive, chemically inert, thermally stable, and biocompatible.

The most commonly investigated silicon-based materials for drug delivery are porous silicon and silica, or silicon dioxide. Architectures include calcified nanopores, platinum-containing nanopores, porous nanoparticles, and nanoneedles. The density and diameter of the nanopores can be accurately controlled to achieve a constant drug delivery rate through the pores [40].

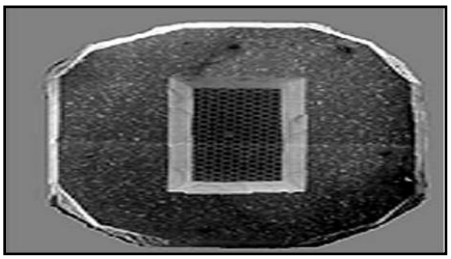

Figure 11: Silicon based nanoparticles

9. Metal structures:

Hollow metal nanoshells are being investigated for drug delivery applications. Typical fabrication methods involve templeting of the thin metal shell around a core material such as a silica nanoparticle. Typical metals include gold, silver, platinum, and palladium. When linked to or embedded within polymeric drug carriers, metal nanoparticles can be used as thermal release triggers when irradiated with infrared light or excited by an alternating magnetic field [29].

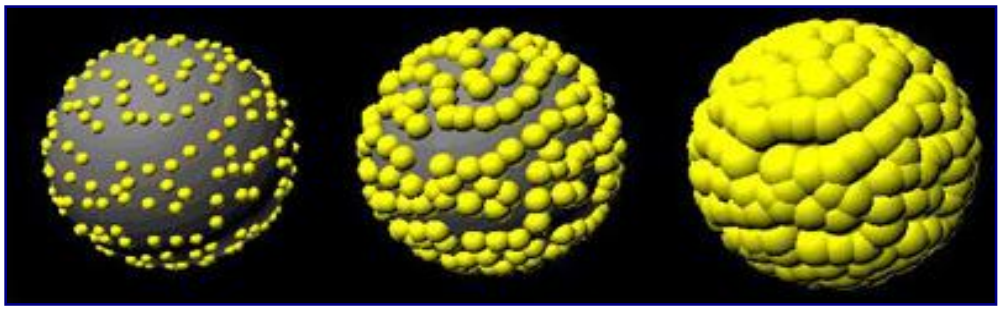

Figure 12: Metal structures

10. Quantum dot (QD):

QDs are inorganic semiconductor nanocrystals having typical diameter between 2-8 nm that possess unique luminescent properties. They are generally composed of atoms from groups II and VI elements (e.g. CdSe and CdTe) or groups III and V elements (e.g. InP and InAs) of the periodic table. Their physical dimensions are smaller than the exciton Bohr radius that leads to quantum confinement effect, which is responsible for their unique optical and electronic properties [41].

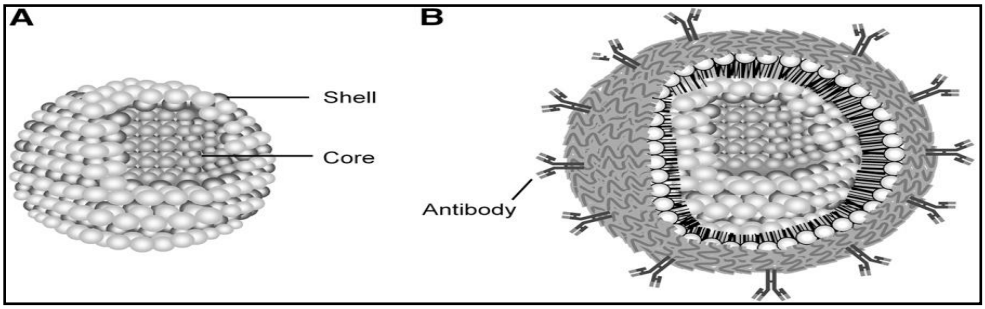

Figure 14: Quantum dots

The most commonly used QD system is the inner semiconductor core of CdSe coated with the outer shell of ZnS. The ZnS shell is responsible for the chemical and optical stability of the CdSe core. QDs can be made to emit fluorescent light in the ultraviolet to infrared spectrum just by varying their size. Most commonly, QDs are linked to polyethylene glycol (PEG) or similar ligands to make them biocompatible and to reduce nonspecific binding. They are made specific to the target site by conjugating them to various bioaffinity ligands such as peptides, antibodies and oligonucleotides etc. using different strategies[42].

APPLICATION OF NANOTECHNOLOGY IN MEDICINE AND HEALTH:

One of the most promising applications of nanotechnology is nanomedicine. Nanomedicine is defined as the application and development of nanoscale tools and machines designed to monitor health care, deliver drugs, cure diseases and repair damaged tissues. Nanomedical research will be an essential tool to diagnose, treat and to do follow-up care in major diseases such as cardiovascular diseases, cancer, diabetes, and other diseases.

1. Cardiovascular diseases:

Cardiovascular diseases are the most frequent cause of death in the world, according to the World Health Organization. The National Heart, Lung and Blood Institute and the National Institutes of Health have establish a new research program focused on creating advanced nanotechnologies to analyze plaque formation on the molecular level and to detect plaque at its early stages. Plaques, containing cholesterol and lipids, may build up during the life of blood vessels. When these plaques become unstable and rupture they can block the vessels, leading to heart attack and stroke.

The scientists will use three types of nanostructured probes. They include molecular beacons, semiconductor quantum dots, and magnetic nanoparticles. A molecular beacon is a biosensor. This biosensor is 4 to 5 nm in size, which seek out and detect specific target genes in the cells. Semiconductor quantum dot-based probes can be used to study interactions in live cells or to detect diseased cells. These ultrasensitive probes may help cardiologists to understand the formation of early stage plaques and to improve detection sensitivity. The magnetic nanoparticles will target the surface of cells in a plaque and provide an image of the plaque formation

2. Cancer detection and diagnosis: Detection of cancer at an early stage is a critical step in improving cancer treatment. Nanotechnology offers a wealth of tools that are providing cancer researchers with new and innovative ways to diagnose and treat cancer. Nanoscale drug delivery

devices are being developed to deliver anticancer therapeutics specifically to tumors.

Examples of nanotechnology in cancer research today include the following:

(i) Nanoscale cantilevers and nanowire sensors that can detect a cancer from a single cell. (ii) Nanoparticles can aid in imaging malignant lesions, so surgeons know where the cancer is and how to remove it. (iii) Nanoshells can kill tumor cells selectively, so patients do not suffer terrible side effects from healthy cells being destroyed. (iv) Dendrimers can sequester drugs to reduce side effects and deliver multiple drugs to maximize therapeutic impact.

3. Diabetes and nanotechnology: People with diabetes must check their blood sugar levels several times a day to keep their diabetes under control for many of the million people diagnosed with diabetes, their daily orders are to watch what they eat and then test their blood glucose levels. Such procedures are uncomfortable and extremely inconvenient. Smart cell technology may help diabetics to maintain their glucose levels without needing blood sample glucose monitoring and injecting insulin. The rise in blood glucose will result in breakage of protein matrix of Smart cell and subsequent release of insulin proportionate to blood glucose [43]. Many scientists and researchers are working on ways to solve the diabetic riddle. Nanotechnology offers tools such as; a nanorobot, biosensors, polymeric nanoparticles, tattoos etc. to solve the diabetic riddle.

4. Diagnosis and therapy: The main advantage of nanomedicine is to get earlier diagnosis of a disease. Diagnosing a disease early leads to less severe and costly therapeutic demands and an improved clinical care. But the human body is dark place to observe. So, you need special instruments that can cut through the darkness and provide a window in to the body. These kinds of instruments are called imaging tools. They include ultrasound, magnetic resonance imaging (MRI) and positron emission tomography (PET). Nanotechnology offers tools such as molecular imaging diagnosis and Lab-on-a-chip diagnosis for earlier and quicker diagnosis of a disease.

5. Drug delivery: Researchers believe that the potential benefits of nanotechnology will be to provide vast improvements in drug delivery and drug targeting techniques. These new strategies are often called drug delivery systems (DDS). The goal of a DDS is to deliver the medications to a specific part of the body and to control the time-release rate of the medication. The DDS will minimize drug degradation and loss and prevent harmful side effects by delivering therapeutic drugs to the desired site of the body. DDS will have potential for many applications, including antitumor therapy, gene therapy and the delivery of antibiotics and vaccines.

6. Respiratory disorders: Polymeric nanopartcles with polylactid-co-glycolide have demonstrated clear advantage over traditional drug carriers in case of intermittent chemotherapy

in experimental tuberculosis.

In veterinary field however the progress in targeted NDDS is very slow in India. To treat tuberculosis, Gantrez-based nanoparitcles entrapped with antituberculosis drugs like rifmapicin and ethambutol is under clinical trials. They also found that by incorporating folic acid in the formulation targetting efficiency is significantly enhanced since it is known that infected RE cells express folic acid receptors. In vitro studies have shown high targeting and bactericidal efficacy of the NDDS formulation. Limited clinical studies indicate that this formulation would hold great potential in treating tuberculosis in animals. For Theilariasis, NDDS based on solid lipid nano-particles containing Buparvaquone has been developed. This formulation has been shown up have quite high entrapment and targeting efficiency. Clinical trials with buparvaquone - nanoparticulate formulation has shown that even at $1/5^{th}$ dose rate drug is very effective in eliminating infection. The clinical improvement is recorded within 24 hours of administration and no relapse has been observed up to three months. For treating *Ehrlichia* infections in animals, which are very refractive to treat, they have developed a novel nanocarrier named 'Lipomer' which has been found to have excellent entrapment efficiency for drug doxycycline which is highly hydrophobic. Clinical trials in canines have shown that even at one tenth dose and five injections, it is possible to eliminate ehrlichia in dogs. Most of these formulations are now patented and hopefully should be available for commercial use in future years [44].

CONCLUSION

Nanotechnology is an emerging field that could potentially make a major impact for improving effectiveness and efficiency of delivery of drug to improve human and animal health. Nanotechnology by manipulation of characteristics of materials such as polymers and fabrication of nanostructures is able to provide superior drug delivery systems for better management and treatment of diseases. The nanostructures employed as drug delivery systems have multiple advantages which make them superior to conventional delivery systems. The emergence of nanotechnology is likely to have a significant impact on drug delivery sector, affecting just about every route of administration from oral to injectable. And the payoff for doctors and patients should be lower drug toxicity, reduced cost of treatments, improved bioavailability and an extension of the economic life of proprietary drugs. Nanoparticles represent a promising drug delivery system of controlled and targeted release. It is clear that an era will emerge when soluble drug will be intentionally made to insoluble complex to take advantage of nanotechnology. However, significant challenges remain in pushing this field into clinically

viable therapies. As Feynman had predicted, there has been plenty of room at the bottom to modify and Ravichandran enhance existing technologies by controlling material properties at the nanoscale. Therefore, with sufficient time and research, the promise of nanotechnology-based drug delivery system may become a reality. Nanotechnology will essentially be a revolutionizing technique in near future for diagnosis and treatment of diseases in man and animals.

REFERENCES:

1. Feynman R. There's plenty of room at the bottom. Science 1991; 254: 1300-1301.
2. Murray CB, Kagan CR, Bawendi MG. Synthesis and characterization of monodisperse nanocrystals and close-packed nanocrystal assemblies. Annu Rev Mater Sci 2000; 30:545-610.
3. Mazzola L. Commercializing nanotechnology. Nature Biotechnology 2003; 21:1137-1143.
4. Taton TA. Nanostructures as tailored biological probes. Trends Biotechnol 2002; 20:277-279.
5. Whitesides GM. The 'right' size in Nanobiotechnology. Nature Biotechnology 2003; 21:1161-1165.
6. Kingsley JD, Huanyu D, Morehead J, Rabinow B, Destache CJ. Nanotechnology: a focus on nanoparticles as a drug delivery system. J Neuroimmune Pharmacol 2006; 1:340–350.
7. Scott NR. Nanoscience in veterinary medicine. Vet Res Commun (Suppl 1) 2007; 31:139–144.
8. Kreuter J. Nanoparticles: a historical perspective. International Journal of Pharmaceutics 2007; 331: 1–10.
9. Feneque J. Brief Introduction to the Veterinary Applications of Nanotechnology. Nanotechnology Now, (http://www.nanotech-now.com/Jose-Feneque/Veterinary-Applications- Nanotechnology.htm), 2003.
10. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov 2004; 3: 785-796.
11. Persson EM, Gustafsson AS, Carlsson AS, Nilsson RG, Abrahamsson B. The effects of food on the dissolution of poorly soluble drugs in human and in model small intestinal fluids. Pharm Res 2005; 22: 2141–2151.
12. Lysik MA, Wu-Pong S. Innovations in oligonucleotide drug delivery. J Pharm Sci 2003; 92:1559–1579.
13. Singh SS. Preclinical pharmacokinetics: an approach towards safer and efficacious drugs. Curr Drug Metab 2006; 7:165–182.
14. Ferrari M. Nanovector therapeutics. Curr Opin Chem Biol 2005; 9: 343–346.

15. Moghimi SM, Murray JC. Nanomedicine: current status and future prospects. FASEB J 2005; 19:11–30.
16. Vasir JK, Reddy MK, Labhasetwar VD. Nanosystems in drug targeting: opportunities and challenges. Current Nanoscience 2005; 1: 47-64.
17. Tachibana R, Harashima H, Shono M, Azumano M, Niwa M, Kiwada H. Intracellular regulation of macromolecules using pH-sensitive liposomes and nuclear localization signal: qualitative and quantitative evaluation of intracellular trafficking. Biochem Biophys Res Commun 1998; 251: 538-544.
18. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science 2004; 303: 1818–1822.
19. Nitesh Kumar. Prodrug activating systems in suicide gene therapy of cancer: a review. Pharma Science Monitor 2011; 2(3): 153-179.
20. Rapoport N, Pitt WG, Sun H, Nelson JL. Drug delivery in polymeric micelles: from in vitro to in vivo. J Control Release 2003; 91:85-95.
21. Hoya K, Guterman LR, Miskolczi L, Hopkins LN. A Novel Intravascular Drug Delivery Method Using Endothelial Biotinylation and Avidin-Biotin Binding. Drug Deliv 2001; 8: 215-222.
22.Robson T, Hirst DG, Transcriptional targeting in cancer gene therapy. J Biomed Biotechnol 2003; 2003(2): 110-137.
23. Kim NW, Piatyszek MA, Prowse KR, Shay JW. Science 1994; 266: 2011-15.
24. Torchilin VP. Targeted polymeric micelles for delivery of poorly soluble drugs. Cell Mol Life Sci 2004; 61:2549-2559.
25. Lasic DD. Mixed micelles in drug delivery. Nature 1992; 355: 279–280.
26. Cammas S, Suzuki K, Sone C, Sakurai Y, Kataoka K, Okano T. Thermorespensive polymer nanoparticles with a core-shell micelle structure as site specific drug carriers. J Control Release 1997; 48: 157–164.
27. Torchilin VP, Trubetskoy VS, Whiteman KR, Caliceti P, Ferruti P, Veronese FM. New sunthetic amphiphilic polymers for steric protection of liposomes in vivo. J Pharm Sci 1995; 84:1049–1053.
28. Namazi H, Adeli M. Dendrimers of citric acid and poly (ethylene glycol) as the new drug-delivery agents. Biomaterials 2004; 26:1175-1183.
29. Hughes GA. Nanostructure-mediated drug delivery. Nanomedicine: Nanotechnology, Biology and Medicine 2005; 1: 22–30.

30. Klajnert B, Bryszewska M. Dendrimers: properties and application. Acta Biochimica Polonica 2001; 1(48):199-208.
31. Sopczynski BP. A new anti-tumor drug delivery system: dendrimers. MMG 445 Basic Biotechnology eJournal 2008; 2: 87–92.
32. Thakral S, Mehta RM. Fullerenes: an introduction and overview of their biological properties. Indian J Pharm Sci 2006; 68 (1):13-19.
33. Lacerda L, Bianco A, Prato M, Kostarelos K. Carbon nanotubes as nanomedicines: from toxicology to pharmacology. Advanced Drug Delivery Reviews 2006; 58:1460–1470.
34. Shaheen SM, Ahmed FR. Liposome as a carrier for advanced drug delivery. Pakistan J Biological Sci 2006; 9:1181-1191.
35. Nitesh Kumar. Liposomal targeted drug delivery system: a review. Pharma Science Monitor 2011; 2(3):62-81.
36. Woodle MC, Storm G, Newman MS, Jekot LR, Collins FC, Szoka FC. Pronloged systemic delivery of peptide drugs by long-circulating liposomes: illustration with vasopressin in the Brattleboro rat. Pharma Res 1992; 9: 260-265.
37. Krishna R, Webb MS, Onge G, Mayer LD. Liposomal and nonliposomal drug pharmacokinetics after administration of liposome-encapsulated vincristine and their contribution to drug tissue distribution properties. J Pharm Exp Ther 2001; 298: 1206–1212.
38. Malhotra M, Jain NK. Niosomes as Drug Carriers. Indian Drugs 1994; 31(3):81-86.
39. Pankhurst QA, Connolly J, Jones SK, Dobson J. Applications of magnetic nanoparticles in biomedicine. J. Phys D: Appl Phys 2003; 36:167–181.
40. Prinz AV, Prinz VY, Seleznev VA. Semiconductor micro- and nanoneedles for microinjections and ink-jet printing. Microelectronic Eng 2003; 67: 782-788.
41. Chan WCW, Maxwell DJ, Gao X, Nie S. Luminescent QDs for multiplexed biological detection and imaging. Curr Opin Biotechnol 2002; 13: 40-46.
42. Vashist SK, Tewari R, Bajpai RP, Bharadwaj LM, Raiteri R. Review of Quantum Dot Technologies for Cancer Detection and Treatment. J Nanotechnology Online 2006; 2:1-14.
43. Martinac K, Metelko Z. Nanotechnology and diabetes. Diabetologia Croatica 2005; 34: 105-110.
44. Samad A. Nanotechnology- Based Novel Targeted Veterinary Drug Delivery Systems in 29th ISVM Convention & National Symposium on "Recent Developments in Diagnostics and Therapeutics Including Applications of Nanotechnology In Veterinary Medicine", 17th -19th February 2011: 1-2.