Nanotechnology based devices and applications in medicine: An overview

Abstract

Nanotechnology has been the most explored and extensively studied area in recent times. Many devices which were earlier impossible to imagine, are being developed at a lightning speed with the application of nanotechnology. To overcome the challenges offered by the most dreaded diseases, such as cancer or any disease involving the central nervous system or other inaccessible areas of the human body, nanotechnology has been proved to be a boon in making the treatment more target specific and minimizing the toxicities. This review describes a handful of important devices and applications based on nanotechnology in medicine made in recent times. This article also describes in brief the regulatory concerns and the ethical issues pertaining to nanomedical devices.

Key words:
Nanosensors, nanosuspensions, nanotechnology, nanotubes

Introduction

Nanotechnology is the development of engineered devices at atomic, molecular, and macromolecular level in nanometer range. It is an approach to problem solving and can be considered as a collection of tools and ideas which can be applied in the pharmaceutical industry. Materials and devices designed by nanotechnology interact with the cells and tissues with high degree of functional specificity, thus, allowing integration between the device and biological system not previously attainable. Nanotechnology is the design, characterization, production and application of structures, devices and systems by controlling shape and size at nanometer scale. The size range of few nanometers and 100 nm is one where many interesting things happen. All sorts of physical properties change and many biological systems function in this length scale.[1-4]

Nanotechnology plays an important role in advanced biology and medical research particularly in the development of potential site specific delivery systems with lower drug toxicities and greater efficiencies.[5] The era of nanotechnology has allowed novel research strategies to flourish in the field of drug delivery. Nanotechnology designed drug delivery systems have been seen to be suitable for treating chronic intracellular infections.[6] These drug delivery systems have been seen to have distinct advantages over traditional drug carriers. The technology's continual and the ease of use and more desirable delivery for systemic drugs has increased the attraction of many scientists to this field. Recent progress in cancer nanotechnology gives rise to exciting opportunities in which diagnosis and treatment are based on the molecular profiles of individual patients.[7]

"Nanotechnology" was first defined by Tokyo Science University, Norio Taniguchi in 1974.[8] Although the application of nanotechnology to medicine appears to be a relatively recent trend, the basic nanotechnology approaches for medical application dates back to several decades.[9] Lipid vesicles which were named as liposomes, were described in 1965,[10] in 1976 the description about the first controlled release polymer system of macromolecules was given,[11]

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the first long circulating stealth polymeric nanoparticle was described in 1994,[12] the first quantum dot bioconjugate was described in 1998,[13] and the first nanowire nanosenser was described in 2001.[14]

Devices Based on Nanotechnology

Nanotechnology tools are used in process development and product development. Process development refers to both synthesis of drugs, drug intermediates, and to the development of analytical tools for diagnostics. One of the most important tool is miniaturization and automation in organic synthesis and biological screening on a nanoscale. In addition to the miniaturization of synthetic methods, nanomaterials are being developed as efficient catalysts and supports for solid-phase organic synthesis. Magnetic nanoparticle supported chiral Ruthenium complexes are known to catalyze heterogeneous asymmetric hydrogenation of aromatic ketones with remarkably high activity and enantioselectivity. Magnesium oxide nanoparticles are utilized for residue-free catalytic process for production of Nabumetone, an anti-inflammatory agent, in high yield and high selectivity. One of the most obvious and important nanotechnology tool for product development is the opportunity to convert existing drugs having poor water solubility and dissolution rate into readily water soluble dispersions by converting them into nanosize drugs. Simply by reducing the particle size of drugs to the nanometer range, the exposed surface area of the drug is increased and hence its ability to be absorbed. Once the drug is in nano form, it can be converted into different dosage forms such as oral, inhalation, nasal, and injectable.[15,16]

One of the major applications of nanotechnology in relation to medicine is drug delivery. The problems with the new chemical entities such as insolubility, degradation, bioavailability, toxicologic effects, targeted drug delivery, and controlled drug release are solved by nanotechnology. For example, encapsulated drugs can be protected from degradation. Specific nanosized receptors present on the surface of the cell can recognize the drug and elicit appropriate response by delivering and releasing the therapy exactly wherever needed. Because of their small size and large surface area relative to their volume, nanoscale devices can readily interact with biomolecules. Nanoscale devices include: nanoparticles [Figure 1], nanotubes, cantilevers, semiconductor nanocrystals, and liposomes.

Nanotubes

Nanotubes are smaller than nanopores [Figure 2]. Nanotubes help to identify Dioxyribonucleic acid (DNA) changes associated with cancer cells. They are about half the diameter of a molecule of DNA. It helps to exactly pin point location of the changes. Mutated regions associated with cancer are first tagged with bulky molecules. The physical shape of the DNA can be traced with the help of the nano tube tip. A computer translates the information into topographical map. The bulky molecules identify the regions on the map where mutations are present. Since the location of mutations can influence the effects they have on a cell, these techniques are important in predicting disease.[3,17,18]

Quantum dotes

These are tiny crystals that glow when these are stimulated by ultraviolet light [Figure 3]. The latex beads filled with these crystals when stimulated by light, emit the color that lights up the sequence of interest. By combining different

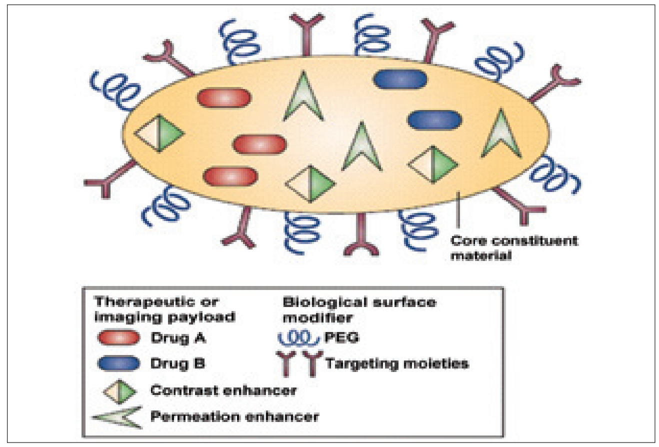

Figure 1: Multifunctional nanoparticle[26]

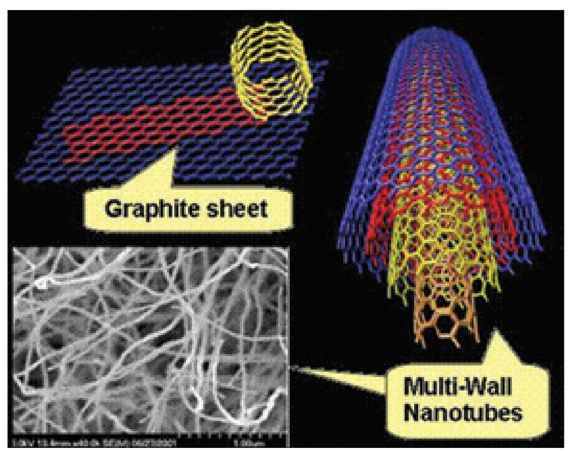

Figure 2: Nanotubes[38]

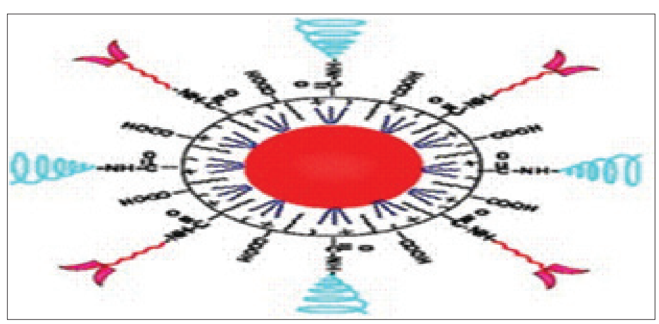

Figure 3: Antibody conjugated quantum dotes[39]

sized quantum dotes within a single bead, probes can be created that release a distinct spectrum of various colors and intensities of lights, serving as sort of spectral bar code. Latex beads filled with crystals can be designed to bind to specific DNA sequences. When the crystals are stimulated by light, the colors they emit serve as dyes and light up the sequences of interest.[3,19-21]

Nanoshells

Nanoshells (NS) are gold coated miniscule beads [Figure 4]. The wavelength of light which the beads absorb is related to the thickness of the coatings. Thus, by manipulating the thickness of the layers making up the NS, the beads can be designed that absorb specific wavelength of light. The most useful NS are those that absorb near infrared light that can easily penetrate several centimeters in human tissues. Absorption of light by NS creates an intense heat that is lethal to cells. Metal NS which are intense near-infrared absorbers are effective both *in-vivo* and *in-vitro* on human breast carcinoma cells.[17]

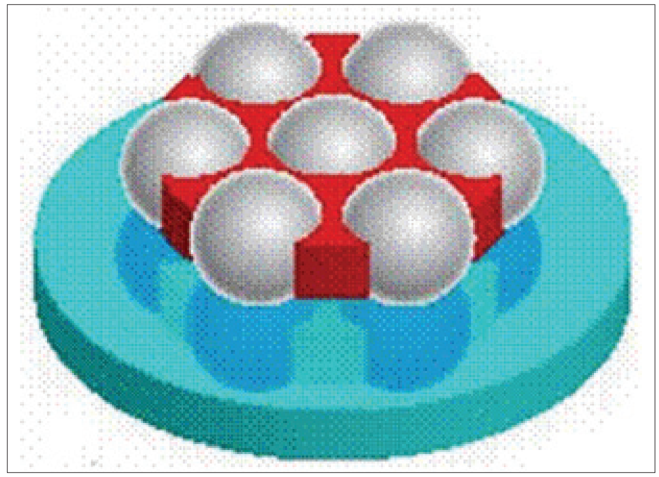

Figure 4: Nanoshells[40]

Liposomes

Liposomes are self-assembling, spherical, closed colloidal structures composed of lipid bilayers that surround a central aqueous space. Liposomal formulations have shown an ability to improve the pharmacokinetics and pharmacodynamics of associated drugs. Liposome based formulations of several anticancer agents have been approved for the treatment of metastatic breast cancer and Kaposi's sarcoma.[22-24]

Cantilevers

Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer [Figure 5]. These molecules may bind to altered DNA proteins that are present in certain types of cancer monitoring the bending of cantilevers; it would be possible to tell whether the cancer molecules are present and hence detect early molecular events in the development of cancer cells.[25,26]

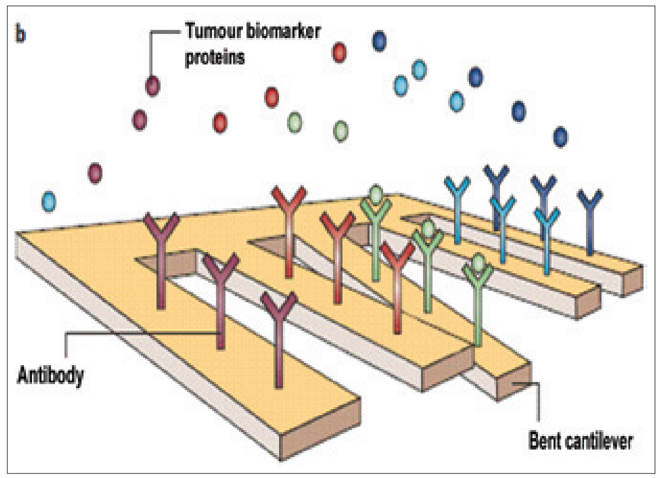

Figure 5: Nanocantilever array[26]

Dendrimers

Dendrimers are new class of macromolecules which have a symmetric core and form the 3-D spherical structure [Figure 6]. These have branching shape which gives them vast amounts of surface area to which therapeutic agents or other biologically active molecules can be attached. A single dendrimer can carry a molecule that recognizes cancer cells, a therapeutic agent to kill those cells, and a molecule that recognizes the signals of cell death. It is said that dendrimers can be manipulated to release their contents only in the presence of certain trigger molecules associated with cancer.[27-29]

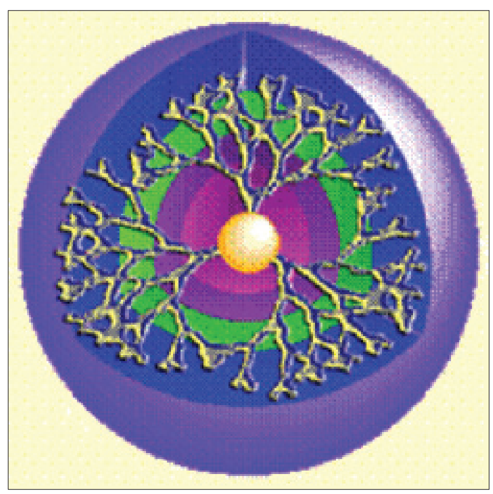

Figure 6: Dendrimer[41]

Application of Nanotechnology in Medicine

Recent developments in nanotechnology have led to the emergence of nanomedicine, a new field which includes many diagnostic and therapeutic applications involving nanomaterials and nanodevices.[30,31] The main aim of any new therapeutic application is to reduce the toxicity or any adverse action of the agents by making them more target specific and hence reduce its dose.[32,33] Nanotechnology has a potential application in the stem research which includes tracking of stem cell surface molecules, non-invasive tracking of stem cells and progenitor cells transplanted *in vivo*, tracking stem cell delivery system, and intracellular delivery of DNA, Ribonucleic acid interference (RNAi), proteins, peptides, and small drugs for stem cell differentiation.[34-36] Nanotechnology also finds its way in bacterial and toxin detection.[37]

The following paragraphs discuss in brief about the applications of nanotechnology in targeting various systems for treating different diseases and disorders efficiently.

Inhibition of neointimal hyperplasia

Atherosclerosis affects many of whom require arterial intervention, treatment often fail due to the development of neointimal hyperplasia, necessitating reintervention. It is well understood that Nitric Oxide (NO) inhibits neointimal hyperplasia. Diazeniumdiolates {1-[N-(3-Aminopropyl)-N-(3-ammoniopropyl)]diazen-1-ium-1,2-diolate [DPTA/NO] or disodium 1-[(2-Carboxylato)pyrrolidin-1-yl]diazen-1-ium-1,2-diolate} are a class of NO donors that release NO spontaneously when placed in an aqueous environment. These diazeniumdiolates were formulated using nanofiber gels.[42,43]

Management of tuberculosis

The management of tuberculosis (TB) treatment is either preventive (i.e., vaccination) or therapeutic (i.e., chemotherapy). Liposomes and lipid nanoparticles are successfully used to deliver the anti-TB drugs with sustained release profiles for long-term therapy and also improved pharmacokinetic profile of the agent.[44,45]

Nanotechnology in pharmaceutical aerosols

Most of the drugs are very poor candidates for developing aerosols, but with nanotechnological principles applied to prepare nanosuspensions for drugs insoluble in aqueous medium as well as in oily medium, gave improved pharmacokinetics which subsequently improved the bioavailability of drugs administrated as aerosols. Furthermore, development of bioadhesive nanoparticles helped increased the mucosal residence time of the drugs which increased the absorption of the drugs and subsequently resulted in enhanced bioavailability.[46-48]

Cancer detection and targeting

Detection and targeting of the cancerous tissues or cells have always been a challenge to the formulator. Cancerous tissues or cells being self becomes very difficult to target the specific cells or organs; as a result, many normal cells are being killed in the process. Many devices based on nanotechnology have come to the rescue of the formulators, wherein, using biomarkers, the anticancer agents can be targeted only to specific cells or organs.[26,49] One such method to detect cancer is use of Photodynamic Therapy (PDT) using 5-aminolaevulinic acid which in metabolized in body to protoporphyrin IX which is a photosensitizer.[50] Quanum dotes (QD) are very useful in lymph node mapping which is an important technique for cancer mapping during surgery and *in vivo* cancer imaging using semiconductor QD is also well documented in the literature.[51,52]

Nucleic acid delivery

Lipid bilayer of the cell membrane poses the major barrier for the delivery of nucleic acids such as small interfering RNA or plasmid DNA. Several viral and polymeric nanocapsules, cationic liposomes, and non-viral vectors (lipoplexes, polyplexes, and inorganic nanoparticles) have been developed that can actively cross the lipid membrane and deliver nucleic acids with ease and reduced toxicity *in vitro*.[53,54]

Biochemical sensors

One of the most important function of nanoparticles is catalysis, especially with noble metal nanoparticles which have high catalytic activity for many chemical reactions. Because nanomaterials also have good biocompatibility, they are used to immobilize biomolecules for the fabrication of biosensors. Glucose nanosensors are being used for the detection of glucose levels in diabetics. Nanosensors of triglycerides are extremely useful in detecting hyperlipidemia.[55] Free gold colloid-based optical biosensors are available for qualitative and quantitative determination of biomolecular interactions and recent advances in the construction of gold colloid-based localized surface plasmon resonance (LSPR) biosensors and their applications in immunosensing, nucleic acid detection, and quantification of toxins has added much value to this technology.[56-58] Oligonucleotide-capped gold nanoparticles have also been reported for polynucleotide or protein detection using various detection/characterization methods such as atomic force microscopy, gel electrophoresis, Raman spectroscopy, and surface plasmon resonance imaging.[59-64]

Regulatory Challenges

In India, the government has been playing a central role in promoting nanotechnology research and development, and their applications.[65] The role of the state is also of prime importance in defining regulatory objectives, developing the ambit, and then selecting the tools from the toolkit that would best facilitate the achievement of the objectives. The current focus of government action on promotion is evident from the mission mode it has approached under Nano-Mission. This focus may get reflected in the way regulations are designed/modified for the technology. The main challenges faced by regulatory institutions currently or the ones which are likely to make the task of regulating nanotechnology difficult are the following:

a) Regulatory capacity
b) Information asymmetry
c) Inter-agency coordination
d) Overlapping roles and mandates

Ethical Issues

Nanotechnology raises many ethical and social issues that are associated with many emerging technologies, such as questions concerning risks to human beings and the environment and access to the technology, and several new questions, such as the use of nanotechnology to enhance human traits. Two main types of nanomedicine products are currently in clinical trials: diagnostic tests and drug delivery devices. The main difference between this diagnostic test and a standard biochemical assay is that the indicators are nanoparticles. A study of the efficacy of this diagnostic test would pose minimal risk to human participants because the subjects would not need to be exposed to nanomaterials, only their tissue samples would be exposed. Since the risks of human exposure to nanomaterials have not been well studied at this time, understanding and predicting risks is the most significant challenge for risk minimization. A new discipline known as nanotoxicology examines the effects of nanomaterials on organisms and the environment.[66-68]

Approved Products of Nanotechnology

Due to the stringent food and drug act (FDA) regulations, only a few products based on nanotechnology are available for clinical use. Doxil® (Centocor Ortho Biotech Products L.P, New Jersey, USA.) and Abraxane® (Abraxis Bioscience, Los Angeles, USA.) are among the two available for clinical use.[69] Doxil®, approved by FDA in 1995, was originally developed to treat HIV-related Kaposi's sarcoma and has now evolved as a second-line treatment for ovarian cancer and multiple myeloma. Doxil®, a reformulation of doxorubicin, with the drug encased in a PEGylated liposome, increases its functionality and specificity while decreasing its cardiotoxicity. Abraxane®, developed for the treatment of breast cancer, comprises the drug, paclitaxel encased in an albumin shell.[70-73]

Conclusion

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

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