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APPLICATIONS OF NANOMEDICINE, NANOPARTICLE DRUG SYSTEM FOR ORAL, OCULAR AND NASAL ADMINISTRATION

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ABSTRACT- *Nanomaterials are finding their way into biology in the form of drug carriers. This is probably the most important application of nonmaterial right now. The property utilizes the large surface area available to load materials. Due to their small size, nanomaterials can be transported into cells and nuclei. Specificity to the target can be achieved by appropriate labelling. The materials put in can be subjected to magnetic fields, photons etc. and can respond to all these situations. The diagnostic and therapeutic applications of such systems are being suggested. Here we present an overview of this area.*

Key Words: Nanomedicine, Nano Shell,Nano dot, Nano pores, Nano Laser etc.,

INTRODUCTION

The objective of nanotechnology is to gain atomic and molecular control over matter. It involves the creation of functional materials with control over their physical sizes, Which exhibit novel physical and chemical properties that are drastically different from the corresponding bulk forms. The concept of the effective use of nanotechnology disease treatment was suggested as early as 1959 by Noble Richard Feynman in his famous talk on, "Plenty of room at the bottom". A friend of mine suggests a very interesting possibility for relatively small machines. Today nano medicines are being developed to have accurate, controllable, economic and rapid responsive diagnostic and treatment solutions for various kinds of diseases. Various studies confirm the fact that particle size should be sufficiently small for it to get transported across the membrane and this transport occurs more readily for nano particles rather than for micro particles. Here we discuss the various approaches

that are currently being researched for developing nano medicines. Additionally; we also discuss various nano materials which are strong candidates for use in nano medicines.

NANOMEDINICE

Nanomedicine is defined as the application of nanobiotechnology to medicine .It is a discipline at interface of medicine and nanobiotechnology but is not a subspecialty of either of these. Its broad scope covers the use of nanoparticles and nanodevices in healthcare for diagnosis as well as therapeutics. Safely, ethical and regulatory issues are also included .the relationship of various biotechnologies to nanomedicine

APPROACH TO DEVELOPING NANOMEDICINES

Depending on the method of preparation and the capping agent present, nano particles vary in size from 10 to 1000 nm. Drugs can be associated with the nano particles in entrapped, encapsulated or attached form. Nano drugs are being synthesized in various forms such as nano spheres, nano capsules, nona pores, dendrites, etc. Encapsulated nano-system based drugs are observed to show nearly zero-order kinetic profile whereas conventional oral drugs follow first –order kinetics leading to unsteady drug release at the location of drug delivery

Various research groups have also established the use of polymeric nano particles for nasal and ophthalmic delivery of drugs group of nano particles has also shown prominence for use neuro-disorders, in which large number of other drugs fails. Furthermore, nano size carriers of vitamin molecules such as vitamin A and E, have potential applications in dermatology and cosmetics.

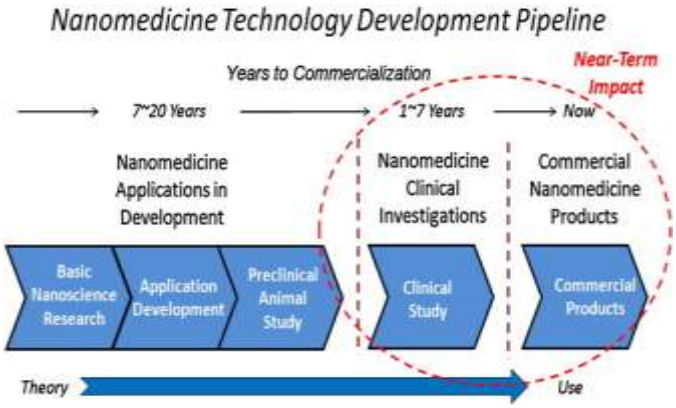

Figure 1 Process of Nanomedicine technology development

CLASSIFICATION OF NANOBIOTECHNOLOGIES

It is not easy to classify the vast range of nanobiotechnologies. Some just represent motion on a nanoscale but most of them are based on nanoscale structures, which come in a variety of shape and sizes. A few occur in nature but most are engineered. The word nano is prefixed to just about anything that deals with nanoscale .It is not just biotechnology but many other disciplines such as nanophysics, nano-biology etc., Some technologies such as nanoarrays and nanochips are further developments.

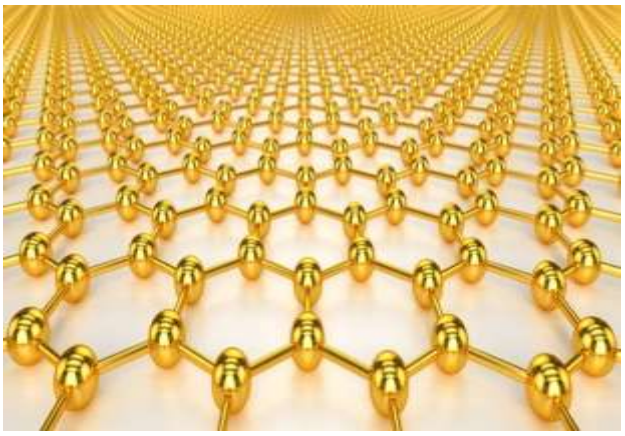

Figure 2 Atomic Structure

RELATION OF NANOBIOTECHNOLOGY TO NANOMEDICINE

Technical achievement in nanotechnology are being applied to improve drug discovery ,drug delivery and pharmaceutical manufacturing .A vast range of applications has spawned many new terms ,which are defined as they are described in various chapters .Numerous applications in the pharmaceutical industry can also be covered under the term "nanobiopharmaceuticals"

NANOMEDICINE AS A PART OF EVOLUTION OF MEDICINE

Medicine is constantly evolving and new technologies are incorporated into the diagnosis and treatment of patients. This process is sometimes slow and there can be a gap of years before new technologies are integrated in medical practice. The reasons for the delay are;

1. Establishing the safety and efficacy of innovative treatment is a long process, particularly with clinical trials and regulatory reviews.

2. Current generation of physicians are still not well oriented towards biotechnology and conservative elements of the profession may be slow in accepting and learning about nanobiotechnology , which is at the cutting edge of biotechnology.

3. High cost of new technologies is a concern for the healthcare providers .Cost-benefit studies are needed to convince the sceptics that some of the new technologies may reduce the overall cost of healthcare.

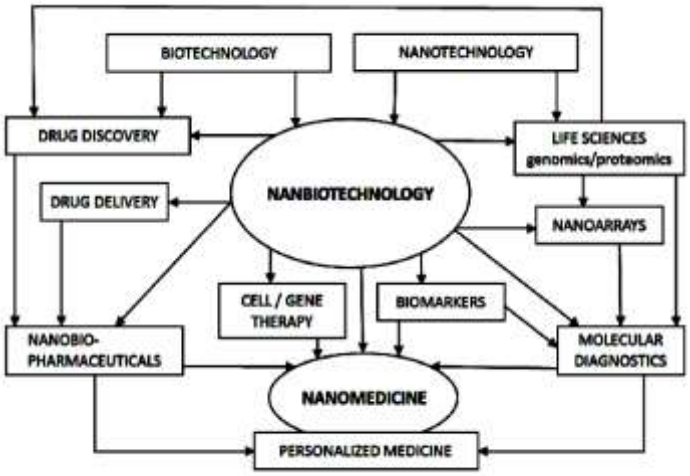

Figure 3 Relation between Nanobiotechnology and Nanomedicine

Various There can be electrostatic interaction or covalent binding between the nano particle and the drug .The nano particle surface can be made electrically neutral or charged, depending on the functional group present on the surface .the surface properties can be tuned depending on the drug-nano particle interaction required. kinds of approaches can be used to attach drugs to nano systems.

VARIOUS KINDS OF NANOSYSTEMS IN USE

Metal nano particles themselves are used as drug delivery vehicles. However, there are several other systems for this application which are briefly reviewed here.

1) NANOSHELLS

Nano shells represent a unique class of medically prominent nano particles. These are made of drug- coated metal nano spheres/dielectric metal nano spheres .Typical metals include gold, silver, platinum and palladium. It quite evident that the response of these nano shells is a function of the thickness of the shell/capping agent. When these nano particle surface .The release process can be accomplished with the use of alternating magnetic field as well.

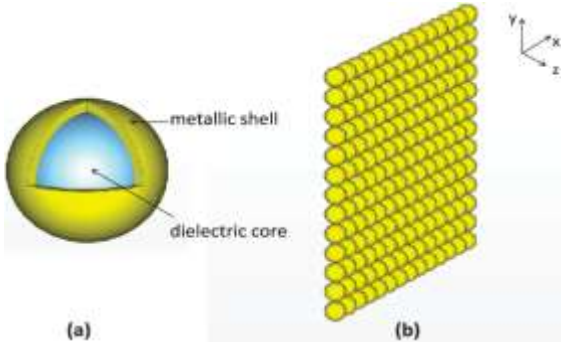

Figure 4 (a) Gold nanoshell (b) Metallic shell structure

This approach to the release of capping agent can have implications in cancer treatment. A high surface –to-volume ratio for nano particles enables large quantity of drugs to be transported into the affected region.

Attempts have also been made to coat nano particle surfaces with antibody molecules; specific to a particular protein present in the human body .this can have profound implications in cancer detection, protein immunoassay and bio sensing.

Drug molecule attached to metal nano particle via covalent/ionic interaction.

NANOPORES

Nano pores are essentially nano particles whose surface contains pores, which can be used for containing drugs. Uniformly spaced holes are created on the surface in which a drug molecule is contained. The pore size imposes a restriction on the size of the bio molecules present. This means that small molecules like oxygen, glucose, insulin, neurotransmitters, etc. can move across the pore surface while large immune system molecules like immunoglobulin cannot. The released molecule can therefore be used in neural disorders, etc.

Cross section of nano pores with drug molecule contained inside the pore.

Attempts are also being made to control the flow of the molecules across the pore for highly specific molecular transport capabilities, by the use of voltage gating and immobilized biochemical molecular –recognition agents. On developing a positive charge on tubule, positive ions were not transported inside the nano pore to undergo a reaction with the drug molecule trapped inside. Similar, only positive ions could pass on applying a negative voltage. The aim is to gain a significant improvement in isolating the targeted molecule with drug molecules have to interact, by the use of combinatory tools such as voltage gating, pore size and shape

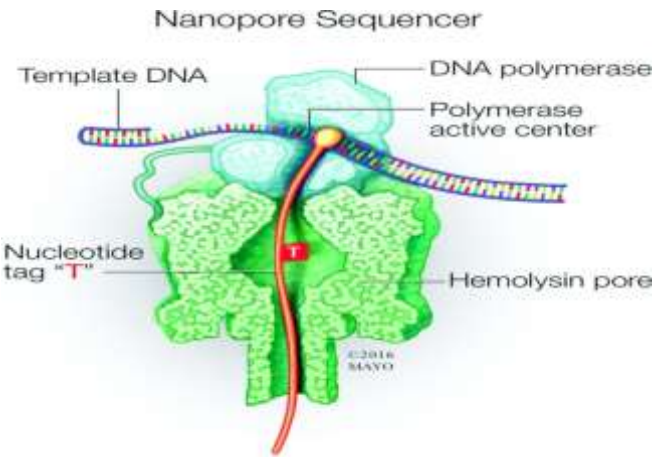

Figure 5 Nonopore sequencer

NANOLASERS

A nanolaser is a laser (light amplifier by stimulated emission of radiation) that has nanoscale dimensions. This tiny laser can be modulated quickly and ,combined with its small footprint, makes it an ideal candidate for on-chip optical computing .The intense optical fields of such a nanolaser also enable the enhancement effect in non-liner optics or surface –enhanced- raman-scattering (SERS), and therefore paves the way toward integrated nanophotonic circuitry .A working room-temperature nanolaser was based on 3D Au bowtie (nanopartices) and supported by an organic gain material (such et al.2012). The extreme field compression, and thus ultra small mode volume , within the bowtie gaps produces laser oscillations at the localized Plasmon.

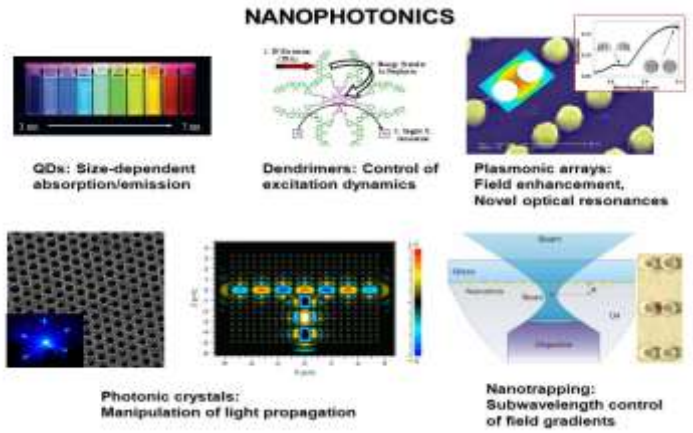

Figure 6 nanophotonics

TECTODENDRIMERS

Dendrites are branched tree-shaped nano particles, which have an immense potential for use in clinical diagnostics and therapeutics. Various research groups have also synthesized multi-component nano devices called 'TECTODENDRIMERS 'which are formed by attaching different types of dendrites with each other through their branches.

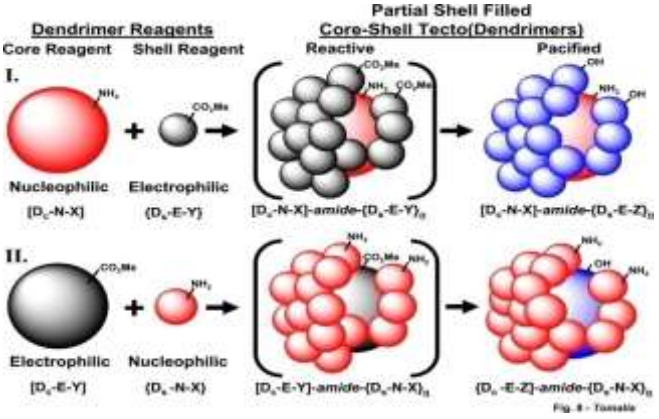

Figure 7 Synthesis of tectodendrimers

These smart nano devices have been synthesized for applications ranging from the detection to treatment of diseases

PROTOCOLS FOR NANODRUG ADMINISTRATION

NANO PARTICLE –DRUG SYSTEM FOR ORAL ADMINISTRATION

Various kinds of approaches are being attempted for the delivery of nano particle-drug complex to target particular locations in the human body. An analysis of conventional oral administration indicates that the basic requirements for the successful delivery of a nano particle-drug system via oral administration are;

1. The complex should be stable in the gastrointestinal tract.
2. Digestive system enzymes should act on the complex and digest it, and the product should subsequently get transported across the intestinal epithelium.
3. Products from the digestion of nano particle system complex should not be cytotoxic for the human body.

In order to avoid the disintegration of the complex before the digestive enzymes start interacting with it, a hybrid system of hydrophobic core-hydrophilic shell has been designed which acts as a carrier for drug molecules. The core is made of hydrophobic material such as oils or lipids whereas the shell is hydrophilic in nature and composed of polyethylene glycol or chatoyant .Chatoyant is a naturally occurring substance. Chemically similar to cellulose,-NH2 group in chatoyant is replaced by –OH group in with the ability to significantly bind fat without itself being digested. The various reported applications for chatoyant are that it;

1. Absorbs and binds fat/promotes weight loss.
2. Promotes healing of ulcers and lesions.
3. Is used as anti-bacterial agent and antacid.
4. Inhibits the formation of plaque/tooth Decay.
5. Help control blood pressure and prevent constipation.
6. Has an anti-tumour action.

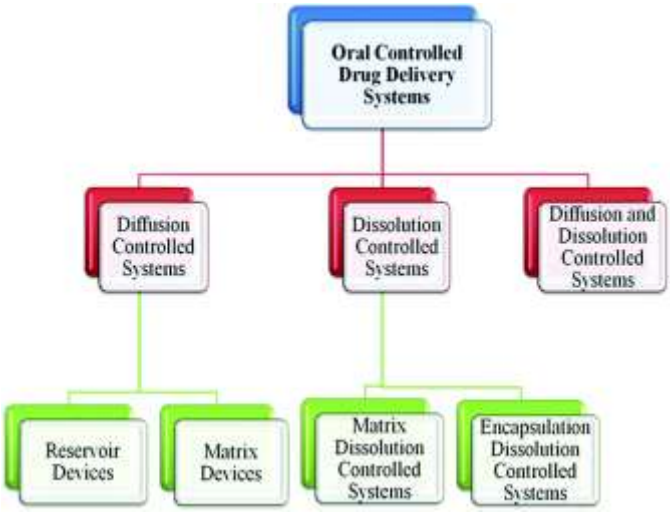

Figure 8 Types of Oral controlled drug delivery systems

NANOPARTICLE-DRUG SYSTEM FOR NASAL ADMINISTRATION

It has been established that the nasal route of drug delivery is more effective due to a better transport process and lower enzymatic activity for nasal mucosa. Studies show that the nanoparticle-drug system is capable of crossing the nasal epithelium with the strong influence of nanoparticle surface composition on transport rates.

PEG was used as a surface cover on the bare nanoparticle. Similary, improved nasal transport of the tetanus toxoid protein was observed when it was encapsulated in a chitosan –coated nanoparticle. This is because of the facilitated interaction and internalization of these nanosystems in the nasal epithelium.

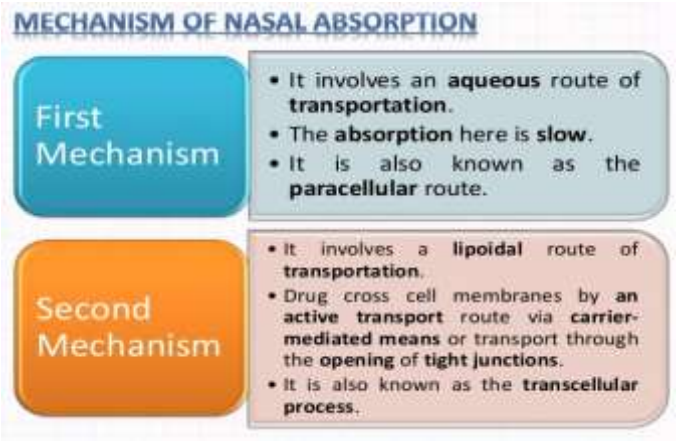

Figure 9 Mechanism of Nasal Administration

NANOPARTICLE-DRUG SYSTEM FOR OCULAR ADMINISTRATION

It was observed that poly alkylcrylate nano particles were able to enter the well-organized corneal epithelium though it caused a slight damage to the epithelial cells. Due to better organization of cells in the corneal epithelium, the

dimension of the carrier must be in the sub-micron region. It has also been established that the coating present on the surface of the nano particle has an important effect on drug transport through the corneal epithelium. This nano particle complex was also able to provide a selective and prolonged delivery of cyclosporine A to the ocular mucosa without QUANTUM DOTS

Compromising the inner ocular tissues by avoiding systemic absorption. This prolonged delivery was attributed to the ocular retention of chitosan nano particles.

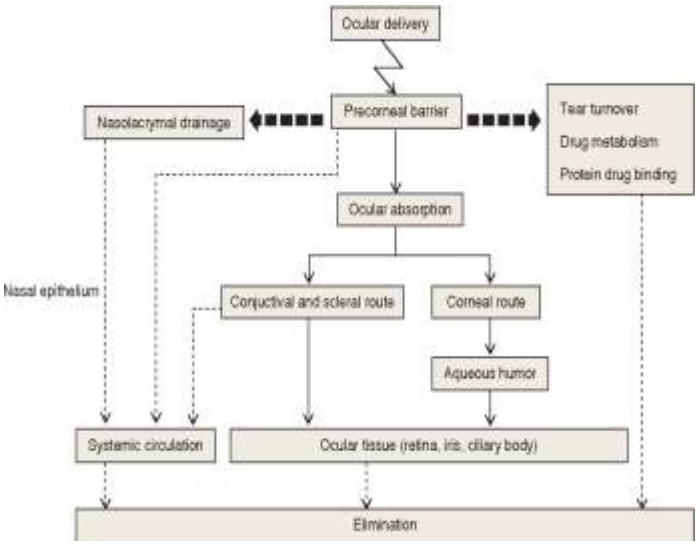

Figure 10 Nanoparticle drug system for Ocular delivery

NANOTECHNOLOGY IN DIAGNOSTIC APPLICATIONS

Research efforts are being driven in the direction of using nanotechnology for molecular diagnostic purposes such as biological research, clinical diagnostics, detection of bio molecules and drug discovery. The focus of this section is on understanding the use of nanosystems for clinical diagnostics, especially in the early diagnosis of various forms of cancer.

Various approaches are being followed for improving clinical diagnostic capabilities. Essentially these approaches have to be molecular in nature .Here we discuss two approaches to develop molecular –based diagnostic tools, which can detect cancer in the very early stages.

Several groups have reported intra-as well as extra-cellular synthesis of metal nano particles using bacteria, fungi and viruses. This process involves the reduction of metal ions added to cells under suitable conditions, and the resultant appearance of nano particles or their aggregates, both inside as well as outside the cell boundary.

When the growth of gold nano particles was observed over duration of 96 hours after incubation various cell lines with 1mm chloroaurate ion solution, it was found that there existed difference in the UV-visible feature for the cancer and non-cancer cells. What one observes is that as a function of incubation time, the peak at 560nm, corresponding to the Plasmon excitation of gold nano particles, increases in intensity

In the second approach, research attempts are being made to read the state of various kinds of bio marks for different types of cancer. The feasibility of reading the state of biomarker has been demonstrated by the use of a molecular –based tool developed by Digene Corporation, the hybrid capture system .this protocol involves releasing the target DNA of HPV and combining it with an RNA probe .DNA-RNA hybrid is captured by using the antibody specific to the hybrid.

MATERIALS FOR USE IN DIAGNOSTIC AND THERAPEUTIC APPLICATIONS

Gold Nano particles

Gold nano particles are extraordinarily efficient for clinical diagnostic purposes as they give strong signatures in optical absorption and fluorescence spectroscopy, X-ray diffraction and electrical conductivity.

Various bio molecules bound to the gold nano particle surface can be detected by using various analytical measurement tools such as MALDI –TOF MS and confocal Raman spectroscopy.

Gold nano particle characterization can be done by UV- Vis spectroscopy in which a surface Plasmon band appears at 500-700 nm. This happens because of electronic oscillations in the conduction band of metals, on exposure to electromagnetic waves. The surface Plasmon resonance phenomenon occurs due to a matching of the frequency of the oscillation of the electron cloud and that of the incident light.

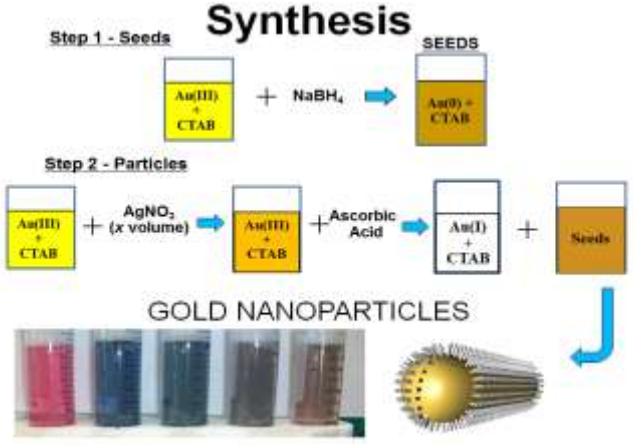

Figure 11 Synthesis of Gold Nanoparticle

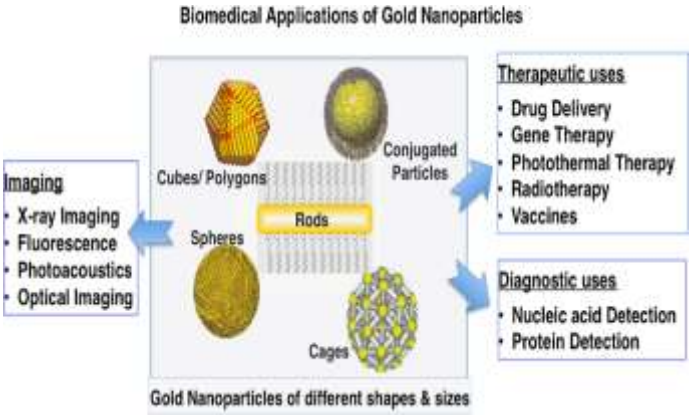

Figure 12 Applications of Gold Nanoparticles

QUANTUM DOTS

Quantum dots are nanoscale crystals synthesized with semiconductor materials. QDs are generating strong research interests in biology due to their fluorescence property seen when they are excited by a laser. Their fluorescence intensity is also significantly higher and are more stable as compared to conventional fluorescence markers.

QD technology holds special promise for use with bio molecules. QDs can be specifically attached to molecules like proteins and nucleic acid. Some of the value additions that QDs can bring are:

- It is easy to excite QDs which means that the possibility of drug degradation due to a high intensity excitation beam is discounted.
- Whole blood assays can be done with the use of QDs because they can emit light throughout the electromagnetic spectrum.
- This technology has high sensitivity and is easy to use.

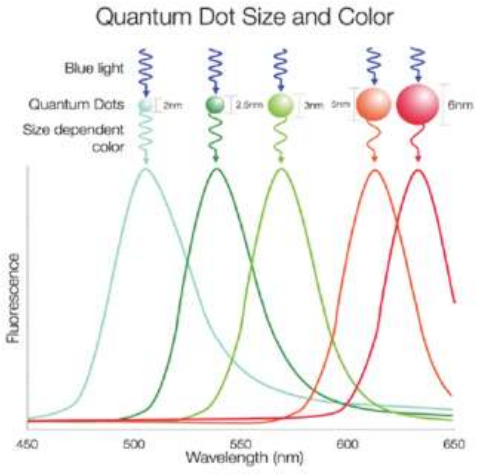

Figure 13 Quantum Dot Size and Color

- Photo bleaching does not occur with QDs which is a serious limitation in the case of fluorescent dyes.

CONCLUSION

Nanosize materials have found practical implementation in the field of diagnoses with the proper and efficient delivery of pharmaceuticals. While on the one hand, attempts are being made to develop accurate and versatile biomarkers for various kinds of disease, on the other hand, research is constantly being driven to develop new protocols for the practical application of nano mechanical tools into the fields of medical research and clinical practice. Such nano tools still await construction, but they may become a reality in the near futureThis step for researching the ultimate objective of gaining control over various kinds of disease that humans suffer from, will involve a three-dimensional approach, i.e. development of a better understanding of biological systems, creation of nano systems and integration of nano-bio system. It may seem impossible to develop a kind of nano machine which when injected into the human body, will itself do the job of finding the location of the disease treating/killing it and providing transitory support for the metabolic processes but a step-by-step approach to nano-bio integration could make this possibility real in the distant future.

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