A REVIEW ON THE APPLICATION OF NANOTECHNOLOGY IN PHARMACEUTICAL SCIENCE

A DISSERTATON SUBMITTED TO DEPARTMENT OF PHARMACY, EAST EST UNIVERSITY, IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF PHARMAY (M.PHARM)

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DEPARTMENT OF PHARMACY

EAST WEST UNIVERSITY

Dedicated To My Parents
&
Honourable Teachers

DECLARATION

I, Rayhan Chowdhury (ID-2013-1-79-007), hereby declare that the dissertation entitled "A Review on the Application of Nanotechnology in Pharmaceutical Science" submitted by me to the Department of Pharmacy, East West University, in the partial fulfillment of the requirements for the degree of Masters of Pharmacy is a genuine & authentic thesis work carried out by me during Spring 2014-Spring 2015 under the supervision and guidance of Dr. Chowdhury Faiz Hossain, Professor, Department of Pharmacy, East West University.

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May ALLAH bless and help us all to render something for the cause of the mankind.

August,2015 Rayhan Chowdhury

Author

ABSTRACT

Nanotechnology deals with the molecule between 1 to 100 nm in size. Buckyball is the first application of nanotechnology which composed of C_{60} atom bonded to three other carbon atoms by covalent bonds. Now a days Nanotechnology widely used in our modern life such as- Electronics and information Technology, Sustainable Energy, Environmental Remediation, Cosmetics, Food Industry, Biotechnology, Pharmaceutical Sector etc. In Pharmaceutical Sector Nanotechnology used in various purpose. Drugs can deliver intracellularly easily by using nanotechnology. Nanorobot can be diagnosis and prevent disease. Tissue damage can be reconstruction by using Nanotechnology. In Pharmaceutical Biotechnology, Nanotechnology is used for manufacturing vaccine for cancer immunotherapy. Cancer cell can be damaged by using this technology. Some nanotechnology based drugs are already in market such as- Daunoxome® [Daunorubicin (liposomal)], Doxil®/Caelyx® (Doxorubicin HCl liposome), Ambisome® [amphotericin B (liposomal)] etc.

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1.0 Nanometer

The **nanometre** or **nanometer** (American spelling) is a unit of length in the metric system, equal to one billionth of a metre. The name combines the SI prefix *nano-* (from the Ancient Greekνάνος, *nanos*, "dwarf") with the parent unit name *metre* (from Greek μέτρον, *metron*, "unit of measurement"). It can be written in notation 1×10^{-9} m, in engineering notation as 1 E−9 m, and is simply 1 / 1,000,000,000 m. One nanometer equals ten angstroms.

1 nanometre =	
SI units	
1×10^{-9} m	1×10^{-3} μm
US customary / Imperial units	
3.2808×10^{-9} ft	39.370×10^{-9} in

1.1 History

The nanometer was formerly known as the **millimicrometer** – or, more commonly, the **millimicron** for short – since it is 1/1000 of a micron (micrometre), and was often denoted by the symbol **mμ** or (more rarely) **μμ**.[1, 2, 3] In 1960, the U.S. National Bureau of Standards adopted the prefix "nano-" for "a billionth".[4] The nanometre is often associated with the field of nanotechnology. Since the late 1980s, it has also been used to describe generations of the manufacturing technology in the semiconductor industry.

2.0 Nanoparticle

Nanoparticles are particles between 1 and 100 nanometers in size. In nanotechnology, a particle is defined as a small object that behaves as a whole unit with respect to its transport and properties. Particles are further classified according to diameter.[5] Ultrafine particles are the same as nanoparticles and between 1 and 100 nanometers in size. Coarse particles cover a range between 2,500 and 10,000 nanometers. Fine particles are sized between 100 and 2,500 nanometers.

Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications in biomedical, optical and electronic fields.[6,7,8,9] The National Nanotechnology Initiative has led to generous public funding for nanoparticle research in the United States.

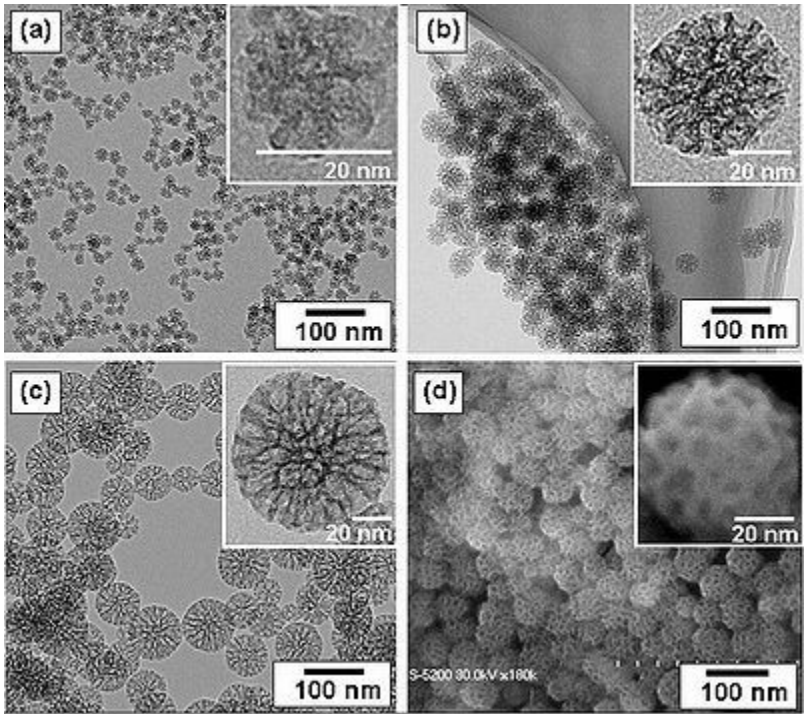


Figure.2.0: Transmission electron microscopy (a, b, and c) images of prepared mesoporous silica nanoparticles with mean outer diameter: (a) 20nm, (b) 45nm, and (c) 80nm. Scanning electron microscopy (d) image corresponding to (b). The insets are a high magnification of mesoporous silica particle.

2.1 IUPAC definition

Particle of any shape with dimensions in the 1×10^{-9} and 1×10^{-7} m range.

***Note 1*:** Modified from definitions of nanoparticle and nanogel. [10, 11]

***Note 2*:** The basis of the 100-nm limit is the fact that novel properties that differentiate particles from the bulk material typically develop at a critical length scale of under 100 nm.

***Note 3*:** Because other phenomena (transparency or turbidity, ultrafiltration, stable dispersion, etc.) that extend the upper limit are occasionally considered,

the use of the prefix nano is accepted for dimensions smaller than 500 nm, provided reference to the definition is indicated.

***Note 4*:** Tubes and fibers with only two dimensions below 100 nm are also nanoparticles.[12]

Figure 2.1: Comparison of Nanomaterials Sizes

2.2 Background

In general, nanoparticles are believed to discoveries of modern science, but they have a really long history. Nanoparticles were used by artisans as far back as the ninth century in Mesopotamia for generating a glittering effect on the surface of pots. [13, 14]

Even these days, pottery from the Middle Ages and Renaissance often retain a distinct gold- or copper-colored metallic glitter. This luster is caused by a metallic film that was applied to the transparent surface of a glazing. The luster can still be visible if the film has resisted atmospheric oxidation and other weathering. [13, 14]

The luster originated within the film itself, which contained silver and copper nanoparticles dispersed homogeneously in the glassy matrix of the ceramic glaze. These nanoparticles were created by the artisans by adding copper and silver salts and oxides together with vinegar, ochre, and clay on the surface of previously-glazed pottery. The object was then placed into a kiln and heated to about 600 °C in a reducing atmosphere. [14]

In the heat the glaze would soften, causing the copper and silver ions to migrate into the outer layers of the glaze. There the reducing atmosphere which reduced the ions back to metals, which then came together forming the nanoparticles that give the color and optical effects. [14]

Luster technique showed that ancient craftsmen had a rather sophisticated empirical knowledge of materials. The technique originated in the Muslim world. As Muslims were not

allowed to use gold in artistic representations, they sought a way to create a similar effect without using real gold. The solution they found was using luster. [14, 15]

Michael Faraday provided the first description, in scientific terms, of the optical properties of nanometer-scale metals in his classic 1857 paper. In a subsequent paper, the author (Turner) points out that: "It is well known that when thin leaves of gold or silver are mounted upon glass and heated to a temperature that is well below a red heat (~500 °C), a remarkable change of properties takes place, whereby the continuity of the metallic film is destroyed. The result is that white light is now freely transmitted, reflection is correspondingly diminished, while the electrical resistivity is enormously increased." [16, 17 , 18]

Buckminsterfullerene (or **bucky-ball**) is a spherical fullerene molecule with the formula C_{60}. It has a cage-like fused-ring structure which resembles a soccer ball, made of twenty hexagons and twelve pentagons, with a carbon atom at each vertex of each polygon and a bond along each polygon edge. Buckyballs was one of the first discovered nanoparticles. This finding happened by Richard Smalley, Harry Kroto and Robert Curl of Rice University in 1985 by the trio of work researchers.

Buckyballs are composed of carbon atom bonded to three other carbon atoms by covalent bonds. However, the carbon atom to give a spherical structure of buckyballs, are connected to the same pattern hexagonal and pentagonal find in soccer ball. Fullerenes are stable, but not totally unreactive. The sp^2-hybridized carbon atoms, which are at their energy minimum in planar graphite, must be bent to form the closed sphere or tube, which produces angle strain. The characteristic reaction of fullerenes is electrophilic addition at 6,6-double bonds, which reduces angle strain by changing sp^2-hybridized carbons into sp^3-hybridized ones. The change in hybridized orbitals causes the bond angles to decrease from about 120° in the sp^2 orbitals to about 109.5° in the sp^3 orbitals. This decrease in bond angles allows for the bonds to bend less when closing the sphere or tube, and thus, the molecule becomes more stable.

Figure.2.2.1: A buckyball

The most common buckyballs contains 60 carbon atoms, and is sometimes referred to as C_{60}. Other sizes of buckyballs extend to 20 carbon atoms to more than 100 carbon atoms.

Versatility of carbon-carbon-based nanomaterials nanotechnology is particularly useful. Carbon atoms are very strong covalent bond, because it forms a bond to atom electrons to share with each other, this might.

In fact, the world's most popular bling, diamond, is one of the toughest materials known and is made up entirely of carbon atoms. In a diamond, each carbon atom is covalently bonded to four other carbon atoms in a three-dimensional lattice that makes it very strong indeed.

Figure.2.2.2: Each carbon atom bonds to four other carbon atoms to form a diamond.

They result in the formation of many other materials, and in that they can form a number of other types of covalent bonds of atoms, carbon atoms, also are very versatile. Molecules that

constitute our range of materials of the cells of the body from the timber and are composed of carbon atoms bonded to other types of atoms provide different properties to the molecule covalently attached. Covalent bonds between carbon atoms, the buckyball is very strong, the carbon atoms are readily form various covalent bonds with other atoms. Buckyballs are used in composite materials in order to strengthen the material.

Buckyballs have the interesting electrical property of being very good electron acceptors, which means they accept loose electrons from other materials. This feature is useful, for example, in increasing the efficiency of solar cells in transforming sunlight into electricity.

2.3 Properties

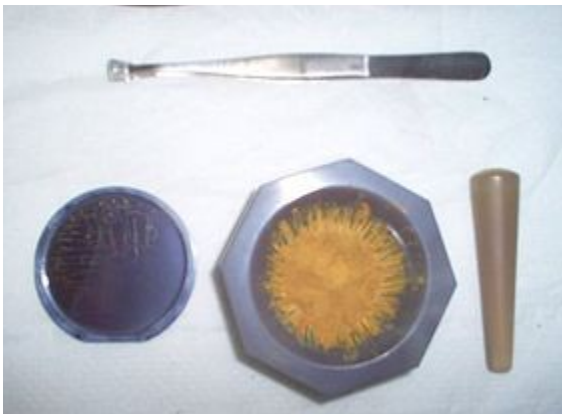


Figure.2.3.1: Silicon Powder

1 kg of particles of 1 mm^3 has the same surface area as 1 mg of particles of 1 nm^3

Nanoparticles are of great scientific interest as they are, in effect, a bridge between bulk materials and atomic or molecular structures. A bulk material should have constant physical properties regardless of its size, but at the nano-scale size-dependent properties are often observed. Thus, the properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant. For bulk materials larger than one micrometer (or micron), the percentage of atoms at the surface is insignificant in relation to the number of atoms in the bulk of the material. The interesting and sometimes unexpected properties of nanoparticles are therefore largely due to the large surface area of the material, which dominates the contributions made by the small bulk of the material.

Nanoparticles often possess unexpected optical properties as they are small enough to confine their electrons and produce quantum effects.[19] For example gold nanoparticles appear deep-red to black in solution. Nanoparticles of yellow gold and grey silicon are red in color. Gold nanoparticles melt at much lower temperatures (~300 °C for 2.5 nm size) than the gold slabs (1064 °C).[20] Absorption of solar radiation is much higher in materials composed of nanoparticles than it is in thin films of continuous sheets of material. In both solar PV and solar thermal applications, controlling the size, shape, and material of the particles, it is possible to control solar absorption. Other size-dependent property changes include quantum confinement in semiconductor particles, surface Plasmon resonance in some metal particles and super Para magnetism in magnetic materials.[20] What would appear ironic is that the changes in physical properties are not always desirable. Ferromagnetic materials smaller than 10 nm can switch their magnetization direction using room temperature thermal energy, thus making them unsuitable for memory storage.[21] Suspensions of nanoparticles are possible since the interaction of the particle surface with the solvent is strong enough to overcome density differences, which otherwise usually result in a material either sinking or floating in a liquid. The high surface area to volume ratio of nanoparticles provides a tremendous driving force for diffusion, especially at elevated temperatures. Sintering can take place at lower temperatures, over shorter time scales than for larger particles. In theory, this does not affect the density of the final product, though flow difficulties and the tendency of nanoparticles to agglomerate complicates matters. Moreover, nanoparticles have been found to impart some extra properties to various day to day products. For example, the presence of titanium dioxide nanoparticles imparts what we call the self-cleaning effect, and, the size

being nano-range, the particles cannot be observed. Zinc oxide particles have been found to have superior UV blocking properties compared to its bulk substitute. This is one of the reasons why it is often used in the preparation of sunscreen lotions, and is completely photostable.[22] Clay nanoparticles when incorporated into polymer matrices increase reinforcement, leading to stronger plastics, verifiable by a higher glass transition temperature and other mechanical property tests. These nanoparticles are hard, and impart their properties to the polymer (plastic). Nanoparticles have also been attached to textile fibers in order to create smart and functional clothing. Metal, dielectric, and semiconductor nanoparticles have been formed, as well as hybrid structures (e.g., core–shell nanoparticles).[23] Nanoparticles made of semiconducting material may also be labeled quantum dots if they are small enough (typically sub 10 nm) that quantization of electronic energy levels occurs. Such nanoscale particles are used in biomedical applications as drug carriers or imaging agents.

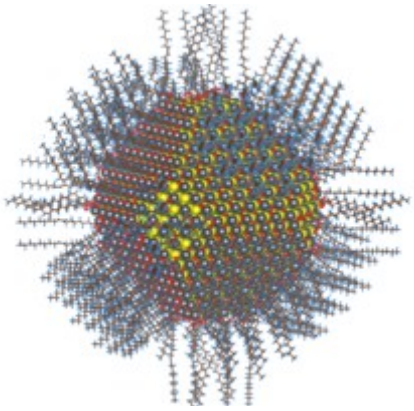


Figure.2.3.2: Semiconductor nanoparticle (quantum dot) of lead sulfide with complete passivation by oleic acid, oleyl and hydroxyl (size ~5nm)

Semi-solid and soft nanoparticles have been manufactured. A prototype nanoparticle of semi-solid nature is the liposome. Various types of liposome nanoparticles are currently used clinically as delivery systems for anticancer drugs and vaccines.

Nanoparticles with one half hydrophilic and the other half hydrophobic are termed Janus and are particularly effective for stabilizing emulsions. They can self-assemble at water/oil interfaces and act as solid surfactants.

2.4 Synthesis

There are several methods for creating nanoparticles, including attrition, pyrolysis and hydrothermal synthesis.

In attrition, macro- or micro-scale particles are ground in a ball mill, a planetary ball mill, or other size-reducing mechanism. The resulting particles are air classified to recover nanoparticles.

In pyrolysis, a vaporous precursor (liquid or gas) is forced through an orifice at high pressure and burned. The resulting solid (a version of soot) is air classified to recover oxide particles from by-product gases. Traditional pyrolysis often results in aggregates and agglomerates rather than single primary particles. Ultrasonic nozzle spray pyrolysis (USP) on the other hand aids in preventing agglomerates from forming.

A thermal plasma can also deliver the energy necessary to cause vaporization of small micrometer-size particles. The thermal plasma temperatures are in the order of 10,000 K, so that solid powder easily evaporates. Nanoparticles are formed upon cooling while exiting the plasma region. The main types of the thermal plasma torches used to produce nanoparticles are dc plasma jet, dc arc plasma, and radio frequency (RF) induction plasmas. In the arc plasma reactors, the energy necessary for evaporation and reaction is provided by an electric arc formed between the anode and the cathode. For example, silica sand can be vaporized with an arc plasma at atmospheric pressure. The resulting mixture of plasma gas and silica vapor can be rapidly cooled by quenching with oxygen, thus ensuring the quality of the fumed silica produced.

In RF induction plasma torches, energy coupling to the plasma is accomplished through the electromagnetic field generated by the induction coil. The plasma gas does not come in contact with electrodes, thus eliminating possible sources of contamination and allowing the operation of such plasma torches with a wide range of gases including inert, reducing, oxidizing, and other corrosive atmospheres. The working frequency is typically between 200 kHz and 40 MHz Laboratory units run at power levels in the order of 30–50 kW, whereas the large-scale industrial units have been tested at power levels up to 1 MW. As the residence time of the injected feed droplets in the plasma is very short, it is important that the droplet sizes are small enough in order to obtain complete evaporation. The RF plasma method has been used to synthesize different nanoparticle materials, for example synthesis of various ceramic nanoparticles such as oxides, carbours/carbides, and nitrides of Ti and Si.

Inert-gas condensation is frequently used to make nanoparticles from metals with low melting points. The metal is vaporized in a vacuum chamber and then super cooled with an inert gas stream. The super cooled metal vapor condenses into nanometer-size particles, which can be entrained in the inert gas stream and deposited on a substrate or studied in situ.

Nanoparticles can also be formed using radiation chemistry. Radiolysis from gamma rays can create strongly active free radicals in solution. This relatively simple technique uses a minimum number of chemicals. These including water, a soluble metallic salt, a radical scavenger (often a secondary alcohol), and a surfactant (organic capping agent). High gamma doses on the order of 10^4 Gray are required. In this process, reducing radicals will drop metallic ions down to the zero-valence state. A scavenger chemical will preferentially interact with oxidizing radicals to prevent the re-oxidation of the metal. Once in the zero-valence state, metal atoms begin to coalesce into particles. A chemical surfactant surrounds the particle during formation and regulates its growth. In sufficient concentrations, the surfactant molecules stay attached to the particle. This prevents it from dissociating or forming clusters with other particles. Formation of nanoparticles using the radiolysis method allows for tailoring of particle size and shape by adjusting precursor concentrations and gamma dose.[24]

2.4.1 Sol-gel

The sol-gel process is a wet-chemical technique (also known as chemical solution deposition) widely used recently in the fields of materials science and ceramic engineering. Such methods are used primarily for the fabrication of materials (typically a metal oxide) starting from a chemical solution (*sol*, short for solution), which acts as the precursor for an integrated network (or *gel*) of either discrete particles or network polymers. [25]

Typical precursors are metal alkoxides and metal chlorides, which undergo hydrolysis and poly-condensation reactions to form either a network "elastic solid" or a colloidal suspension (or dispersion) – a system composed of discrete (often amorphous) sub micrometer particles dispersed to various degrees in a host fluid. Formation of a metal oxide involves connecting the metal centers with oxo (M-O-M) or hydroxo (M-OH-M) bridges, therefore generating metal-oxo or metal-hydroxo polymers in solution. Thus, the sol evolves toward the formation of a gel-like diphasic system containing both a liquid phase and solid phase whose morphologies range from discrete particles to continuous polymer networks.[26]

In the case of the colloid, the volume fraction of particles (or particle density) may be so low that a significant amount of fluid may need to be removed initially for the gel-like properties to be recognized. This can be accomplished in a number of ways. The most simple method is to allow time for sedimentation to occur, and then pour off the remaining liquid. Centrifugation can also be used to accelerate the process of phase separation.

Removal of the remaining liquid (solvent) phase requires a drying process, which is typically accompanied by a significant amount of shrinkage and densification. The rate at which the solvent can be removed is ultimately determined by the distribution of porosity in the gel. The ultimate microstructure of the final component will clearly be strongly influenced by changes implemented during this phase of processing. Afterward, a thermal treatment, or firing process, is often necessary in order to favor further poly condensation and enhance mechanical properties and structural stability via final sintering, densification, and grain growth. One of the distinct advantages of using this methodology as opposed to the more traditional processing techniques is that densification is often achieved at a much lower temperature. The precursor sol can be either deposited on a substrate to form a film (e.g.by dip-coating or spin-coating), cast into a suitable container with the desired shape (e.g. to obtain a monolithic ceramics, glasses, fibers, membranes, aerogels) or used to synthesize powders (e.g., microspheres, nanospheres). The sol-gel approach is a cheap and low-temperature technique that allows for the fine control of the product's chemical composition. Even small quantities of dopants, such as organic dyes and rare earth metals, can be introduced in the sol and end up uniformly dispersed in the final product. It can be used in ceramics processing and manufacturing as an investment casting material, or as a means of producing very thin films of metal oxides for various purposes. Sol-gel derived materials have diverse applications in optics, electronics, energy, space, (bio) sensors, medicine (e.g., controlled drug release) and separation (e.g., chromatography) technology.[27, 28]

2.5 Morphology

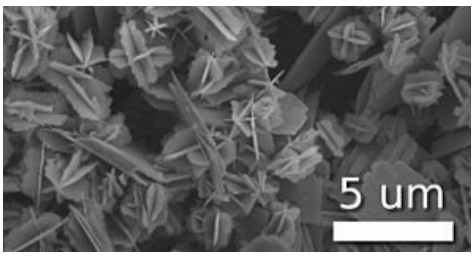


Figure.2.5: Nano stars of vanadium (IV) oxide

Scientists have taken to naming their particles after the real-world shapes that they might represent. Nanospheres, nanoreefs, nanoboxes and more have appeared in the literature. These morphologies sometimes arise spontaneously as an effect of a templating or directing agent present in the synthesis such as miscellar emulsions or anodized alumina pores, or from the innate crystallographic growth patterns of the materials themselves.[29] Some of these morphologies may serve a purpose, such as long carbon nanotubes used to bridge an electrical junction, or just a scientific curiosity like the stars shown at right.

Amorphous particles usually adopt a spherical shape (due to their microstructural isotropy), whereas the shape of anisotropic microcrystalline whiskers corresponds to their particular crystal habit. At the small end of the size range, nanoparticles are often referred to as clusters. Spheres, rods, fibers, and cups are just a few of the shapes that have been grown. The study of fine particles is called micromeritics.

2.6 Functionalization

The surface coating of nanoparticles is crucial to determining their properties. In particular, the surface coating can regulate stability, solubility, and targeting. A coating that is multivalent or polymeric confers high stability. Functionalized nanomaterial-based catalysts can be used for catalysis of many known organic reactions.

2.7 Surface Coating for Biological Applications

For biological applications, the surface coating should be polar to give high aqueous solubility and prevent nanoparticle aggregation. In serum or on the cell surface, highly charged coatings promote non-specific binding, whereas polyethylene glycol linked to terminal hydroxyl or methoxy groups repel non-specific interactions.[30, 31] Nanoparticles can be linked to biological molecules that can act as address tags, to direct the nanoparticles to specific sites within the body, specific organelles within the cell, or to follow specifically the movement of individual

protein or RNA molecules in living cells.[32] Common address tags are monoclonal antibodies, aptamers, streptavidin or peptides. These targeting agents should ideally be covalently linked to the nanoparticle and should be present in a controlled number per nanoparticle. Multivalent nanoparticles, bearing multiple targeting groups, can cluster receptors, which can activate cellular signaling pathways, and give stronger anchoring. Monovalent nanoparticles, bearing a single binding site, avoid clustering and so are preferable for tracking the behavior of individual proteins.

3.0 Nanotechnology

Nanotechnology ("nanotech") is the manipulation of matter on an atomic, molecular, and supra molecular scale. The earliest, widespread description of nanotechnology referred to the particular technological goal of precisely manipulating atoms and molecules for fabrication of macroscale products, also now referred to as molecular nanotechnology. A more generalized description of nanotechnology was subsequently established by the National Nanotechnology Initiative, which defines nanotechnology as the manipulation of matter with at least one dimension sized from 1 to 100 nanometers. This definition reflects the fact that quantum mechanical effects are important at this quantum-realm scale, and so the definition shifted from a particular technological goal to a research category inclusive of all types of research and technologies that deal with the special properties of matter that occur below the given size threshold. It is therefore common to see the plural form "nanotechnologies" as well as "nanoscale technologies" to refer to the broad range of research and applications whose common trait is size. Because of the variety of potential applications (including industrial and military), governments have invested billions of dollars in nanotechnology research. Through its National Nanotechnology Initiative, the USA has invested 3.7 billion dollars. The European Union has invested 1.2 billion and Japan 750 million dollars.

Nanotechnology as defined by size is naturally very broad, including fields of science as diverse as surface science, organic chemistry, biology, semiconductor, micro fabrication, etc.[33] The associated research and applications are equally diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale to direct control of matter on the atomic scale.

Scientists currently debate the future implications of nanotechnology. Nanotechnology may be able to create many new materials and devices with a vast range of applications, such as in medicine, electronics, biomaterials and energy production. On the other hand, nanotechnology raises many of the same issues as any new technology, including concerns about the toxicity and environmental impact of nanomaterials,[34] and their potential effects on global economics, as well as speculation about various doomsday scenarios. These concerns have led to a debate among advocacy groups and governments on whether special regulation of nanotechnology is warranted.

3.0.1 The Meaning of Nanotechnology

When K. Eric Drexler (right) popularized the word 'nanotechnology' in the 1980's, he was talking about building machines on the scale of molecules, a few nanometers wide—motors, robot arms, and even whole computers, far smaller than a cell. Drexler spent the next ten years describing and analyzing these incredible devices, and responding to accusations of science fiction. Meanwhile, mundane technology was developing the ability to build simple structures on a molecular scale. As nanotechnology became an accepted concept, the meaning of the word shifted to encompass the simpler kinds of nanometer-scale technology. The U.S. National Nanotechnology Initiative was created to fund this kind of nanotech: their definition includes anything smaller than 100 nanometers with novel properties.

Much of the work being done today that carries the name 'nanotechnology' is not nanotechnology in the original meaning of the word. Nanotechnology, in its traditional sense, means building things from the bottom up, with atomic precision. This theoretical capability was envisioned as early as 1959 by the renowned physicist Richard Feynman.

“I want to build a billion tiny factories, models of each other, which are manufacturing simultaneously. The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom. It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big”. Richard Feynman

Based on Feynman's vision of miniature factories using nanomachines to build complex products, advanced nanotechnology (sometimes referred to as molecular manufacturing) will make use of positionally-controlled mechanochemistry guided by molecular machine systems. Formulating a roadmap for development of this kind of nanotechnology is now an objective of a broadly based technology roadmap project led by Battelle (the manager of several U.S. National Laboratories) and the Foresight Nanotech Institute.

Shortly after this envisioned molecular machinery is created, it will result in a manufacturing revolution, probably causing severe disruption. It also has serious economic, social, environmental, and military implications.

3.1 History of Nanotechnology

The concepts that seeded nanotechnology were first discussed in 1959 by renowned physicist Richard Feynman in his talk There's Plenty of Room at the Bottom, in which he described the possibility of synthesis via direct manipulation of atoms. The term "nano-technology" was first used by Norio Taniguchi in 1974, though it was not widely known.

Inspired by Feynman's concepts, K. Eric Drexler used the term "nanotechnology" in his 1986 book Engines of Creation: The Coming Era of Nanotechnology, which proposed the idea of a nanoscale "assembler" which would be able to build a copy of itself and of other items of arbitrary complexity with atomic control. Also in 1986, Drexler co-founded The Foresight Institute (with which he is no longer affiliated) to help increase public awareness and understanding of nanotechnology concepts and implications.

Thus, emergence of nanotechnology as a field in the 1980s occurred through convergence of Drexler's theoretical and public work, which developed and popularized a conceptual framework for nanotechnology, and high-visibility experimental advances that drew additional wide-scale attention to the prospects of atomic control of matter. In 1980s two major breakthroughs incepted the growth of nanotechnology in modern era.

First, the invention of the scanning tunneling microscope in 1981 which provided unprecedented visualization of individual atoms and bonds, and was successfully used to manipulate individual atoms in 1989. The microscope's developers Gerd Binnig and Heinrich Rohrer at IBM Zurich Research Laboratory received a Nobel Prize in Physics in 1986.[35] Binnig, Quateand Gerber also invented the analogous atomic force microscope that year.

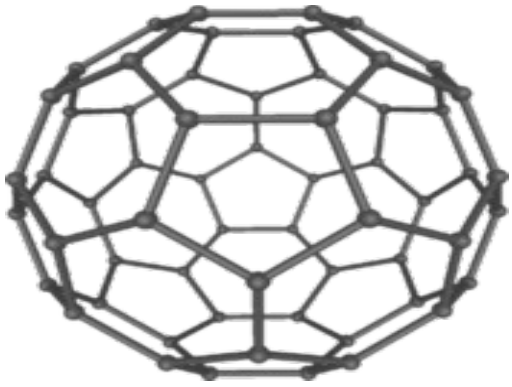


Figure.3.1: Buckyball

Buckminster fullerene C_{60}, also known as the buckyball, is a representative member of the carbon structures known as fullerenes. Members of the fullerene family are a major subject of research falling under the nanotechnology umbrella.

Second, Fullerenes were discovered in 1985 by Harry Kroto, Richard Smalley, and Robert Curl, who together won the 1996 Nobel Prize in Chemistry. C_{60} was not initially described as nanotechnology; the term was used regarding subsequent work with related graphene tubes (called carbon nanotubes and sometimes called Bucky tubes) which suggested potential applications for nanoscale electronics and devices.

In the early 2000s, the field garnered increased scientific, political, and commercial attention that led to both controversy and progress. Controversies emerged regarding the definitions and potential implications of nanotechnologies, exemplified by the Royal Society's report on nanotechnology. Challenges were raised regarding the feasibility of applications envisioned by advocates of molecular nanotechnology, which culminated in a public debate between Drexler and Smalley in 2001 and 2003.

Meanwhile, commercialization of products based on advancements in nanoscale technologies began emerging. These products are limited to bulk applications of nanomaterials and do not involve atomic control of matter. Some examples include the Silver Nano platform for using silver nanoparticles as an antibacterial agent, nanoparticle-based transparent sunscreens, and carbon nanotubes for stain-resistant textiles.[36]

Governments moved to promote and fund research into nanotechnology, beginning in the U.S. with the National Nanotechnology Initiative, which formalized a size-based definition of nanotechnology and established funding for research on the nanoscale.

By the mid-2000s new and serious scientific attention began to flourish. Projects emerged to produce nanotechnology roadmaps which center on atomically precise manipulation of matter and discuss existing and projected capabilities, goals, and applications.

3.2 Four Generations

Mihail (Mike) Roco of the U.S. National Nanotechnology Initiative has described four generations of nanotechnology development (see chart below). The current era, as Roco depicts

it, is that of passive nanostructures, materials designed to perform one task. The second phase, which we are just entering, introduces active nanostructures for multitasking; for example, actuators, drug delivery devices, and sensors. The third generation is expected to begin emerging around 2010 and will feature nanosystems with thousands of interacting components. A few years after that, the first integrated nanosystems, functioning much like a mammalian cell with hierarchical systems within systems, are expected to be developed.

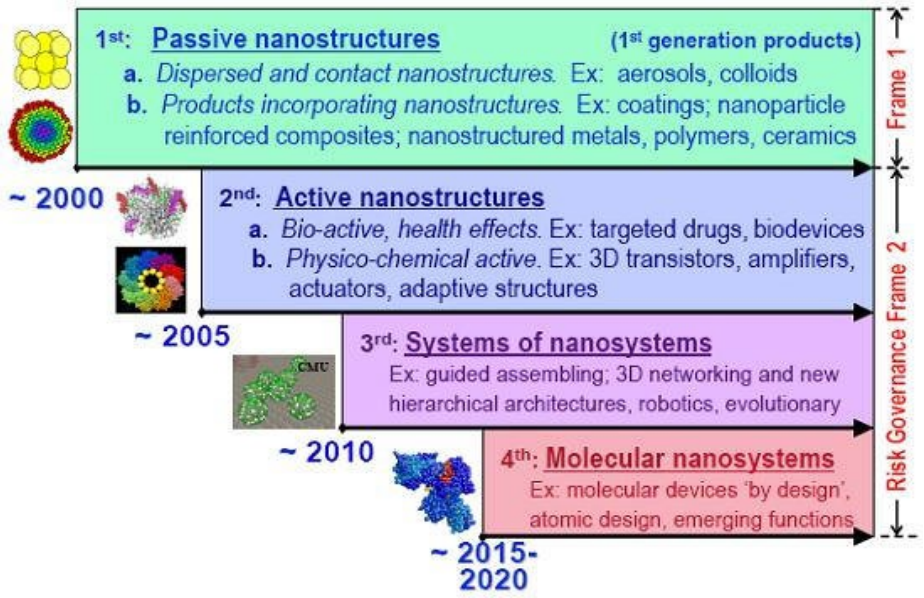


Figure.3.2: Four Generation of Nanotechnology

Some experts may still insist that nanotechnology can refer to measurement or visualization at the scale of 1-100 nanometers, but a consensus seems to be forming around the idea that control and restructuring of matter at the nanoscale is a necessary element.

3.3 General-Purpose Technology

Nanotechnology is sometimes referred to as a general-purpose technology. That's because in its advanced form it will have significant impact on almost all industries and all areas of society. It will offer better built, longer lasting, cleaner, safer, and smarter products for the home, for communications, for medicine, for transportation, for agriculture, and for industry in general.

Imagine a medical device that travels through the human body to seek out and destroy small clusters of cancerous cells before they can spread or a box no larger than a sugar cube that contains the entire contents of the Library of Congress or materials much lighter than steel that possess ten times as much strength. — U.S. National Science Foundation

3.3.1 Dual-Use Technology

Like electricity or computers before it, nanotech will offer greatly improved efficiency in almost every facet of life. But as a general-purpose technology, it will be dual-use, meaning it will have many commercial uses and it also will have many military uses—making far more powerful weapons and tools of surveillance. Thus it represents not only wonderful benefits for humanity, but also grave risks. A key understanding of nanotechnology is that it offers not just better products, but a vastly improved manufacturing process. A computer can make copies of data files essentially as many copies as you want at little or no cost. It may be only a matter of time until the building of products becomes as cheap as the copying of files. That's the real meaning of nanotechnology, and why it is sometimes seen as "the next industrial revolution."

"My own judgment is that the nanotechnology revolution has the potential to change America on a scale equal to, if not greater than, the computer revolution." — U.S. Senator Ron Wyden

The power of nanotechnology can be encapsulated in an apparently simple device called a personal nanofactory that may sit on your countertop or desktop. Packed with miniature chemical processors, computing, and robotics, it will produce a wide-range of items quickly, cleanly, and inexpensively, building products directly from blueprints.

Figure.3.3.1: Exponential Proliferation

Nanotechnology not only will allow making many high-quality products at very low cost, but it will allow making new nanofactories at the same low cost and at the same rapid speed. This unique (outside of biology that is) ability to reproduce its own means of production is why nanotech is said to be an exponential technology. It represents a manufacturing system that will be able to make more manufacturing systems—factories that can build factories—rapidly, cheaply, and cleanly. The means of production will be able to reproduce exponentially, so in just a few weeks a few nanofactories conceivably could become billions. It is a revolutionary, transformative, powerful, and potentially very dangerous—or beneficial—technology. How soon will all this come about? Conservative estimates usually say 20 to 30 years from now, or even much later than that. This is because of the rapid progress being made in enabling technologies, such as optics, nanolithography, mechanochemistry and 3D prototyping. If it does arrive that soon, we may not be adequately prepared, and the consequences could be severe. We believe it's not too early to begin asking some tough questions and facing the issues:

- Who will own the technology?
- Will it be heavily restricted, or widely available?
- What will it do to the gap between rich and poor?
- How can dangerous weapons be controlled, and perilous arms races be prevented?

Many of these questions were first raised over a decade ago, and have not yet been answered. If the questions are not answered with deliberation, answers will evolve independently and will take us by surprise; the surprise is likely to be unpleasant. It is difficult to say for sure how soon this technology will mature, partly because it's possible (especially in countries that do not have open societies) that clandestine military or industrial development programs have been going on for years without our knowledge. We cannot say with certainty that full-scale nanotechnology will not be developed with the next ten years, or even five years. It may take longer than that, but prudence—and possibly our survival—demands that we prepare now for the earliest plausible development scenario.

3.4 Fundamental Concepts

Nanotechnology is the engineering of functional systems at the molecular scale. This covers both current work and concepts that are more advanced. In its original sense, nanotechnology refers to the projected ability to construct items from the bottom up, using techniques and tools being developed today to make complete, high performance products.

One nanometer (nm) is one billionth, or 10^{-9}, of a meter. By comparison, typical carbon-carbon bond lengths, or the spacing between these atoms in a molecule, are in the range 0.12–0.15 nm, and a DNA double-helix has a diameter around 2 nm. On the other hand, the smallest cellular life-forms, the bacteria of the genus Mycoplasma, are around 200 nm in length. By convention, nanotechnology is taken as the scale range 1 to 100 nm following the definition used by the National Nanotechnology Initiative in the US. The lower limit is set by the size of atoms (hydrogen has the smallest atoms, which are approximately a quarter of a nm diameter) since nanotechnology must build its devices from atoms and molecules. The upper limit is more or less arbitrary but is around the size that phenomena not observed in larger structures start to become apparent and can be made use of in the nano device.[37] These new phenomena make nanotechnology distinct from devices which are merely miniaturized versions of an equivalent macroscopic device; such devices are on a larger scale and come under the description of micro technology.[38]

To put that scale in another context, the comparative size of a nanometer to a meter is the same as that of a marble to the size of the earth. Or another way of putting it: a nanometer is the amount an average man's beard grows in the time it takes him to raise the razor to his face.

Two main approaches are used in nanotechnology. In the "bottom-up" approach, materials and devices are built from molecular components which assemble themselves chemically by principles of molecular recognition. In the "top-down" approach, nano-objects are constructed from larger entities without atomic-level control.

3.4.1 Larger to smaller: a materials perspective

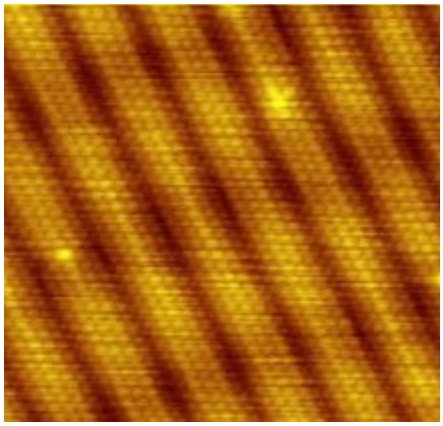


Figure3.4.1: Image of reconstruction on a clean Gold (100) surface, as visualized using scanning tunneling microscopy. The positions of the individual atoms composing the surface are visible.

Several phenomena become pronounced as the size of the system decreases. These include statistical mechanical effects, as well as quantum mechanical effects, for example the "quantum size effect" where the electronic properties of solids are altered with great reductions in particle size. This effect does not come into play by going from macro to micro dimensions. However, quantum effects can become significant when the nanometer size range is reached, typically at distances of 100 nanometers or less, the so-called quantum realm. Additionally, a number of physical (mechanical, electrical, optical, etc.) properties change when compared to macroscopic systems. One example is the increase in surface area to volume ratio altering mechanical, thermal and catalytic properties of materials. Diffusion and reactions at nanoscale, nanostructures materials and nanodevices with fast ion transport are generally referred to nanoionics. Mechanical properties of nanosystems are of interest in the nanomechanics research. The catalytic activity of nanomaterials also opens potential risks in their interaction with biomaterials.

Materials reduced to the nanoscale can show different properties compared to what they exhibit on a macroscale, enabling unique applications. For instance, opaque substances can become transparent (copper); stable materials can turn combustible (aluminum); insoluble materials may become soluble (gold). A material such as gold, which is chemically inert at normal scales, can serve as a potent chemical catalyst at nanoscales. Much of the fascination with nanotechnology stems from these quantum and surface phenomena that matter exhibits at the nanoscale.[39]

3.4.2 Simple to complex: a molecular perspective

Modern synthetic chemistry has reached the point where it is possible to prepare small molecules to almost any structure. These methods are used today to manufacture a wide variety of useful chemicals such as pharmaceuticals or commercial polymers. This ability raises the question of extending this kind of control to the next-larger level, seeking methods to assemble these single molecules into supramolecular assemblies consisting of many molecules arranged in a well defined manner.

These approaches utilize the concepts of molecular self-assembly and/or supramolecular chemistry to automatically arrange themselves into some useful conformation through a bottom-up approach. The concept of molecular recognition is especially important: molecules can be designed so that a specific configuration or arrangement is favored due to non-covalent intermolecular forces. The Watson–Crick base pairing rules are a direct result of this, as is the specificity of an enzyme being targeted to a single substrate, or the specific folding of the protein itself. Thus, two or more components can be designed to be complementary and mutually attractive so that they make a more complex and useful whole.

Such bottom-up approaches should be capable of producing devices in parallel and be much cheaper than top-down methods, but could potentially be overwhelmed as the size and complexity of the desired assembly increases. Most useful structures require complex and thermodynamically unlikely arrangements of atoms. Nevertheless, there are many examples of self-assembly based on molecular recognition in biology, most notably Watson–Crick base pairing and enzyme-substrate interactions. The challenge for nanotechnology is whether these principles can be used to engineer new constructs in addition to natural ones.

3.4.3 Molecular Nanotechnology: a long-term view

Molecular nanotechnology, sometimes called molecular manufacturing, describes engineered nanosystems (nanoscale machines) operating on the molecular scale. Molecular nanotechnology is especially associated with the molecular assembler, a machine that can produce a desired structure or device atom-by-atom using the principles of mechano-synthesis. Manufacturing in the context of productive nanosystems is not related to, and should be clearly distinguished from, the conventional technologies used to manufacture nanomaterials such as carbon nanotubes and nanoparticles.

When the term "nanotechnology" was independently coined and popularized by Eric Drexler (who at the time was unaware of an earlier usage by Norio Taniguchi) it referred to a future manufacturing technology based on molecular machine systems. The premise was that molecular scale biological analogies of traditional machine components demonstrated molecular machines were possible: by the countless examples found in biology, it is known that sophisticated, stochastically optimized biological machines can be produced.

It is hoped that developments in nanotechnology will make possible their construction by some other means, perhaps using biomimetic principles. However, Drexler and other researchers[40] have proposed that advanced nanotechnology, although perhaps initially implemented by biomimetic means, ultimately could be based on mechanical engineering principles, namely, a manufacturing technology based on the mechanical functionality of these components (such as gears, bearings, motors, and structural members) that would enable programmable, positional assembly to atomic specification. The physics and engineering performance of exemplar designs were analyzed in Drexler's book Nanosystems.

In general it is very difficult to assemble devices on the atomic scale, as one has to position atoms on other atoms of comparable size and stickiness. Another view, put forth by Carlo Montemagno, is that future nanosystems will be hybrids of silicon technology and biological molecular machines. Richard Smalley argued that mechanosynthesis are impossible due to the difficulties in mechanically manipulating individual molecules.

This led to an exchange of letters in the ACS publication Chemical & Engineering News in 2003. Though biology clearly demonstrates that molecular machine systems are possible, non-biological molecular machines are today only in their infancy. Leaders in research on non-biological molecular machines are Dr. Alex Zettl and his colleagues at Lawrence Berkeley Laboratories and UC Berkeley. They have constructed at least three distinct molecular devices whose motion is controlled from the desktop with changing voltage: a nanotube nanomotor, a molecular actuator,[41] and a nanoelectromechanical relaxation oscillator. See nanotube nanomotor for more examples.

An experiment indicating that positional molecular assembly is possible was performed by Ho and Lee at Cornell University in 1999. They used a scanning tunneling microscope to move an

individual carbon monoxide molecule (CO) to an individual iron atom (Fe) sitting on a flat silver crystal, and chemically bound the CO to the Fe by applying a voltage.

3.5 Current Research

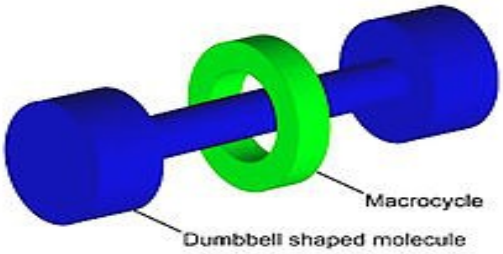


Figure.3.5.1: Graphical representation of arotaxane, useful as a molecular switch.

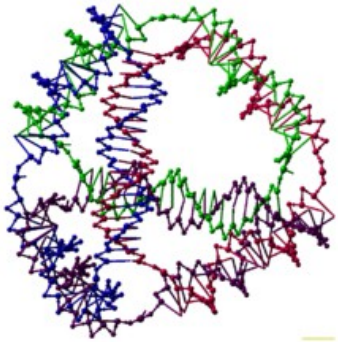


Figure.3.5.2: Nanostructure of DNA Tetrahedron

This DNA tetrahedron is an artificially designed nanostructure of the type made in the field of DNA nanotechnology. Each edge of the tetrahedron is a 20 base pair DNA double helix, and each vertex is a three-arm junction.

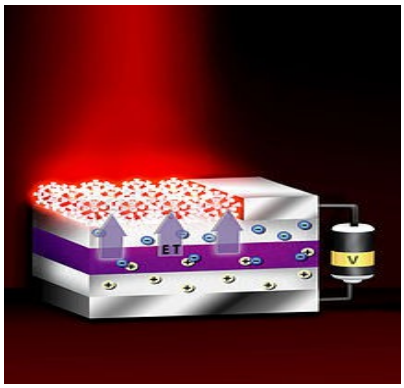


Figure.3.5.3: Nano Device of Energy Transfer

This device transfers energy from nano-thin layers of quantum wells to nanocrystals above them, causing the nanocrystals to emit visible light.

The nanomaterials field includes subfields which develop or study materials having unique properties arising from their nanoscale dimensions.[42]

- Interface and colloid science has given rise to many materials which may be useful in nanotechnology, such as carbon nanotubes and other fullerenes, and various nanoparticles and nanorods. Nanomaterials with fast ion transport are related also to nanoionics and nanoelectronics.

- Nanoscale materials can also be used for bulk applications; most present commercial applications of nanotechnology are of this flavor.

- Progress has been made in using these materials for medical applications.

- Nanoscale materials such as nanopillars are sometimes used in solar cells which combats the cost of traditional Silicon solar cells.

- Development of applications incorporating semiconductor nanoparticles to be used in the next generation of products, such as display technology, lighting, solar cells and biological imaging; see quantum dots.

3.5.1 Bottom-up Approaches

These seek to arrange smaller components into more complex assemblies.

- DNA nanotechnology utilizes the specificity of Watson–Crick base pairing to construct well-defined structures out of DNA and other nucleic acids.

- Approaches from the field of "classical" chemical synthesis (inorganic and organic synthesis) also aim at designing molecules with well-defined shape (e.g. bis-peptides).

- More generally, molecular self-assembly seeks to use concepts of supramolecular chemistry, and molecular recognition in particular, to cause single-molecule components to automatically arrange themselves into some useful conformation.

- Atomic force microscope tips can be used as a nanoscale "write head" to deposit a chemical upon a surface in a desired pattern in a process called dip pen nanolithography. This technique fits into the larger subfield of nanolithography.

3.5.2 Top-Down Approaches

These seek to create smaller devices by using larger ones to direct their assembly.

- Many technologies that descended from conventional solid-state silicon methods for fabricating microprocessors are now capable of creating features smaller than 100 nm, falling under the definition of nanotechnology. Giant magneto-resistance-based hard drives already on the market fit this description,[43] as do atomic layer deposition (ALD) techniques. Peter Grünbergand Albert Fert received the Nobel Prize in Physics in 2007 for their discovery of Giant magneto-resistance and contributions to the field of spintronics.

- Solid-state techniques can also be used to create devices known as nanoelectromechanical systems or NEMS, which are related to micro electromechanical systems or MEMS.

- Focused ion beams can directly remove material, or even deposit material when suitable precursor gasses are applied at the same time. For example, this technique is used routinely to create sub-100 nm sections of material for analysis in Transmission electron microscopy.

- Atomic force microscope tips can be used as a nanoscale "write head" to deposit a resist, which is then followed by an etching process to remove material in a top-down method.

3.5.3 Functional Approaches

These seek to develop components of a desired functionality without regard to how they might be assembled.

- Molecular scale electronics seeks to develop molecules with useful electronic properties. These could then be used as single-molecule components in a nanoelectronic device.

- Synthetic chemical methods can also be used to create synthetic molecular motors, such as in a so-called nanocar.

3.5.4 Biomimetic Approaches

- Bionics or biomimicry seeks to apply biological methods and systems found in nature, to the study and design of engineering systems and modern technology. Biomineralization is one example of the systems studied.

- Bio-nanotechnology is the use of biomolecules for applications in nanotechnology, including use of viruses and lipid assemblies.[44] Nanocellulose is a potential bulk-scale application.

3.5.5 Speculative

These subfields seek to anticipate what inventions nanotechnology might yield, or attempt to propose an agenda along which inquiry might progress. These often take a big-picture view of nanotechnology, with more emphasis on its societal implications than the details of how such inventions could actually be created.

- Molecular nanotechnology is a proposed approach which involves manipulating single molecules in finely controlled, deterministic ways. This is more theoretical than the other subfields, and many of its proposed techniques are beyond current capabilities.

- Nanorobotics centers on self-sufficient machines of some functionality operating at the nanoscale. There are hopes for applying nanorobots in medicine,[45, 46, 47] but it may not be easy to do such a thing because of several drawbacks of such devices. Nevertheless, progress on innovative materials and methodologies has been demonstrated with some patents granted about new nanomanufacturing devices for future commercial applications, which also progressively helps in the development towards nanorobots with the use of embedded nanobioelectronics concepts.

- Productive nanosystems are "systems of nanosystems" which will be complex nanosystems that produce atomically precise parts for other nanosystems, not necessarily using novel nanoscale-emergent properties, but well-understood fundamentals of

manufacturing. Because of the discrete (i.e. atomic) nature of matter and the possibility of exponential growth, this stage is seen as the basis of another industrial revolution. Mihail Roco, one of the architects of the USA's National Nanotechnology Initiative, has proposed four states of nanotechnology that seem to parallel the technical progress of the Industrial Revolution, progressing from passive nanostructures to active nanodevices to complex nanomachines and ultimately to productive nanosystems.

- Programmable matter seeks to design materials whose properties can be easily, reversibly and externally controlled though a fusion of information science and materials science.

- Due to the popularity and media exposure of the term nanotechnology, the words Pico technology and femto technology have been coined in analogy to it, although these are only used rarely and informally.

3.5.6 Tools and techniques

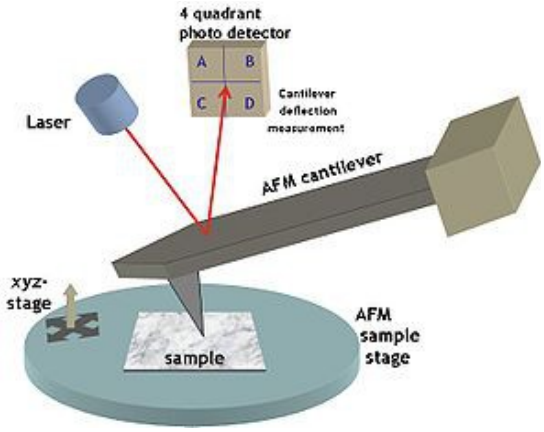


Fig.3.5.6: Typical Atomic Force Microscope (AFM) setup.

A microfabricated cantilever with a sharp tip is deflected by features on a sample surface, much like in a phonograph but on a much smaller scale. A laser beam reflects off the backside of the cantilever into a set of photo detectors, allowing the deflection to be measured and assembled into an image of the surface.

There are several important modern developments. The atomic force microscope (AFM) and the Scanning Tunneling Microscope (STM) are two early versions of scanning probes that

launched nanotechnology. There are other types of scanning probe microscopy. Although conceptually similar to the scanning confocal microscope developed byMarvin Minsky in 1961 and the scanning acoustic microscope (SAM) developed by Calvin Quate and coworkers in the 1970s, newer scanning probe microscopes have much higher resolution, since they are not limited by the wavelength of sound or light.

The tip of a scanning probe can also be used to manipulate nanostructures (a process called positional assembly). Feature-oriented scanning methodology suggested by Rostislav Lapshin appears to be a promising way to implement these nanomanipulations in automatic mode.[48, 49] However, this is still a slow process because of low scanning velocity of the microscope.

Various techniques of nanolithography such as optical lithography, X-ray lithography dip pen nanolithography, electron beam lithography or nanoimprint lithography were also developed. Lithography is a top-down fabrication technique where a bulk material is reduced in size to nanoscale pattern.

Another group of nanotechnological techniques include those used for fabrication of nanotubes and nanowires, those used in semiconductor fabrication such as deep ultraviolet lithography, electron beam lithography, focused ion beam machining, nanoimprint lithography, atomic layer deposition, and molecular vapor deposition, and further including molecular self-assembly techniques such as those employing di-block copolymers. The precursors of these techniques preceded the nanotech era, and are extensions in the development of scientific advancements rather than techniques which were devised with the sole purpose of creating nanotechnology and which were results of nanotechnology research.

The top-down approach anticipates nanodevices that must be built piece by piece in stages, much as manufactured items are made. Scanning probe microscopy is an important technique both for characterization and synthesis of nanomaterials. Atomic force microscopes and scanning tunneling microscopes can be used to look at surfaces and to move atoms around. By designing different tips for these microscopes, they can be used for carving out structures on surfaces and to help guide self-assembling structures. By using, for example, feature-oriented scanning approach, atoms or molecules can be moved around on a surface with scanning probe microscopy techniques. At present, it is expensive and time-consuming for mass production but very suitable for laboratory experimentation.

In contrast, bottom-up techniques build or grow larger structures atom by atom or molecule by molecule. These techniques include chemical synthesis, self-assembly and positional assembly. Dual polarization interferometry is one tool suitable for characterization of self-assembled thin films. Another variation of the bottom-up approach is molecular beam epitaxy or MBE. Researchers at Bell Telephone Laboratories like John R. Arthur. Alfred Y. Cho, and Art C. Gossard developed and implemented MBE as a research tool in the late 1960s and 1970s. Samples made by MBE were key to the discovery of the fractional quantum Hall effect for which the 1998 Nobel Prize in Physics was awarded. MBE allows scientists to lay down atomically precise layers of atoms and, in the process, build up complex structures. Important for research on semiconductors, MBE is also widely used to make samples and devices for the newly emerging field of spintronics.

However, new therapeutic products, based on responsive nanomaterials, such as the ultra-deformable, stress-sensitive Transfer some vesicles, are under development and already approved for human use in some countries.

3.6 Implications

An area of concern is the effect that industrial-scale manufacturing and use of nanomaterials would have on human health and the environment, as suggested by nanotoxicology research. For these reasons, some groups advocate that nanotechnology be regulated by governments. Others counter that overregulation would stifle scientific research and the development of beneficial innovations. Public health research agencies, such as the National Institute for Occupational Safety and Health are actively conducting research on potential health effects stemming from exposures to nanoparticles.

Some nanoparticle products may have unintended consequences. Researchers have discovered that bacteriostatic silver nanoparticles used in socks to reduce foot odor are being released in the wash. These particles are then flushed into the waste water stream and may destroy bacteria which are critical components of natural ecosystems, farms, and waste treatment processes.[50]

Public deliberations on risk perception in the US and UK carried out by the Center for Nanotechnology in Society found that participants were more positive about nanotechnologies for energy applications than for health applications, with health applications raising moral and ethical dilemmas such as cost and availability.

Experts, including director of the Woodrow Wilson Center's Project on Emerging Nanotechnologies David Rejeski, have testified that successful commercialization depends on adequate oversight, risk research strategy, and public engagement. Berkeley, California is currently the only city in the United States to regulate nanotechnology; Cambridge, Massachusetts in 2008 considered enacting a similar law, but ultimately rejected it. Relevant for both research on and application of nanotechnologies, the insurability of nanotechnology is contested. Without state regulation of nanotechnology, the availability of private insurance for potential damages is seen as necessary to ensure that burdens are not socialized implicitly.

3.7 Health and Environmental Concerns

Nanofibers are used in several areas and in different products, in everything from aircraft wings to tennis rackets. Inhaling airborne nanoparticles and nanofibers may lead to a number of pulmonary diseases, e.g. fibrosis. Researchers have found that when rats breathed in nanoparticles, the particles settled in the brain and lungs, which led to significant increases in biomarkers for inflammation and stress response and that nanoparticle induce skin aging through oxidative stress in hairless mice.[51, 52]

A two-year study at UCLA's School of Public Health found lab mice consuming nano-titanium dioxide showed DNA and chromosome damage to a degree "linked to all the big killers of man, namely cancer, heart disease, neurological disease and aging".[53]

A major study published more recently in Nature Nanotechnology suggests some forms of carbon nanotubes – a poster child for the "nanotechnology revolution" – could be as harmful as asbestos if inhaled in sufficient quantities. Anthony Seaton of the Institute of Occupational Medicine in Edinburgh, Scotland, who contributed to the article on carbon nanotubes said "We know that some of them probably have the potential to cause mesothelioma. So those sorts of materials need to be handled very carefully."[54] In the absence of specific regulation forthcoming from governments, Paull and Lyons (2008) have called for an exclusion of engineered nanoparticles in food. A newspaper article reports that workers in a paint factory developed serious lung disease and nanoparticles were found in their lungs.

3.8 Regulation

Calls for tighter regulation of nanotechnology have occurred alongside a growing debate related to the human health and safety risks of nanotechnology. There is significant debate about who is responsible for the regulation of nanotechnology. Some regulatory agencies currently cover some nanotechnology products and processes (to varying degrees) – by "bolting on" nanotechnology to existing regulations – there are clear gaps in these regimes. Davies (2008) has proposed a regulatory road map describing steps to deal with these shortcomings. Stakeholders concerned by the lack of a regulatory framework to assess and control risks associated with the release of nanoparticles and nanotubes have drawn parallels with bovine spongiform encephalopathy ("mad cow" disease),thalidomide, genetically modified food, nuclear energy, reproductive technologies, biotechnology, and asbestosis. Dr. Andrew Maynard, chief science advisor to the Woodrow Wilson Center's Project on Emerging Nanotechnologies, concludes that there is insufficient funding for human health and safety research, and as a result there is currently limited understanding of the human health and safety risks associated with nanotechnology. As a result, some academics have called for stricter application of the precautionary principle, with delayed marketing approval, enhanced labeling and additional safety data development requirements in relation to certain forms of nanotechnology.

4.0 Application of Nanotechnology

After more than 20 years of basic Nano science research and more than a decade of focused R&D under the NNI, applications of nanotechnology are delivering in both expected and unexpected ways on nanotechnology's promise to benefit society.

Nanotechnology is helping to considerably improve, even revolutionize, many technology and industry sectors: information technology, energy, environmental science, medicine, homeland security, food safety, and transportation, among many others. Described below is a sampling of the rapidly growing list of benefits and applications of nanotechnology.

Most benefits of nanotechnology depend on the fact that it is possible to tailor the essential structures of materials at the nanoscale to achieve specific properties, thus greatly extending the well-used toolkits of materials science. Using nanotechnology, materials can effectively be made to be stronger, lighter, more durable, more reactive, more sieve-like, or better electrical conductors, among many other traits. There already exist over 800 everyday commercial products that rely on nanoscale materials and processes:

- Nanoscale additives in polymer composite materials for baseball bats, tennis rackets, motorcycle helmets, automobile bumpers, luggage, and power tool housings can make them simultaneously lightweight, stiff, durable, and resilient.

- Nanoscale additives to or surface treatments of fabrics help them resist wrinkling, staining, and bacterial growth, and provide lightweight ballistic energy deflection in personal body armor.

- Nanoscale thin films on eyeglasses, computer and camera displays, windows, and other surfaces can make them water-repellent, antireflective, self-cleaning, resistant to ultraviolet or infrared light, antifog, antimicrobial, scratch-resistant, or electrically conductive.

- Nanoscale materials in cosmetic products provide greater clarity or coverage; cleansing; absorption; personalization; and antioxidant, anti-microbial, and other health properties in sunscreens, cleansers, complexion treatments, creams and lotions, shampoos, and specialized makeup.

- Nano-engineered materials in the food industry include nanocomposites in food containers to minimize carbon dioxide leakage out of carbonated beverages, or reduce oxygen inflow, moisture outflow, or the growth of bacteria in order to keep food fresher and safer, longer. Nanosensors built into plastic packaging can warn against spoiled food. Nanosensors are being developed to detect salmonella, pesticides, and other contaminates on food before packaging and distribution.

Figure.4.0: High-resolution image of a polymer-silicate nanocomposite.This material has improved thermal, mechanical, and barrier properties and can be used in food and beverage containers, fuel storage tanks for aircraft and automobiles, and in aerospace components. (Image courtesy of NASA.)

- Nano-engineered materials in automotive products include high-power rechargeable battery systems; thermoelectric materials for temperature control; lower-rolling-resistance tires; high-efficiency/low-cost sensors and electronics; thin-film smart solar panels; and fuel additives and improved catalytic converters for cleaner exhaust and extended range.

- Nano-engineered materials make superior household products such as degreasers and stain removers; environmental sensors, alert systems, air purifiers and filters; antibacterial cleansers; and specialized paints and sealing products.

- Nanostructured ceramic coatings exhibit much greater toughness than conventional wear-resistant coatings for machine parts. In 2000, the U.S. Navy qualified such a coating for use on gears of air-conditioning units for its ships, saving $20 million in maintenance

costs over 10 years. Such coatings can extend the lifetimes of moving parts in everything from power tools to industrial machinery.

- Nanoparticles are used increasingly in catalysis to boost chemical reactions. This reduces the quantity of catalytic materials necessary to produce desired results, saving money and reducing pollutants. Two big applications are in petroleum refining and in automotive catalytic converters.

4.1 Electronics and Information Technology Application

Nanotechnology is already in use in many computing, communications, and other electronics applications to provide faster, smaller, and more portable systems that can manage and store larger and larger amounts of information. These continuously evolving applications include:

- Nano scale transistors that are faster, more powerful, and increasingly energy-efficient; soon your computer's entire memory may be stored on a single tiny chip.

- Magnetic random access memory (MRAM) enabled by nanometer-scale magnetic tunnel junctions that can quickly and effectively save even encrypted data during a system shutdown or crash, enable resume-play features, and gather vehicle accident data.

- Displays for many new TVs, laptop computers, cell phones, digital cameras, and other devices incorporate nanostructured polymer films known as organic light-emitting diodes, or OLEDs. OLED screens offer brighter images in a flat format, as well as wider viewing angles, lighter weight, better picture density, lower power consumption, and longer lifetimes.

- Other computing and electronic products include Flash memory chips for iPod nano ultra-responsive hearing aids; antimicrobial/antibacterial coatings on mouse/keyboard/cell phone casings; conductive inks for printed electronics for RFID/smart cards/smart packaging; more life-like video games; and flexible displays for e-book readers.

4.2 Sustainable Energy Application

The difficulty of meeting the world's energy demand is compounded by the growing need to protect our environment. Many scientists are looking into ways to develop clean, affordable,

and renewable energy sources, along with means to reduce energy consumption and lessen toxicity burdens on the environment.

- Prototype solar panels incorporating nanotechnology are more efficient than standard designs in converting sunlight to electricity, promising inexpensive solar power in the future. Nanostructured solar cells already are cheaper to manufacture and easier to install, since they can use print-like manufacturing processes and can be made in flexible rolls rather than discrete panels. Newer research suggests that future solar converters might even be "paintable."

Figure.4.2: New solar panel films incorporate nanoparticles to create lightweight, flexible solar cells.

- Nanotechnology is improving the efficiency of fuel production from normal and low-grade raw petroleum materials through better catalysis, as well as fuel consumption efficiency in vehicles and power plants through higher-efficiency combustion and decreased friction.

- Nano-bioengineering of enzymes is aiming to enable conversion of cellulose into ethanol for fuel, from wood chips, corn stalks (not just the kernels, as today), unfertilized perennial grasses, etc.

- Nanotechnology is already being used in numerous new kinds of batteries that are less flammable, quicker-charging, more efficient, lighter weight, and that have a higher power density and hold electrical charge longer. One new lithium-ion battery type uses a common, nontoxic virus in an environmentally benign production process.

- Nanostructured materials are being pursued to greatly improve hydrogen membrane and storage materials and the catalysts needed to realize fuel cells for alternative transportation technologies at reduced cost. Researchers are also working to develop a safe, lightweight hydrogen fuel tank.

- Various nanoscience-based options are being pursued to convert waste heat in computers, automobiles, homes, power plants, etc., to usable electrical power.

- An epoxy containing carbon nanotubes is being used to make windmill blades that are longer, stronger, and lighter-weight than other blades to increase the amount of electricity that windmills can generate.

- Researchers are developing wires containing carbon nanotubes to have much lower resistance than the high-tension wires currently used in the electric grid and thus reduce transmission power loss.

- To power mobile electronic devices, researchers are developing thin-film solar electric panels that can be fitted onto computer cases and flexible piezoelectric nanowires woven into clothing to generate usable energy on-the-go from light, friction, and/or body heat.

- Energy efficiency products are increasing in number and kinds of application. In addition to those noted above, they include more efficient lighting systems for vastly reduced energy consumption for illumination; lighter and stronger vehicle chassis materials for the transportation sector; lower energy consumption in advanced electronics; low-friction nano-engineered lubricants for all kinds of higher-efficiency machine gears, pumps, and fans; light-responsive smart coatings for glass to complement alternative heating/cooling schemes; and high-light-intensity, fast-recharging lanterns for emergency crews.

4.3 Environmental Remediation Application

Besides lighter cars and machinery that requires less fuel, and alternative fuel and energy sources, there are many eco-friendly applications for nanotechnology, such as materials that provide clean water from polluted water sources in both large-scale and portable applications, and ones that detect and clean up environmental contaminants.

- Nanotechnology could help meet the need for affordable, clean drinking water through rapid, low-cost detection of impurities in and filtration and purification of water. For example, researchers have discovered unexpected magnetic interactions between ultrasmall specks of rust, which can help remove arsenic or carbon tetrachloride from water (see image); they are developing nanostructured filters that can remove virus cells from water; and they are investigating a deionization method using nano-sized fiber electrodes to reduce the cost and energy requirements of removing salts from water.

Figure.4.3: Nano rust cleans arsenic from drinking water. (Image courtesy of Rice University)

- Nanoparticles will someday be used to clean industrial water pollutants in ground water through chemical reactions that render them harmless, at much lower cost than methods that require pumping the water out of the ground for treatment.

- Researchers have developed a nanofabric "paper towel," woven from tiny wires of potassium manganese oxide that can absorb 20 times its weight in oil for cleanup applications.

- Many airplane cabin and other types of air filters are nanotechnology-based filters that allow “mechanical filtration,” in which the fiber material creates nanoscale pores that trap particles larger than the size of the pores. They also may contain charcoal layers that remove odors. Almost 80% of the cars sold in the U.S. include built-in nanotechnology-based filters.

- New nanotechnology-enabled sensors and solutions may one day be able to detect, identify, and filter out, and/or neutralize harmful chemical or biological agents in the air and soil with much higher sensitivity than is possible today. Researchers around the world are investigating carbon nanotube “scrubbers,” and membranes to separate carbon dioxide

from power plant exhaust. And researchers are investigating particles such as self-assembled monolayers on mesoporous supports (SAMMS™), dendrimers, carbon nanotubes, and metalloporphyrinogens to determine how to apply their unique chemical and physical properties for various kinds of toxic site remediation.

4.4 Nanobiosystems, Medical and Health Application

Nanotechnology has the real potential to revolutionize a wide array of medical and biotechnology tools and procedures so that they are more personalized, portable, cheaper, safer, and easier to administer. Below are some examples of important advances in these areas.

- Quantum dots are semiconducting Nano crystals that can enhance biological imaging for medical diagnostics. When illuminated with ultraviolet light, they emit a wide spectrum of bright colors that can be used to locate and identify specific kinds of cells and biological activities. These crystals offer optical detection up to 1,000 times better than conventional dyes used in many biological tests, such as MRIs, and render significantly more information.

- Nanotechnology has been used in the early diagnosis of atherosclerosis, or the buildup of plaque in arteries. Researchers have developed an imaging technology to measure the amount of an antibody-nanoparticle complex that accumulates specifically in plaque. Clinical scientists are able to monitor the development of plaque as well as its disappearance following treatment.

Figure.4.4: Before (left) and after (right) picture of atherosclerotic plaque in a mouse artery. Plaque accumulation is shown in this image by increasing intensity of color, from blue to yellow and red.

- Gold nanoparticles can be used to detect early-stage Alzheimer's disease.
- Molecular imaging for the early detection where sensitive biosensors constructed of nanoscale components (e.g., nanocantilevers, nanowires, and nanochannels) can recognize genetic and molecular events and have reporting capabilities, thereby offering the potential to detect rare molecular signals associated with malignancy.
- Multifunctional therapeutics where a nanoparticle serves as a platform to facilitate its specific targeting to cancer cells and delivery of a potent treatment, minimizing the risk to normal tissues.
- Research enablers such as microfluidic chip-based nanolabs capable of monitoring and manipulating individual cells and nanoscale probes to track the movements of cells and individual molecules as they move about in their environments.
- Research is underway to use nanotechnology to spur the growth of nerve cells, e.g., in damaged spinal cord or brain cells. In one method, a nanostuctured gel fills the space between existing cells and encourages new cells to grow. There is early work on this in the optical nerves of hamsters. Another method is exploring use of nanofibers to regenerate damaged spinal nerves in mice.

4.5 Future Transportation Application

In addition to contributing to building and maintaining lighter, smarter, more efficient, and "greener" vehicles, aircraft, and ships, nanotechnology offers various means to improve the transportation infrastructure:

- Nano-engineering of steel, concrete, asphalt, and other cementitious materials, and their recycled forms, offers great promise in terms of improving the performance, resiliency, and longevity of highway and transportation infrastructure components while reducing their cost. New systems may incorporate innovative capabilities into traditional infrastructure materials, such as the ability to generate or transmit energy.

- Nanoscale sensors and devices may provide cost-effective continuous structural monitoring of the condition and performance of bridges, tunnels, rails, parking structures, and pavements over time. Nanoscale sensors and devices may also support an enhanced transportation infrastructure that can communicate with vehicle-based systems to help drivers maintain lane position, avoid collisions, adjust travel routes to circumnavigate congestion, and other such activities.

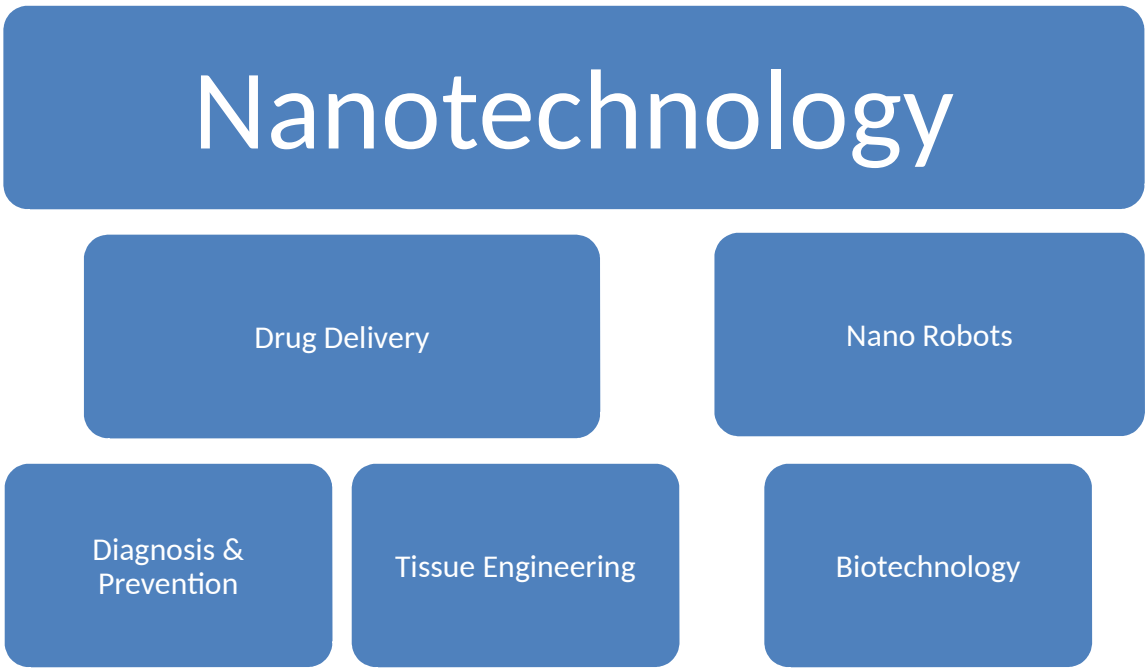
Figure.4.5: Future sensor systems will be able to use multiple physical phenomena to sense many analyses simultaneously for a variety of applications, some of which are noted above. Illustrated here are (*left to right*) an optical transducer, which measures light; an electro/chemical transducer, which measures electrical properties; a magnetic transducer, which measures changes to the local magnetic field; and a mechanical transducer, which detects changes in motion.

Besides moving forward to capture these and many other benefits of nanotechnologies, the NNI is also committed to addressing the potential environmental, health, and safety impacts and various societal, legal, or ethical implications of nanotechnology to avoid or minimize any undesirable or unintended effects of nanotechnology.

5.0 Pharmaceutical Application

Nanotechnology applies in pharmaceutical science for tissue engineering, diagnostic tools, drug delivery systems, production of biomaterials and nanomaterial's (NMs). Nanomaterial's and Nano devices exhibit different properties from bulk materials. Nanomaterial's have large surface area to volume ratio which increases drugs solubility and absorption.

Scientist are attempting to create new nanostructures which will help in the engineering of nanoparticles for use as artificial tissue that could replace infected kidneys and livers and repair damaged nerves and will restore vision and hearing by integrating nano device with nervous system. Nanotechnology are developing in drug delivery system such as- anti-cancer agents hormones and vaccines. Nanomaterial's can be alternative way to deliver drug to brain instead of pro-drugs.



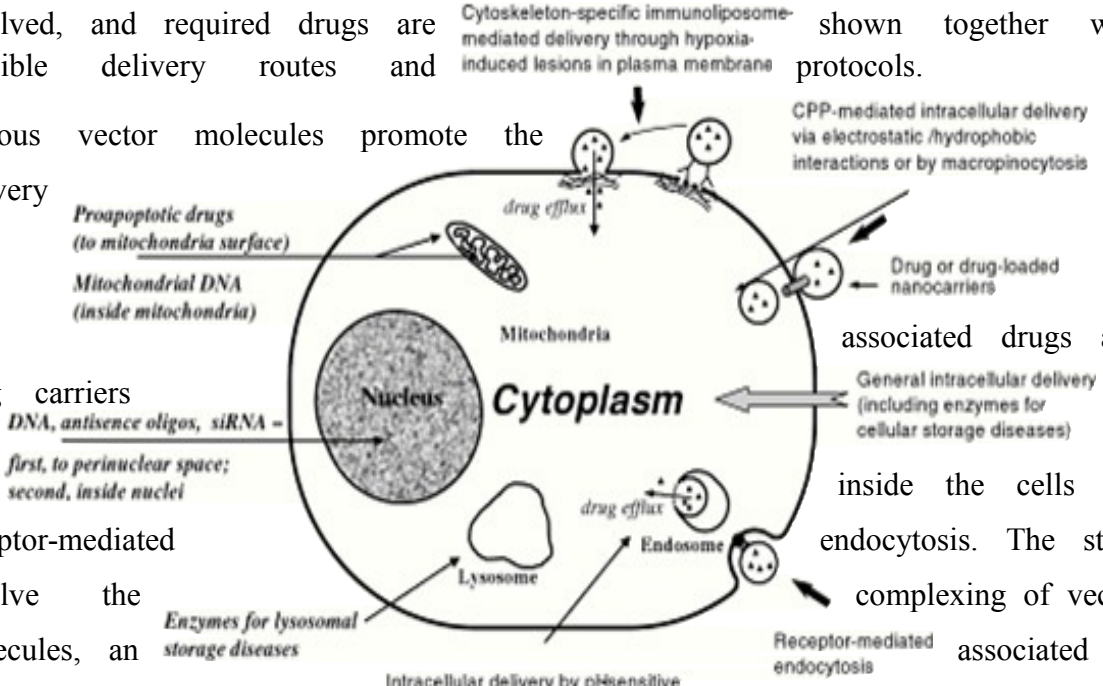
Some nanotechnology-based formulations are already on the market, e.g. Daunoxome®, Doxil®/Caelyx®, Moet® and Ambisome®.

5.1 Drug Delivery

Many pharmaceutical agents or biologically active molecules with therapeutic properties need to be delivered intracellularly to exert their therapeutic action inside cytoplasm or onto the nucleus or other organelles. Among such agents, there are preparations for gene and anti-sense therapy which target the nuclei; pro-apoptotic drugs, which ought to

reach the mitochondria; lysosomal enzymes, for the lysosomal compartment; bacteria and virus as vaccines, and some others. Intracellular drug delivery systems are designed to overcome certain important limitations for drug actions, such as multidrug resistance in cancer chemotherapy. These systems bypass the endocytic pathway to protect the drugs, or DNA from lysosomal degradation, thus enhancing drug efficacy or DNA incorporation into cell genome .

Figure.5.1: General scheme of intracellular drug delivery: types of diseases, organelles involved, and required drugs are shown together with possible delivery routes and protocols.



Various vector molecules promote the delivery of drug carriers associated drugs and inside the cells via receptor-mediated endocytosis. The steps involve the complexing of vector molecules, an associated drug and drug carrier to specific ligand on the surface of target cell membranes, followed by the energy dependent formation of endosomes. The challenge faced is that any molecules being introduced in a cell via the endocytic pathway and becoming entrapped into endosome, later in the lysosome, resulting in the degradation of the drug under the action of numerous lysosomal enzymes. Thus, only a small concentration of the active drug appears in the cell cytoplasm. As a result, even if an efficient cellular uptake via endocytosis is observed, the discovery of intact peptides and proteins is compromised by an insufficient endosomal escape and subsequent lysosomal degradation. In many cases, various pharmaceutical nanocarriers are used to increase the drug stability as well as improve their efficacy and bioavailability and also decrease adverse effects.

5.1.1 Various Approaches for Intracellular Drug Delivery pH Sensitive Pharmaceutical Nanocarriers for Cytosolic Delivery

For cytosolic delivery of drugs and drug products and pharmaceutical nanocarriers

such as liposomes & micelles have been developed.

A) pH sensitive liposomes

Liposome is made up of pH sensitive substance. After being endocytosed in the intact form, it fuses with the endovascular membrane due to the lowered pH inside the endosome (below 6) and destabilizes the latter, releasing its contents directly into the cytoplasm. The presence of fusogenic lipids in the liposomal composition, such as unsaturated dioleoylphosphatidylethanolamine (DOPE), is required to make the liposome pH sensitive. Several types of anticancer drugs have been developed as lipid-based systems by using a variety of preparation methods. Liposomal formulations have shown an ability to improve the pharmacokinetics and pharmacodynamics of associated drugs. [55, 56, 57, 58]

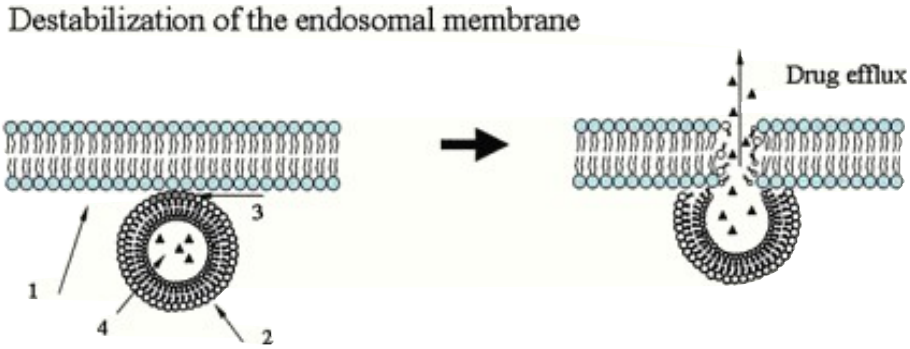


Figure.5.1.1: Schematics of endosomal drug escape with the use of pH-sensitive liposomes. (1) endosomal membrane (2) endocytosed liposome (3) pH- sensitive liposomal component interacting with the endosomal membrane and destabilizing it (4) liposomal drug

B) **pH Sensitive micelles**

Targeting of intracellular organelles can be accomplished by loading the drug in micelles, which can demonstrate pH sensitivity and ability to escape from endosome. Thus micelles is prepared from PEG-poly (aspartate hydrazine adriamycin) that can easily release an active drug at lowered pH value typical for endosomes and facilitate its cytoplasmic delivery and toxicity against cancer cells. [55, 58]

5.1.2 Cytoskeletal Antigen Specific Immunoliposomes for Intra-cytoplasmic Delivery

It is observed that sarcolemma lesion typical of hypoxic myocyte damage and the exposure of intracellular proteins, such as myosin, could be specially identified with the use of the antimyosin antibody. Moreover cytoskeletal antigen (myosin) specific immunoliposomes (CSIL) were shown to seal membrane lesions in hypoxis cardiocytes

by anchoring CSIL to the exposed cytoskeletal antigen. The property was the basis of the fact that artificially imposed hypoxia could be applied for the promotion of intracellular delivery of various drugs. If target cells for drug and/ or gene delivery are exposed to artificially impose hypoxic stress, stress-induced small membrane lesions will allow for the specific attachment to these lesions of loaded liposome rendered specific for an intracellular antigen. [55, 59, 60, 61]

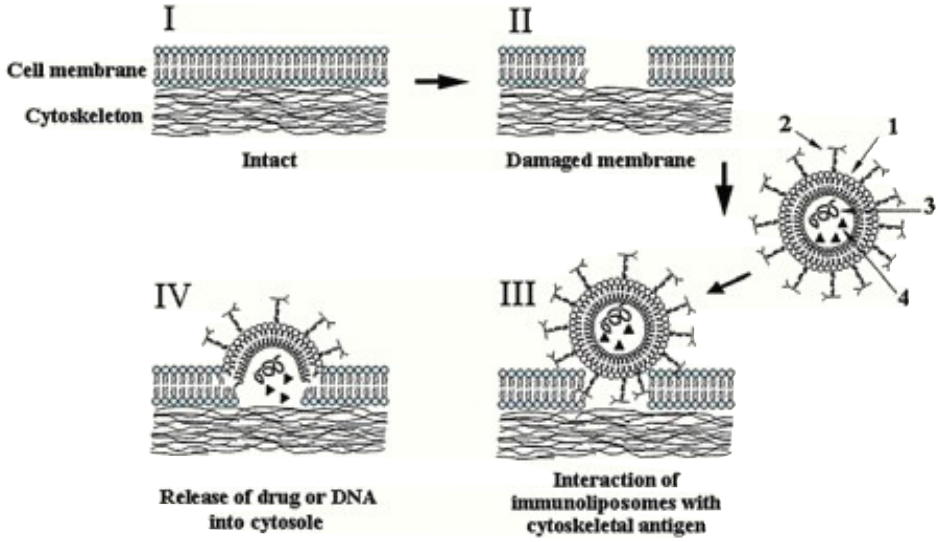


Figure.5.1.2: Schematics of intracellular drug or DNA delivery with the use of cytoskeleton-specific immunoliposomes. When normal cell membrane (I) becomes compromised and perforated under the action of ischemia (II) drug/DNA-loaded immunoliposome attaches to the appearing holes via exposed cytoskeletal antigens (III) and when fusing with the cell membrane, releases its contents into the cell cytoplasm. (1) Liposome; (2) cytoskeleton-specific antibody; (3) drug; (4) DNA

5.1.3 Intracellular Delivery of Nanocarrier by Cell Penetrating Peptides

Certain protein or peptides can be attached to the hydrophilic drug which has ability to translocate across the plasma membrane and delivery the drug intracellularly. This process of translocation is called “protein transduction”. Such proteins or peptides contain domain of less than 20 amino acids, termed as cell-penetrating peptides (CPPs). These peptides have been used for intracellular delivery of various carriers with molecular weights several times greater than their own. This carriers delivered range from peptides, proteins, genetic material, antibiotics, imaging agents and toxin to nanoparticles and liposomes. [55]

5.1.4 New Therapeutics Delivery

Gene therapy and RNA interference (RNAi) hold great promise as treatment and prevention methods for various diseases. But systemic administration of this new therapeutics (e.g., DNA and siRNA) is affected by several barriers such as enzymatic degradation, kidney filtration, and uptake by reticuloendothelial system, and limited intracellular entry. This gene and RNAi can be delivering by cationic nonviral nanocarrier.[62]

5.1.5 Co-delivery

For some drug combinations relative dosage of various drugs can be in single particle levels, and simultaneously deliver them to target sites with a maintained drug ratio. For example, in case of co-delivering chemotherapy and RNAi therapy for treating multidrug resistant cancers, the ideal nanoparticle would be expected to first release siRNA for reducing the expression of multi drug resistance (MDR) transporters, followed by the release of anticancer drugs.[62]

5.1.6 Micro/Nano Electromechanical (MEM/NEM) Devices for Drug Delivery

To deliver drugs for long time implantable microchips containing nanosized reservoirs have been developed in a precisely controlled manner; microneedles are being tested in painless transdermal drug delivery; and the incorporation of nanofeatures (e.g., nanopores, nanochannels, and nanoparticles) in microfabricated systems are perfecting drug delivery and immunoisolation techniques. [62]

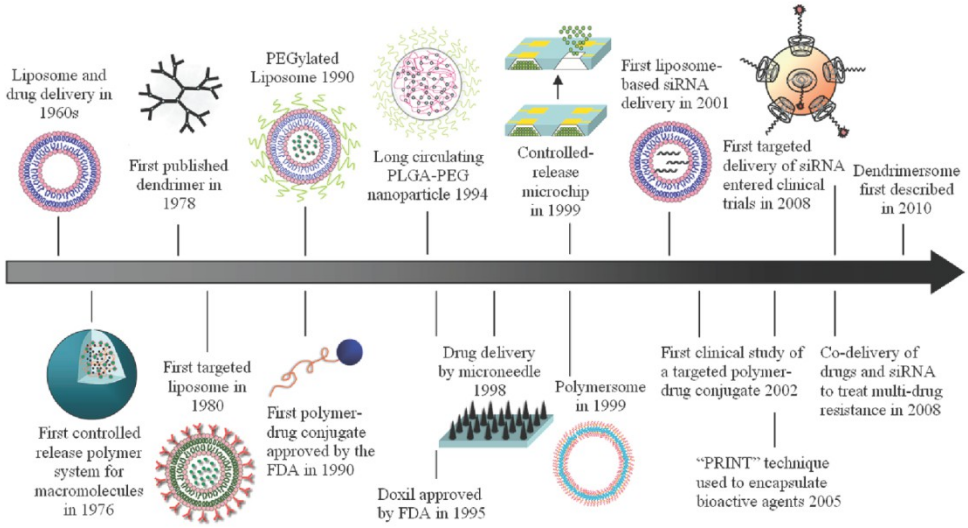


Figure.5.1.6: Timeline of nanotechnology-based drug delivery. Here, we highlight some delivery systems that serve as important milestones throughout the history of drug delivery.

5.2 Nanocarrier for Targeting Lysosomes

Liposomes are suggested as pharmaceutical nanocarriers for replacement enzymes, which could protect them from the inactivation in vivo. Therefore, they enhance their intracellular delivery and transport into lysosomes. The potential ability of liposome-encapsulated enzymes to enter the cytoplasm or lysosomes of liver cells is of primary importance for the treatment of inherited diseases which are caused by the abnormal functioning of some intracellular enzymes. Enzymes for the therapy of lysosomal storage diseases include glucocerebrosidase, various glucosidases, phenylalanine ammonialyase and some others.

5.3 Nanorobot

Nanobots are robots that carry out a very specific function and are just several nanometers wide. They can be used very effectively for drug delivery. Normally, drugs work through the entire body before they reach the disease affected area. Using nanotechnology, the drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects.[63]

5.4 Disease Diagnosis and Prevention

5.4.1 Diagnosis and Imaging

Nanobiotech scientists have successfully produced microchips that are coated with human molecules. The chip is designed to emit an electrical impulse signal when the molecules detect signs of a disease. Special sensor nanobots can be inserted into the blood under the skin where they check blood contents and warn of any possible diseases. They can also be

used to monitor the sugar level in the blood. Advantages of using such nanobots are that they are very cheap to produce and easily.[63]

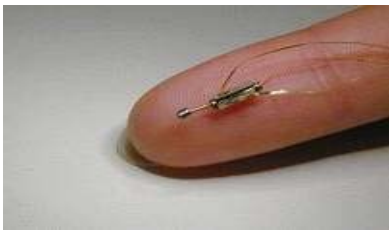


Figure.5.4.1: Device that uses nanobots to monitor the sugar level in the blood.

5.4.2 Preventing diseases

a. heart-attack prevention

Nanobots can also be used to prevent heart-attacks. Heart-attacks are caused by fat deposits blocking the blood vessels. Nanobots can be made for removing these fat deposits.The following figure shows nanobots removing the yellow fat deposits on the inner side of blood vessels.[63]

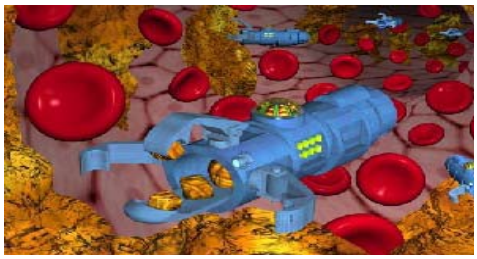


Figure.5.4.2.1: Nanobots Preventing Heart-attacks (Heart View)

b. Frying tumors

Nanomaterials have also been investigated into treating cancer. The therapy is based on "cooking tumors" principle. Iron nanoparticles are taken as oral pills and they attach to the tumor. Then a magnetic field is applied and this causes the nanoparticles to heat up and literally cook the tumors from inside out.[63]

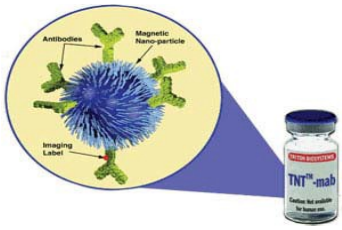


Figure.5.4.2.2: Cancer Cooker- Triton Bio Systems is developing an anticancer therapy using antibody coated iron nanoparticles.

c. Tissue Reconstruction

Nanoparticles can be designed with a structure very similar to the bone structure. An ultrasound is performed on existing bone structures and then bonelike nanoparticles are created using the results of the ultrasound. The bone-like nanoparticles are inserted into the body in a paste form. When they arrive at the fractured bone, they assemble themselves to form an ordered structure which later becomes part of the bone. Another key application for nanoparticles is the treatment of injured nerves. Samuel Stupp and John Kessler at Northwestern University in Chicago have made tiny rod like nano-fibers called *amphiphiles*. They are capped with amino acids and are known to spur the growth of neurons and prevent scar tissue formation. Experiments have shown that rat and mice with spinal injuries recovered when treated with these nano-fibers.[63]

5.5 Cell repair machines

Using drugs and surgery, doctors can only encourage tissues to repair themselves. With molecular machines, there will be more direct repairs Cell repair will utilize the same tasks that living systems already prove possible. Access to cells is possible because biologists can stick needles into cells without killing them. Thus, molecular machines are capable of entering the cell. Also, all specific biochemical interactions show that molecular systems can recognize other molecules by touch, build or rebuild every molecule in a cell, and can disassemble damaged molecules. Finally, cells that replicate prove that molecular systems can assemble every system found in a cell. Therefore, since nature has demonstrated the basic operations needed to perform molecular-level cell repair, in the future, nanomachine based systems will be built that are able to enter cells, sense differences from healthy ones and make modifications to the structure. The possibilities of these cell repair machines are impressive. Comparable to the size of viruses or bacteria, their compact parts would allow them to be more complex. The early machines will be specialized. As they open and close cell membranes or travel through tissue and enter cells and viruses, machines will only be able to correct a single molecular disorder like DNA damage or enzyme deficiency. Later, cell repair machines will be programmed with more abilities with the help of advanced AI systems. Nanocomputers will be needed to guide these machines. These computers will direct machines to examine, take apart, and rebuild damaged molecular structures. Repair machines will be able to repair whole cells by working structure by structure. Then by working cell by cell and tissue by tissue, whole organs can be repaired. Finally, by working organ by organ, health is restored to the body. Cells damaged to the point of inactivity can be repaired

because of the ability of molecular machines to build cells from scratch. Therefore, cell repair machines will free medicine from reliance on self-repair. A new wave of technology and medicine is being created and its impact on the world is going to be monumental. From the possible applications such as drug delivery and *in vivo* imaging to the potential machines of the future, advancements in nanomedicine are being made every day. It will not be long for the 10 billion dollar industry to explode into a 100 billion or 1 trillion dollar industry, and drug delivery, *in vivo* imaging and therapy is just the beginning. Nanomedicine may be defined as the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures. Basic nanostructured materials, engineered enzymes and the many products of biotechnology will be enormously useful in future medical applications. However, the full promise of nanomedicine is unlikely to arrive until after the development of precisely controlled or programmable medical nanomachines and nanorobots. Once nanomachines are available, the ultimate dream of every healer, medicine man, and physician throughout recorded history will at last become a reality.[63]

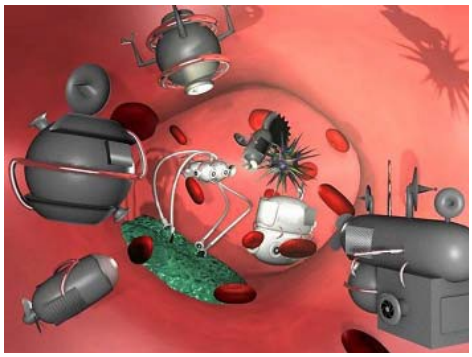


Figure.5.5: Miniature cameras inside blood vessels

5.6 Tissue Engineering

Recent advances in nanotechnology, however, have enabled the design and fabrication of biomimetic microenvironment at the nanoscale, providing an analog to native ECM.48 Notably, these technologies have been applied to create Nanotopographic surfaces and nanofeatured scaffolds, and to encapsulate and control the spatiotemporal release of drugs (e.g., growth factors).[62]

5.6.1 Nanofabricated Scaffolds

Nanofibrous scaffolds exhibit a very similar physical structure to protein nanofibers in ECM. Among the three dominant nanofabrication methods, electro spinning is suitable for the

creation of aligned and complex 3D structures; self-assembly technology emulates the process of ECM assembly and can produce very thin nanofibers; and phase separation allows for continuous fiber network fabrication with tunable pore structure and the formation of sponge-like scaffolding. On the other hand, nanocomposite-based scaffolds (e.g., nanohydroxyapatite/collagen) are very popular in hard tissue engineering, particularly for the reconstruction of bone tissue.[62]

5.6.2 Controlled Release

Controlled delivery of biological factors in 3D scaffolds can achieve by using nanotechnology. For example, the controlled release of angiogenic factors (e.g., vascular endothelial growth factors and basic fibroblast growth factors) can specifically enhance vascularization essential for maintaining continuous blood supply to developing tissues. The strategy of bio macromolecule encapsulation by direct entrapment or chemical conjugation to scaffolds can provide sustained release characteristics. Polymeric micro/nanoparticles, preloaded with growth factors, have been incorporated into porous scaffolds and hydrogels.72 Using PLGA microspheres or nanospheres, single or multiple biological factors can be released in a spatiotemporally.[62]

5.7 Devices Based on Nanotechnology

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, nanotubes, cantilevers, semiconductor nanocrystals, and liposomes.

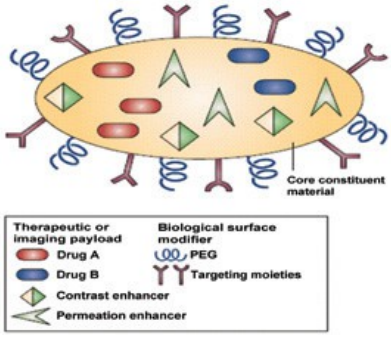


Figure.5.7: Multifunctional nanoparticle

5.7.1 Nanotubes

Nanotubes are smaller than nanopores. Nanotubes help to identify Deoxyribonucleic 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. [64]

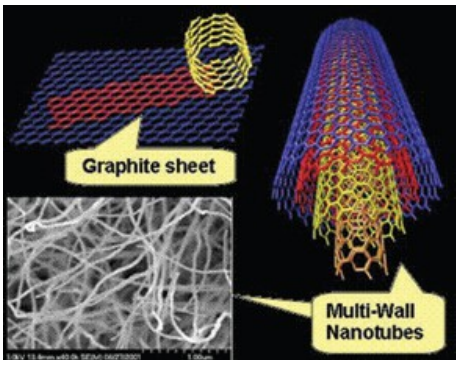


Figure.5.7.1: Nanotubes

5.7.2 Quantum Dotes

These are tiny crystals that glow when these are stimulated by ultraviolet light .The latex beads filled with these crystals when stimulated by light, emit the color that lights up the sequence of interest. By combining different 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.[64, 65]

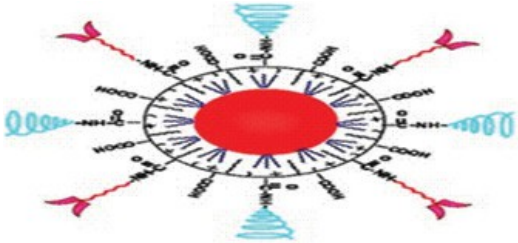


Figure.5.7.2: Antibody conjugated quantum dotes

5.7.2.1 DNA Binding Proteins with Quantum Dots

High-resolution mapping of the DNA-binding proteins is achieved by combining far-field optics with DNA templates that have been extended with a uniform extension

factor, creating arrays of DNA. Two main approaches have been developed to align DNA on a solid support: molecular-combing, which utilizes the surface tension of a receding meniscus to align naked DNA anchored by its extremity on a surface and DNA alignment approaches that use flow and Stokes drag to perform the same feat. Quantum dots (QDs), with their narrow, "tunable" emission spectra, provide an almost unlimited array of colors compared to organic fluorophores and therefore have ideal properties for the simultaneous observation of several components (multiplexing). Furthermore, QDs can be excited with a common excitation wavelength, reducing chromatic aberrations and simplifying microscopy. Finally, QDs are more photo stable than organic fluorophores, facilitating nanometer localization of single QDs8 (Figure in Supporting Information).

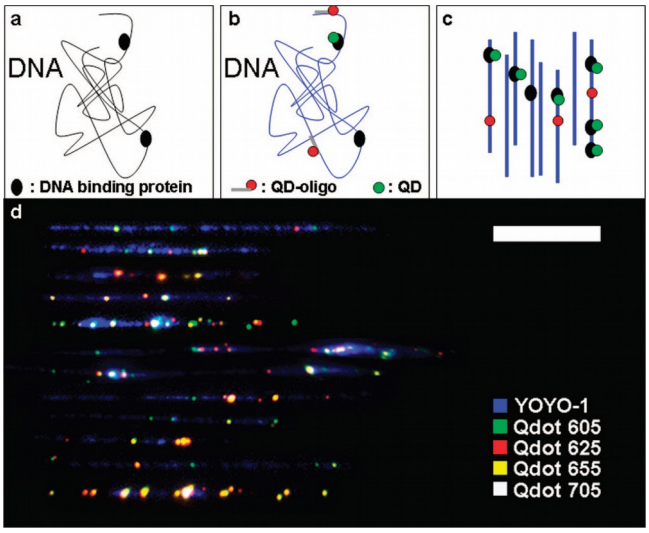


Figure.5.7.2.1: Experimental steps for mapping DNA binding proteins. (a) Cross-linking DNA-binding proteins to DNA. (b) Staining DNA(blue), QD labeling of bound proteins (green), and labeling of specific reference sequences on DNA with QDs (red). (c) Complexes are aligned on a glass coverslip and imaged by a fluorescence microscope. Image analysis provides information on protein location. (d) Cropped images of RNAP-biotin cross-linked to aligned DNA and bound to streptavidin QDs. DNA was stained with YOYO-1 and is displayed in blue while QDs emitting at 605, 625, 655, and 705 nm are displayed in green, red, yellow, and white, respectively. [66]

5.7.3 Nanoshells

Nanoshells (NS) are gold coated miniscule beads. 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.

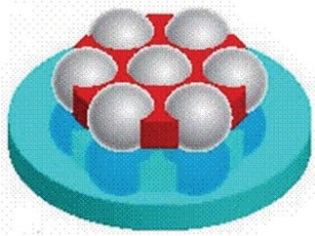


Figure.5.7.3: Nanoshells

5.7.4 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. [67, 68]

5.7.5 Cantilevers

Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer. 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. [69, 70]

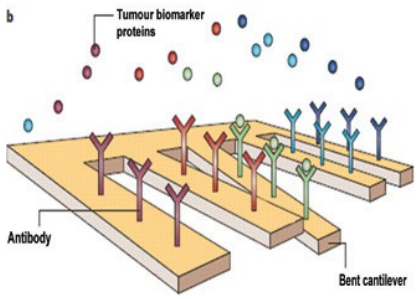


Figure.5.7.5: Nano cantilever array

5.7.6 Dendrimers

Dendrimers are new class of macromolecules which have a symmetric core and form the 3-D spherical structure.

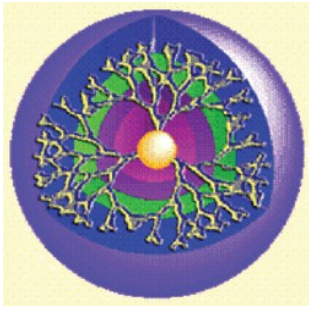


Figure.5.7.6: Dendrimer

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.

5.8 Nanotechnology Tools for Product Development

Some of the tools described above can also be utilized for product development. The term product development encompasses drug discovery as well as development of diagnostic tools. One of the most obvious and important nanotechnology tools 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 nano-size 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. Key implication of this approach is the possibility of life cycle extension for existing drugs, for existing markets. There are a number of well-known drugs that have already been commercialized using this approach for existing markets. For example, immunosuppressant drug Rapamune® (sirolimus), Emend® (aprepitant, MK 869), a substance P antagonist (SPA) for prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) and for prevention of postoperative nausea and vomiting, have nano-size drugs made by Elan Corporation using nanocrystal™ technology. Using micro emulsions as templates for solid nanoparticles, NanoMed Pharmaceuticals is currently developing a number of nano-size drugs using its patented Nanotemplate Engineering™ technology. The insoluble drug delivery (IDD®) technology platform from SkyePharma is utilized in several drugs currently on the market such as SOLARAZE® for skin cancer and antidepressant PAXIL CR™. Finally, RBC Life Sciences® is developing a new line of nutritional and skincare

supplements called NanoCeuticals™ with nanoscale ingredients. This allows RBC to create products which, when consumed, reduce the surface tension of foods and supplements to increase the wetness and absorption of nutrients. As emphasis in drug development is towards controlled delivery and release, nanotechnology offers a number of tools in order to transform current drugs with these capabilities. Nanotechnology tools for developing drug delivery systems and devices are valued at around $300 billion capturing significant applications in the health care market. As controlled release and delivery technologies are patentable, old 'blockbuster drugs' can have continued protection at a relatively low cost. This is immensely attractive for the pharmaceutical industry in order to ward off the generics industry away from their hard earned profits. Additionally, drugs with these new capabilities will likely find applications in new markets. Simplest in this category are polymer encapsulated drugs such as MutliSal™, DermaSal™ and MatrixSal™ from the company Salvona. Such polymer encapsulated drugs can be fine-tuned to deliver the drugs using a number of stimuli such as pH, temperature, and water. In addition to simple polymer encapsulation, more sophisticated nanotechnology tools, such as nano core-shell designs, are also being developed in order to further fine tune delivery and release. For example, in a recent work Sengupta demonstrated a novel approach for treating angiogenesis using a core-shell architecture wherein the polymer core has cytotoxic agent with the encapsulation of the anti-angiogenesis agent in the surrounding phospholipid block-copolymer22. Such a design enables temporal targeting of the tumor vasculature, resulting in the intra-tumoural trapping of the nanoparticles. This resulted in slow release and focal build-up of the cytotoxic agent within the tumor thereby prolonging exposure and an increase in the apoptotic potential, which can overcome hypoxia-induced reactive resistance. Yet another interesting example is gene delivery using multi-segment Au-Ni nanorods23. By attaching selectively plasmids to the nickel segment and a cell-targeting protein, transferrin, to spatially separated Au region, the gene delivery system provides precise control of composition, size and multi-functionality. Such nanotechology tools have potential applications in genetic vaccination.

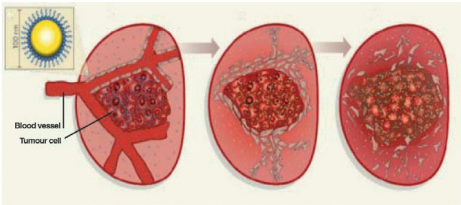


Figure.5.8: Polymer core-lipid shell nanoparticles carrying drug for anti-angiogenesis within the lipid shell and a chemotherapeutic drug within the polymer core.

5.9 Nanotechnology in Pharmaceutical Biotechnology

The application of nanobiotechnology to identifying, curing, abating or resisting human disease is a well-established and yet constantly evolving field. As our knowledge of the physiology of healthy versus diseased states increases, so does the potential for effectively designed curative strategies that exploit the vulnerabilities of disease while inflicting minimal damage on healthy tissue. Cancer is a malignant disease that is characterized by the unregulated proliferation of genetically aberrant and transformed cells. By using Nanotechnology cancer cell can be destroy easily with low side effect.[71]

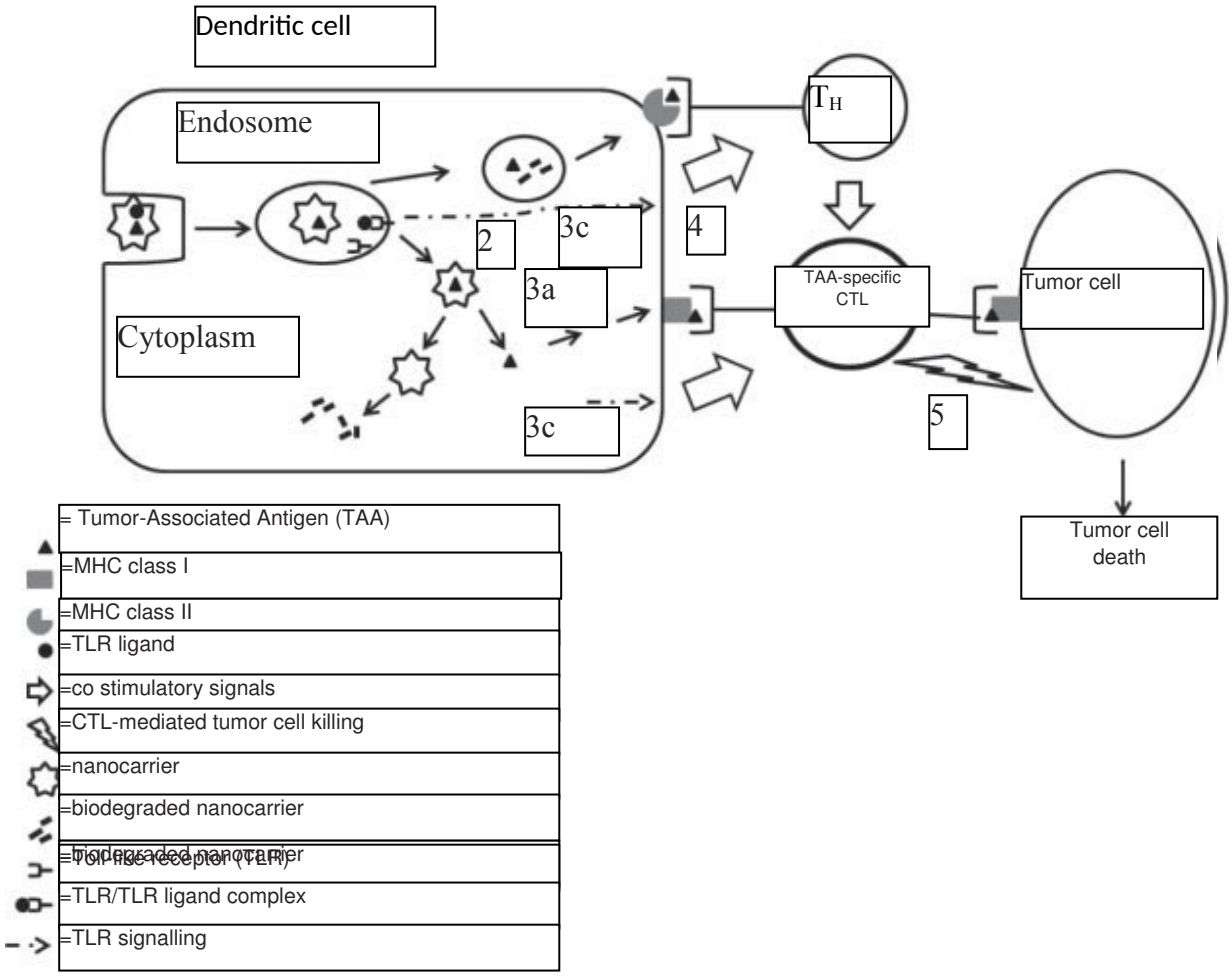


Figure.5.9: Schematic of nanocarrier cancer vaccines (NCVs) proposed mode of stimulation of anti - tumor immunity. 1, Engulfment of NCV by phagocytosis, pinocytosis or receptor - mediated endocytosis; 2, endosomal escape of antigenic cargo (TAA) into cytoplasm; 3a, processing and presentation of TAA epitope in association with MHC class I; 3b, processing and presentation of TAA in association with major histocompatibility complex (MHC) class II via recycling endosome; 3c, up-regulation of co-stimulatory signals via TLR signaling; 4,

activation of TAA - specific CTL and T_H lymphocytes; and 5, release of cytolytic factors by CTL resulting in tumor cell death.

5.10 Nanoparticle-Coated Bacteria as Oral DNA Vaccines for Cancer Immunotherapy

One of the most promising approaches in cancer immunotherapy is oral delivery of DNA vaccine. Some live attenuated strains bacteria have been developed as vaccines for a number of infectious diseases and several types of cancers. For example, Salmonellae harboring cancer-specific antigen-expressing plasmid has been shown to be effective in DNA delivery and efficacious in the subsequent induction of immunity against antigens encoded by the plasmid. But efficiency of Salmonellae in oral infection is low because Salmonellae is digest in acidic stomach. Additionally, Salmonellae lack the ability to escape phagosomes after they are captured by phagocytes. As a result, the induction of MHC class-I-restricted immune response is largely limited, which is the key reason for the failure of DNA vaccination against cancer.

The strong buffering capacity of cationic polymers could effectively help themselves escape from endo/lysosome as a result of "proton sponge" effect.For example, 25 kDa polyethylenimine (PEI) is well known for its excellent transfection activity in vitro largely due to its strong buffering capacity. The PEI/DNA complexes escape the endosomal through a "proton-sponge" mechanism. Similarly, cross-linked β-cyclodextrin-PEI600 (CP) with degradable PEI network was demonstrated as an efficient vector for nucleic acid delivery in vitro and in vivo. A living hybrid system composed of synthetic CP nanoparticles and live attenuated Salmonellae act as an efficient vector to deliver oral DNA vaccines and achieves potent antitumor immune response in vivo.[72]

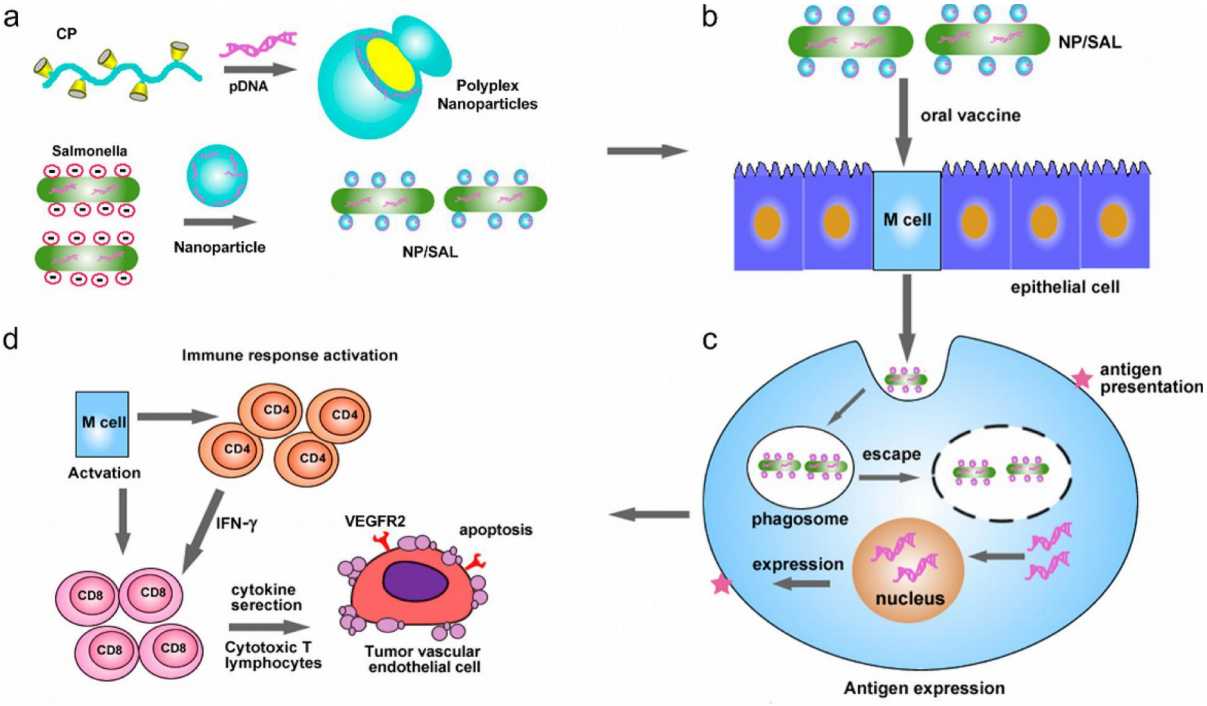


Figure.5.10: Schematic Illustration of the Cationic Nanoparticle-Coated Attenuated Salmonellae for Improved Antigen Expression and Tumor Targeting Immune Responsive Activation. (a) Engineering of polyplex nanoparticle-coated Salmonellae. (b) Oral DNA vaccine delivery mediated by nanoparticle-coated Salmonellae. (c) Intracellular trafficking of nanoparticle-coated Salmonellae and antigen expression. (d) Activation of antitumor immune response.

5.11 In vivo delivery of siRNA to lung vasculature

RNA interference (RNAi) can be suppressed pathologic gene expression in cells. RNAi is triggered when small interfering RNA (siRNA) for a specific gene is introduced into cells, which leads to the degradation of the corresponding mRNA gene transcripts. siRNA payloads can successfully deliver by using Branched polyethylenimines (PEI), which are ionizable polycations. poly(amido amine) and poly(propylenimine) dendrimers have been used in both modified and unmodified forms to deliver siRNA.

By using of modified poly(amido amine) and poly- (propylenimine) dendrimers substituted with hydrophobic lipid tails nanoencapsulation of siRNA and its successful delivery to lung endothelial cells in vivo was achieved. These formulations may have utility in the treatment of injuries and diseases that arise from dysfunctional endothelium. [73]

5.12 A Fluorescent Nanosensor for Apoptotic Cells

Apoptotic cells can be detected by using fluorescent nanosensors. In healthy cells, phosphatidylcholine (PC) is exposed on the external leaflet of the lipid bilayer, whereas phosphatadylserine (PS) is predominantly located on the inner layer. When cells undergo apoptosis, redistribution of phospholipids occurs and PS translocate to the outer layer of the membrane.

A mimetic to Annexin V (AnxV), a 37-kDa protein that recognizes phosphatidylserine (PS) expressed on apoptotic cell surfaces. An unnatural amino acid, diaminopropionic acid (Dpr), use as the building unit of the PS-binding peptide. A dextran-coated iron-oxidenanoparticle is use. [74]

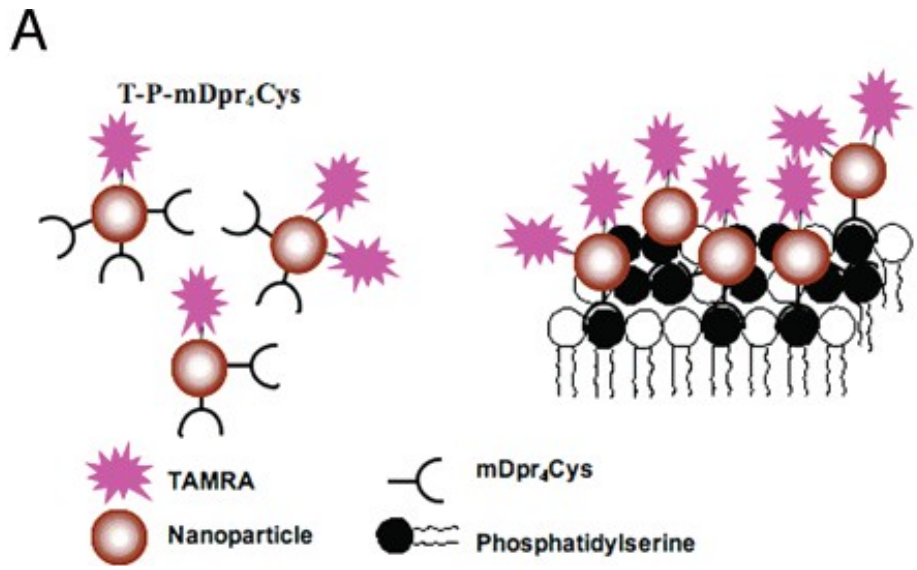


Figure.5.12: Schematic representation of T-P-mDpr4Cys particles and their recognition of phospholipids rich in PS.

5.13 Sustained Antibiotic Release by Si Nanowire Templates

Nanoscale drug delivery systems can be devised to tune release kinetics, regulate biodistribution, adjust bioavailability over time, and minimize toxic side effects, thus enhancing the therapeutic index of a given drug. Biocompatible porous Si is an attractive material for controlled drug delivery applications for many reasons including the versatility and capability of tailoring the pore sizes (from micrometers to nanometers) and volume of the reservoir. It can be used as a template for designing polymeric nanostructures, and it has unique optical properties and exceptional biosensing potential.

Si nanowire (SiNW) arrays were prepared using the electroless chemical etching method. At room temperature (25°C), the SiNW samples were placed in a vacuum (∼10-4Torr) for approximately 5-10 min to rid nanopores (between Si nanowires) of any trapped air. Remaining under vacuum, by opening of a control chamber valve, an antibiotic solution was loaded into the samples.

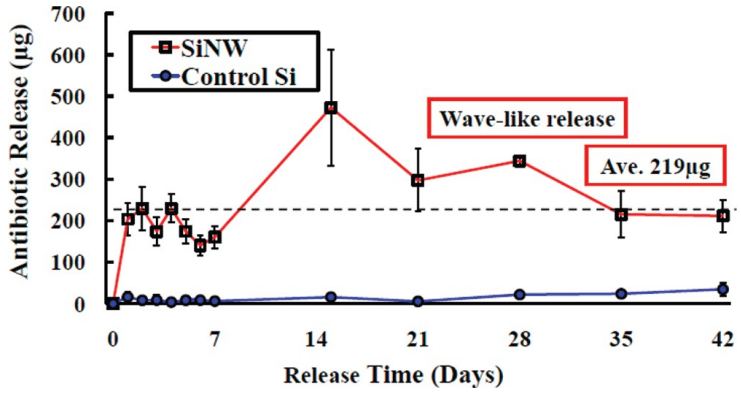


Figure.5.13: Absolute release of antibiotic measured as a function of sampling time. Mean (standard deviation is given (n) 4). A near constant release is shown over 42 days (6 weeks) and the average amount of antibiotics released for all time points was approximately 219 μg indicated by the dotted line.

An antibiotic release profile from the SiNW filled with the Penicillin/Streptomycin (P/S) solution was obtained over 42 days, illustrated in figure. Bare Si wafer controls, without a nanostructured surface topography, showed almost zero antibiotic release as expected. This proved that it was the nanostructure reservoir and surface properties of the SiNW templates that were responsible for the sustained drug release. Note the wavelike aspect of the release in figure which describes the total amount of antibiotic measured per time point. [75]

5.14 Gold Nanorods at the Mitochondria of Cancer Cells

Au nanorods (NRs) have distinct effects on cell viability via killing cancer cells while posing negligible impact on normal cells and mesenchymal stem cells. Obvious differences in cellular uptake, intracellular trafficking, and susceptibility of lysosome to Au NRs by different types of cells resulted in selective accumulation of Au NRs in the mitochondria of cancer cells. Their long-term retention decreased mitochondrial membrane potential and increased reactive oxygen species level that enhances the likelihood of cell death. [76]

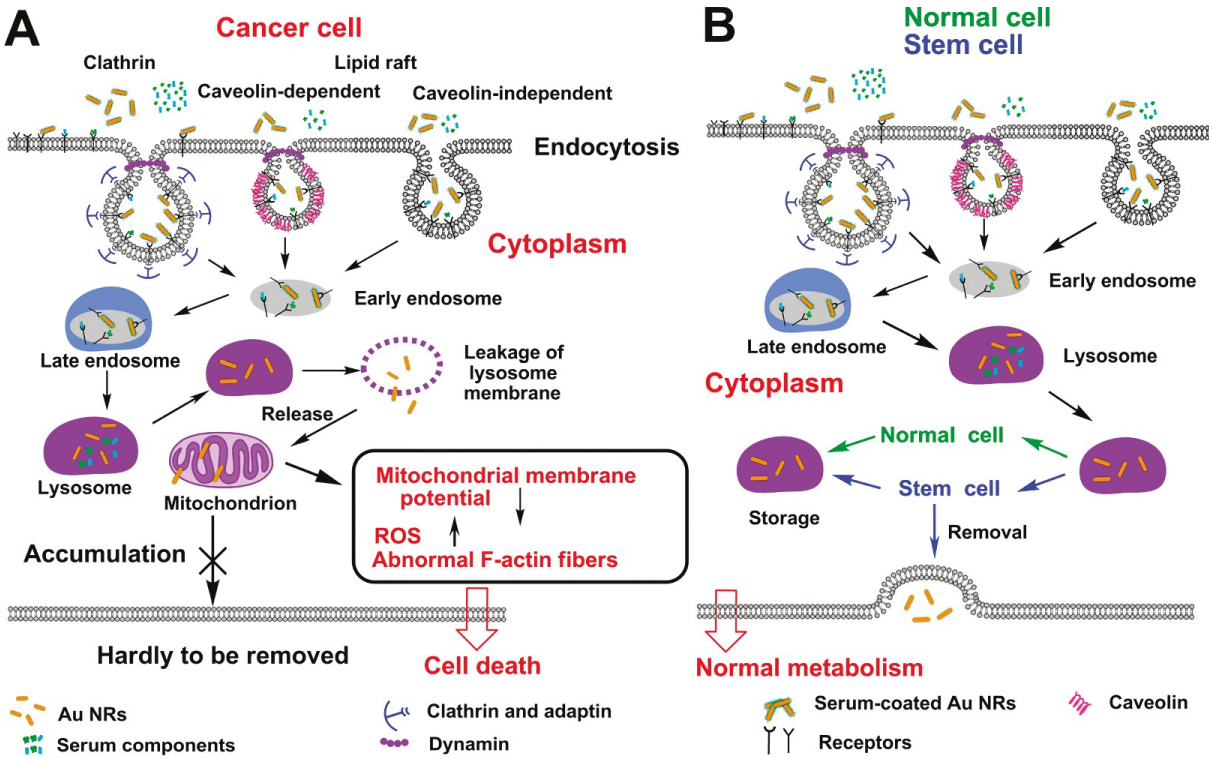


Figure.5.14: Different fates and effects of Au NRs in cancer cell, normal cell, and stem cell due to distinct pathways for cellular trafficking.

6.0 Conclusion

Pharmaceutical nanotechnology offers new tools, opportunities and scope, which are expected to have a great impact on many areas in disease diagnostics and therapeutics. Pharmaceutical nanotechnology has emerged as a discipline having enormous potential as carrier for spatial and temporal delivery of bioactive and diagnostics and provides smart materials for tissue engineering. Pharmaceutical nanotechnology is now well-established as specialized area for drug delivery, diagnostics, prognostic and treatment of diseases through its Nano engineered tools. Few nanotechnology based products and delivery systems are already in market. The main areas in which nanomedical products have made an impact are cancer, CNS diseases, cardiovascular disease, and infection control.

Nanoparticles for Pharmaceutical Applications deals with emerging new technologies for developing customized solutions for drug delivery systems. The drug delivery systems should positively impact the rate of absorption, distribution, metabolism, and excretion of the drug or other related chemical substances in the body. In addition, the drug delivery system should allow the drug to bind to its target receptor and influence that receptor's signaling and activity. Drug delivery materials should be compatible, easy to bind with a particular drug, and able to degrade into fragments after use that are either metabolized or driven out via normal excretory routes.

Few nanotechnology based products and delivery systems are already in market these include- Daunoxome®, Doxil®/Caelyx®, Moet® and Ambisome®

Pharmaceutical nanotechnology provides opportunities to improve materials, medical devices and help to develop new technologies where existing and more conventional technologies may be reaching their limits. Pharmaceutical nanotechnology raises new hope to pharmaceutical industries by providing new cutting age patentable technologies in view of revenue loss caused due to off patent drugs. Scientific societies, industries and governments all over world are looking with great anticipation and contributing their best to clutch the potential of this technology. This technology has the potential to make significant contributions to disease detection, diagnosis, therapy, and prevention. Pharmaceutical nanotechnology could have a profound influence on disease prevention efforts because it offers innovative tools for understanding the cell as well as the differences between normal and abnormal cells. It could provide insights into the molecular basis of disease.

Nanotechnology will provide a good inside view of our human systems. It has a bright future with the emergence of several promising approaches for delivery of therapeutics agent and

imaging using the advantage of nanoscale carriers. Future studies will now be addressing a no. of challenges faced in nanomedicine application. Greater funds are being allocated for clinical and pre-clinical studies but still are studies are lacking in safety data that includes toxicity studies. Also the cost of nanomedicine should be in acceptable range so that it is successful in clinics. Nanotechnology is being applied at all stages of drug development, from formulations for optimal delivery to diagnostic applications in clinical trials. Actual utilization of nanotechnology novel drug delivery techniques lag behind because of perception that such technologies could delay products due to technical or regulatory reasons. So oral drug delivery remains a preferred option. Further the cost factor becomes a hindrance in its daily use. This review deals with promises and uses of nanotechnology in the field of pharmacy to its wide spread application in various fields of imaging, diagnosis, drug delivery and treatment of diseases.

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