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NANO-TECHNOLOGY AND ITS USE: A REVIEW

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ABSTRACT

Nanotechnology derived from the word "Nano" which is derived from the greek word νᾶνος (nanos) meaning dwarf. A nanometer is a billionth of a meter, means, about 1/80,000 of the diameter of a human hair, or 10 times the diameter of a hydrogen atom. Nanotechnology refers to the third category and is the creation of materials, devices, and systems in the nanometer scale. Nanoparticles (NPs) exhibit different optical, electrical, magnetic, chemical, and mechanical properties as compared to their bulk counterparts. Nano-materials are matter containing particles at the nanometer scale (1-100 billionths of a meter) and can occur naturally (as a result of volcanic eruptions, forest fires, ocean spray, hydrothermal vent systems, dust volatilization), be created incidentally (as by-products of industrial processes and combustion engines) or be engineered for a specific application. Exposure to nano-materials in the environment may result from commercial products. The most common ENP (Engineered nanoparticle) listed on a prominent U.S. online consumer product database is silver (Ag NP).

Keywords: Nanotechnology, Fullerenes, dendrimers, bioavailability, proportionality, toxicity

INTRODUCTION

Nanotechnology is defined as the study and use of structures between 1 nanometer and 100 nanometers in size. Nanotechnologies are the designing, production, characterization, and application of structures, devices and systems by controlling shape and size at nanometer scale [1-6].

NEED OF NANO

NANO means small, but special due to various kind of reasons but mostly due to properties of matter like energy change at nanometer scale, the consequence is that nanomaterial when in nano-sized form can assume properties which are very different from those when assumed in bulk form.

Example:

1) Bulk silver is non-toxic whereas silver nanoparticle is capable of killing of virus upon contact .Properties like electrical conductivity, colour change weight change, when nano-scale level is reached.
2) The second exceptional property of nanomaterial is they can be fabricated atom by atom with a process called bottom up.
3) Nano-materials having increased surface to volume ratio as compared to bulk materials [7].

Advantages of nanoparticle:-

1) Increased bioavailability
2) Dose proportionality
3) Decreased toxicity
4) Smaller dosage form (i.e., smaller tablet)
5) Increased active agent surface area and therefore faster dissolution of the active agent in an aqueous environment, such as the human body. Faster dissolution generally equates with greater bioavailability, smaller drug doses, less toxicity.
6) Reduction in fed/fasted variability [8].

Disadvantages of Nanoparticles:

1) Extensive use of polyvinyl alcohol as a detergent – issues with toxicity.
2) Limited targeting abilities.
3) Discontinuation of therapy is not possible.
4) Cytotoxicity.
5) Pulmonary inflammation and pulmonary carcinogenicity.
6) Alveolar inflammation.
7) The disturbance of autonomic imbalance by nanoparticles having direct effect on heart and vascular function [8].

CLASSIFICATION OF NANOTECHNOLOGY

There are three types of classification of nano-particles:-

NANOPARTICLE: - Nanoparticles can be defined as particles less than 100nm in diameter that exhibit new or enhanced size-dependent properties as compared with larger particles of the same material.

1) ONE DIMENSION TYPE: - such as thin films or manufactured surfaces or coatings are included in one dimensional nano-material.

APPLICATIONS OF ONE DIMENSION:-

1) corrosion resistant,
2) hydrophobic and self -cleaning ,
3) dirt repellent,
4) antibacterial,
5) Antimicrobial, catalytically active and chemically functionalized.

2) TWO DIMENSION TYPE: - Nanotubes, nanowires, nano fibers and nano polymers are two dimension nanoparticles

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EXAMPLE:-

a) Carbon Nanotubes:-

These are a new form of carbon molecule. They are of hexagonal network of carbon atoms; these hollow cylinders can have diameters as small as 0.7 nm and reach several millimeters in length [9]. Each end can be opened or closed by a fullerene half-molecule. These nanotubes can have a single layer (like a straw) or several layers (like a poster rolled in a tube) [10].

3) THREE DIMENSION:- Fullerenes, dendrimers and quantum dots are said to be three dimensional nanoparticles.

a) Fullerenes:-

Fullerenes are spherical cages having 28 to more than 100 carbon atoms. They require extreme pressures and regain their original shape when the pressure is released. These molecules do not combine with each other, thus giving them major potential for application as lubricants. Fullerenes products include drug delivering vehicle and electronic circuit.

b) Dendrimers:-They represent a new class of controlled-structure polymers with nano-metric dimensions. They are considered to be basic elements for large-scale synthesis of organic and inorganic nano-structures with dimensions of 1 to 100 nm, displaying unique properties. Having compatible with organic structures such as DNA [11] Starpharma's lead nano pharmaceutical development product is Viva-Gel (SPL7013 Gel); a dendrimers-based gel is currently used in phase 2 trials.

APPLICATIONS OF DENDRIMERS: - These are used in conventional application, drug delivery, environmental and water cleaning.

c) Quantum Dots

It is a special form of spherical nano-crystals from 1 to 10 nm in diameter. They have been developed in the form of semiconductors, insulators, metals, magnetic materials or metallic oxides.

Quantum dots APPLICATIONS:-used to track DNA molecules in cells, efficient alternatives to conventional lighting sources, as biosensors used to detect agents of biological warfare.

Table 1. Nanotechnology used in drug delivery systems

There is various kinds of nanoparticles help in drug delivery system and performs various functions:

Sr. No.	Type of Nanoparticle	Material Used	Application
1	Nano-suspensions and Nano-crystals	Drug powder is disperse-d in surfactant solution	Stable system for controlled delivery of poorly soluble drug [12]
2	Solid lipid Nanoparticles	Melted lipid dispersed in Aqueous surfactant	Least toxic and more stable Colloidal carrier systems as alternative materials To polymers [13]
3	Polymeric nanoparticles	Biodegradable polymers	Controlled and targeted drug delivery [14]
4	Polymeric micelles	Amphiphilic block co-	Controlled and systemic

		polymers	Delivery of water insoluble Drugs [15]
5	Magnetic Nanoparticles	Magnetite Fe2O3,Meghe Mite coated with dextran	Drug targeting diagnostics to in medicine [16]
6	Carbon Nanotubes	Metals ,semiconductors or carbon	Gene and DNA delivery Controlled release of drug [17]
7	Liposomes	Phospholipids vesicles	Controlled targeted drug Delivery [18]
8	Nano-shells	Dielectric core and metal Shell	Tumor targeting [19]
9	Ceramic Nanoparticles	Silica, alumina, titanium	Drug and biomolecule Delivery [20]
10	Nano-pores	Aerogel, which is produced by cell gel chemistry	Controlled release drug Carriers [21]
11	Nano wires	Silicon, cobalt, gold or Copper based nanowires	Transport electron in nano Electronics [22]
12	Quantum dots	cdSe-cdS core shell	Targeting ,imaging agent [23]
13	Nano films	polypeptides	Systemic or local drug delivery [24]
14	Ferro-fluids	Iron oxide magnetic Nanoparticles surrounded by polymeric layer.	For capturing cells and other biological targets [25]

1) Nano-Suspension:- A suspension of drug nanoparticles in a liquid is called as nano-suspension. A size of nanoparticle lies in between 200 to 500nm [26]. The oral administration of drug in the form of nano-suspension resulted to enhance absorption rate and bioavailability. Nano-suspension of ibuprofen is prepared by emulsion-solvent diffusion technique for the purpose of improving ocular availability [27].

2) The solid lipid nano-particles:- are sub-micron colloidal carriers (50-1,000nm) which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. In order to overcome the disadvantages associated with liquid state of oil droplets, liquid lipid replaced by a solid lipid, which is transformed into solid lipid nanoparticles [28].

3) Polymeric Nanoparticle:- The drug is dissolved, entrapped, absorbed, attached or encapsulated into nanoparticle matrix [29].

4) Polymeric micelles:- have been extensively studied as drug carrier [30]. Polymeric micelles have better thermodynamic stability in physiological solution, as indicated by their low critical micellar concentration, which makes polymeric micelles stable and prevent their rapid dissociation in vivo. Micellar systems are useful for the systemic delivery of water-insoluble drugs [31].

5) Magnetic nanoparticles:- Magnetic nano-particles are powerful and versatile diagnostic tool in field of medicine.

EXAMPLE: Magnetic nanoparticle of indomethacin demonstrated selective targeting under magnetic field of 8000 strength, following normal administration, the drug concentration was higher in the liver and spleen where endocytosis and phagocytosis could occur [32].

6)Liposomes:-are small artificial vesicles of spherical shape that can be produced from natural non-toxic phospholipids and cholesterol.

They are therefore classified into three classes based on their size and number of bilayers. Small uni-lamellar vesicles (SUV) are surrounded by a single lipid layer and are 25-50nm in diameter. Large uni-lamellar vesicles (LUV) are heterogeneous group of vesicles similar to SUVs and are surrounded by a single lipid layer.

Multi-lamellar vesicles (MLV) consist of several lipids separated from one another by a layer of aqueous solution .Drugs associated with liposomes have markedly altered pharmacokinetic properties compared to drugs in solution. They are also effective in reducing systemic toxicity and preventing early degradation of the encapsulated drug after introduction to the target organism [33].

7) Gold nanoshells:- are new composite nanoparticles that combine infrared optical activity with the uniquely biocompatible properties of gold colloid. By varying absolute size of the gold nano-shell, it can be made to either selectively absorb (for particle diameter < 75nm) or scatter incident light. Gold nano-shells can be used to ablate breast cancer cells [34].

8) Ceramic nanoparticle: - The advantages of ceramic nanoparticles include easy preparation with desired size, shape and porosity, and no effect on swelling or porosity with no change in pH [35].

9) Nanopores:-Materials with defined pore-sizes in the nanometer range are of special interest for a broad range of industrial application because of their outstanding properties with regard to thermal insulation, controllable material separation and release and their applicability as templates or fillers for chemistry and catalysis [35].

10) Nanowires: - are conductive or semi conductive particles with a crystalline structure of a few dozen nm and a high length /diameter ratio. Silicon, Cobalt, Gold or Copper-based nanowires have already been produced .They are used to transport electrons in nano-electronics they could be composed of different metals, Oxides, sulphides and nitrites [36].

METHOD OF PREPARATION OF NANOPARTICLE

The preparation method of nanoparticles can be classified as follows [37] :-

1) Bottom Up Technique
2) Chemical Reaction Technique
3) Top-Down Technique
4) Combination Technique

1) Bottom Up Technique

This technique starts with drug molecules in solution. In proper conditions, the drug molecule starts to precipitate in larger formation. In this technique, the poorly soluble API is dissolved in a water miscible organic solvent. The precipitation is induced by mixing the drug solution with an aqueous phase. This is referred as Solvent/Antisolvent approach. One interesting approach is known as Evaporative precipitation into aqueous solution (EPAS).For this process, the API is dissolved in an organic solvent which is not miscible in water. The drug solution is sprayed into heated water resulting in an immediate evaporation of the organic solvent, thus nanoparticles are formed instantaneously. Spray freezing into liquid (SFL) & ultra-rapid freezing (URF) are alternative particle engineering process for the development of nanoparticles preparation.

2) Chemical Reaction Technique

Chemical reaction like polymerization is used for the preparation of nanoparticle. They are not used normally for the production of nanoparticles consisting pure API. This technique is very important for the production of pharmaceutical coating materials in the form of latex dispersion. Chemical technique can also be used for the manufacturing of polymeric nanoparticle consisting of a matrix forming polymer in which API is embedded. The drug loads of such particles are normally less than 100 percent and therefore easier to distinguish from drug nanoparticles produced via standard particle size reduction techniques.

3) Top-Down Technique:-

This technique starts with large API and break into smaller drug nanoparticles, therefore this technique is known as TOP-DOWN TECHNIQUE. A very important technique is WET BALL MILLING (WBM).To produce nano-crystalline dispersion, a milling chamber is charged with milling media (zirconium dioxide beads, polystyrene beads), aqueous stabilizers/surfactant solution and micronized API. The moving milling media causes high shear forces and thus attrition of the drug particles. For large scale production, the mill can be run in a circulation mode, which means that suspension is continuously pumped through the milling chamber until the desired particle size of the drug nano-crystal is obtained. The drug particles are separated from the milling media by a separating gap or a filter cartridge. This is the most important and current using technology for the preparation of nanoparticles. HIGH PRESSURE HOMOGENIZATION technology (HPH) is another very important top down technology [38].

4) Combination Technique

The most common combination is a bottom-up process which is combined with a top down process.

In another way, the preparation of nanoparticle can be classified as [39]

1) Dispersion of performed polymers
a) Solvent evaporation method
b) Spontaneous emulsification or solvent diffusion method
2) Polymerization of monomers
3) Ionic gelation or coacervation of hydrophilic polymers
4) Supercritical fluid technology

1) DISPERSION OF PERFORMED POLYMERS [40]

It is the most common technique used to prepare biodegradable nanoparticles from poly (lactic acid) PLA; poly (D, L glycolide), PLG [41].

Solvent evaporation method

Organic solvent such as dichloromethane, chloroform or ethyl acetate are used to dissolve the polymer which is also used as the solvent for dissolving the hydrophobic drugs. The drug is dissolved or dispersed in polymer solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water emulsion. Once stable emulsion is formed, the organic solvent is evaporated either by reducing the pressure or by continuous stirring.

For the preparation of uniform sized particle size, High Speed Homogenizer or Ultrasonication may be employed [42].

b) Solvent Emulsification or Solvent Diffusion Method:-

This is a modification of solvent evaporation method. This technique involves the use of water miscible solvent along with a small amount of water immiscible organic solvent as an oil phase. An interfacial turbulence is generated between the two phase due to the spontaneous diffusion of immiscible solvents leading to the formation of small particles. By increasing the concentration of water miscible solvent decrease the particle size can be achieved. Both solvent evaporation and solvent diffusion method are used for hydrophilic or hydrophobic drugs. For hydrophilic drugs, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase [43].

2) Polymerization Method:-In this method, monomers are polymerized to form nanoparticle in an aqueous solution in which drug may be dissolved. Drug may also be incorporated by adsorption onto the nanoparticles after polymerization completed [44]. The nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles [45]

3) Coacervation or Ionic Gelation Method:-This method involves a mixture of two aqueous phase, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate .In this method, a positively charged amino group of chitosan interacts with negative charge of tripolyphosphate to form coacervates with a size in the range of nanometers [46]. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature [47].

4) Supercritical Fluid Technology ;-Above described conventional methods such as solvent extraction-evaporation method, solvent diffusion method, and organic phase separation method requires the use of enormous amount of organic solvents which are hazards to the environment as well as human beings. Therefore, the supercritical fluid technology has been investigated as alternative to prepare biodegradable micro and nanoparticles. Supercritical fluids are environmentally safe [48]. A supercritical fluid can be defined as a solvent at a temperature above its critical temperature, at which the fluid remains as a single phase regardless of pressure. Supercritical CO2 (SC CO2) is the most widely used supercritical fluid because of its mild critical –conditions, non -toxicity, non-flammability and low price. The most common processing techniques involving supercritical anti-solvent (SAS) and rapid expansion of critical solution (RESS). The process of SAS is to employ the liquid solvent [49] e.g. Methanol which is completely miscible with the supercritical fluid (SC CO2),to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting the formation of nanoparticles. The solvent power of supercritical fluids dramatically decreases and the solute equally precipitates. This technique is clean because the precipitate is solvent free. RESS and its modified process have been used for the product of polymeric nano-particle [50].

Factors Affecting Selection of Polymer

Nanoparticle can be prepared from natural material like such as proteins, polysaccharides and synthetic polymers. The selection of inert matrix material is depends on many factors which are as follows:-

1) Final size of nanoparticle required
2) Drug properties like solubility and stability etc.
3) Surface charge and permeability
4) Degree of biodegradability, biocompatibility and toxicity
5) Desired drug release profile
6) Antigenicity of the final compound [51]

Characterization of Nanoparticles

Nanoparticles are characterized by their size, morphology and surface charge, using such advances microscopic techniques as scanning electron microscopy(SEM),Transmission electron microscopy (TEM), and atomic force microscopy (AFM).The average particle diameter, their size distribution and charge affect the physical stability and the in-vivo distribution of the nanoparticles. Electron microscopy techniques are very useful in ascertaining of the overall shape of polymeric nanoparticle, which may determine their toxicity.

The surface charge of the nanoparticles affects the physical stability and re-dispersibility of the polymer dispersion as well as their in vivo performance.

There are various types of evaluations are as follows:-

1) Particle size:-

Particle size distribution and morphology are the most important parameters of characterization of nanoparticles. Morphology and size are measured by electron microscopy. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affect the drug release. Smaller particles offer the larger surface area. As a result, most of the drug loaded onto them will be exposed to the particle surface leading to the fast drug release. On the other hand, drug slowly diffuse inside larger particles. As a drawback, the smaller particles tend to aggregate during storage and transportation of nanoparticle dispersion. Hence there is a compromise between a small size and maximum stability of nanoparticles [52].

Polymer degradation can also be affected by the particle size. The degradation rate of poly (lactic-co-glycolic acid) was found to increase with increase in particle size in vitro [53].

There is various kinds of tools for determining the particle size as discussed below:-

A) Dynamic Light Scattering :-

Currently this is the most fastest and popular technique for the determination of particle size. It is also known as PHOTON CORRELATION SPECTROSCOPY (PCS). It is widely used to determine the size of Brownian nanoparticles in colloidal suspension in the nano and submicron ranges. Shining monochromatic light (laser) onto a solution of spherical particles in Brownian motion causes a DOPPLER SHIFT when the light hits the moving particles, changing the wavelength of incoming light. This change is related to the size of nanoparticle. The PCS Technique represents the most frequently used technique for accurate estimation of particle size and size distribution based on DLS [54].

B) Scanning Electron Microscopy:-

It is giving the morphological examination with direct visualization. The technique is based on the electron microscopy offer several advantages in morphological and sizing analysis. For this analysis, firstly nanoparticle solution should be converted into the dry powder, which is then mounted on the sample holder followed by coating with a conductive metal, such as gold, using a sputter coater, The sample is then scanned with a focused fine beam of electrons [55].The surface characteristics of the sample can be obtained from the secondary electrons emitted from the sample surface. The nanoparticles must be able to withstand vacuum, and the electron beam can damage the polymer. The mean size obtained by the SEM is to be compared with the result obtained by the Dynamic light scattering. This technique is very much time consuming and costly.

C) Transmission Electron Microscope:-

This technique operates on the different principle than SEM, yet it brings same type of data. The sample preparation for TEM is complex and time consuming because of its requirement to be ultrathin for the electron transmittance. The nanoparticles dispersion is deposited onto support grids or films. To make nanoparticles withstand the instrument vacuum and facilitate handling, they are fixed using either a negative staining material such as phosphor-tungstic acid or derivative, uranyl acetate etc. or by plastic embedding. Alternate method is to expose the sample to liquid nitrogen temperatures after embedding in vitreous ice. The surface characteristic of the sample are obtained when a beam of electrons is transmitted through an ultrathin sample, interacting with the sample as it passes through [56].

D) Atomic Force Microscopy:-

It offers ultra-high resolution in particle size measurement and is based on a physical scanning of samples at submicron level using a probe tip of atomic scale [57].Its instrument provides a topographical map sample based on the forces between the tip and the sample surface. Samples are usually scanned in contact or noncontact mode depending on their properties. In contact mode, the topographical map is generated by tapping the probe on to the surface across the sample and probe overs the conducting surface in non-contact mode.

Advantage: - Its ability to image non- conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and micro structure. It provides the most accurate description of size and size distribution and requires no mathematical treatment [58].

2) Surface Charge:-

The nature and intensity of the surface charge of nanoparticles is very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bio-active compounds. The colloidal stability is analyzed through zeta potential of nanoparticles. This potential is and indirect measure of the surface charge. It corresponds to the potential difference between the outer HELMHOLTZ PLANE & the surface of shear. The measurement of zeta potential allows for predictions about the storage stability of colloidal dispersion. High zeta potential values, either positive or negative, should be achieved in order to ensure stability & avoid aggregation of the particles. The extent of surface hydrophobicity can then be predicted from the values of zeta potential. The zeta potential can also provide information regarding the nature of material encapsulated within the nano-capsules or coated onto the surface [59].

3) **Surface Hydrophobicity: -** This is determined by several techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption of probes, contact angle measurements etc., X-RAY photon correlation spectroscopy permits the identification of specific chemical groups on the surface of nanoparticles [60].

4) **Drug Loading: -** Ideally, a successful nanoparticle system should have a high drug loading capacity thereby reducing the quantity of matrix materials for administration.

Drug loading can be done by two methods:-

1) **Incorporation Method:-**Incorporating at the time of nanoparticles production.

2) **Adsorption/Absorption Technique: -** Adsorbing the drug after formation of nanoparticles by incubating the carrier with a concentrated drug solution.

Drug loading and the entrapment efficiency very much depend upon the solid state drug solubility in matrix material or polymer (solid dispersion or dissolution) which is related to the polymer composition , the molecular weight , the drug polymer interaction and the presence of end functional group (ester or carboxyl) [61].

5) **Drug Release**: - A central major factor for delivery of a drug is to understand the manner and extent of release of drug molecules is very important. One such important method required that drug and its delivery vehicle be separated. The drug loading of the nanoparticles is defined as the amount of drug bound per mass of the polymer (usually moles of drug per mg polymer or mg drug per mg polymer); it could also be given as percentage relative to the polymer. The technique used for this analysis is classical analytical methods like UV spectroscopy, or high performance liquid chromatography (HPLC) after ultracentrifugation, ultrafiltration, gel filtration, or centrifugal ultrafiltration. Quantification is done by UV spectroscopy of HPLC [62].

Various methods used for the evaluation of the release of drug in-vitro from nanoparticles are:-

1) Side by side diffusion cells with artificial or biological membrane.
2) Dialysis bag diffusion technique.
3) Reverse dialysis bag technique.
4) Agitation followed by ultracentrifugation /centrifugation.
5) Ultra- filtration or centrifugal ultrafiltration technique [63].

APPLICATIONS OF NANOTECHNOLOGY:-

There is various kinds of applications which are explained as follows:-

1) GENERAL APPLICATIONS

1) In The Removal of Pollutant: - The nanoparticles are used for the removal of pollutants and make them pollutant free in the environment.

a) Pd/Fe nano-particle: - Its removal target is like Trichloroethene & Tetrachloroethene.

b) Cu/Fe nano-particle: - Its removal target is nitrate.

2) Nanotechnology Used In Water & Waste Water Treatment :-

A) Adsorption:- Carbon nanotubes follows adsorption principle because of having properties like high specific area, high assessable adsorption sites, diverse contaminant – CNT interactions, tunable surface chemistry, easy reuse

B) Photo-Catalysis: - Nano-Tio_2 follows principle photo-catalysis because of their quality of photo-catalytic activity in UV & possibly visible light range, low human toxicity, high stability and low cost.

C) Dis-Infection & Microbial Control :- The nanoparticle Nano – Ag follows Dis infection & microbial control activity which are having strong & wide spectrum antimicrobial activity , low toxicity to humans and ease of use [64].

3) Heavy Metal Removal: - Oxidized Carbon nanotubes have high adsorption capacity for metals and helps in the removal of heavy metals.

4) Carrier For Drug Delivery:

1) Carbon nanohorns (CNHs) are the spherical aggregates of CNTs with irregular horn like shape. Research studies have proved CNTs and CNHs as a potential carrier for drug delivery system.

2) Functionalized carbon nanotubes are reported for targeting of Amophotericin B to cells [64].

3) Cisplatin incorporated oxidized SWNHs have showed slow release of Cisplatin in aqueous environment. The released Cisplatin had been effective in terminating the growth of human lung cancer cells, while the SWNHs alone did not show anticancer activity [65].

4) Anticancer drug Polyphosphazene platinum given with nanotubes had enhanced permeability, distribution and retention in the brain due to controlled lipophilicity of nanotubes [66].

5) Antibiotic, Doxorubicin given with nanotubes is reported for enhanced intracellular penetration [67].

6) The gelatin CNT mixture (hydro-gel) has been used as potential carrier system for bio-medicals.

7) CNT-based carrier system can offer a successful oral alternative administration of Erythropoietin (EPO), which has not been possible so far because of the denaturation of EPO by the gastric environment conditions and enzymes [67].

8) They can be used as lubricants or glidants in tablet manufacturing due to nano-size and sliding nature of graphite layers bound with vander walls forces [67].

2) APPLICATIONS OF NANOPARTICLE ON THE BASIS OF COMPOSTION:-

Nanoparticles with different compositions and characteristics and investigated for various therapeutic applications as follows:-

Carriers of gene and DNA:-

One of the most common techniques used today to analyze DNA sequences is hybridization, or the pairing of separated strands of DNA with complementary DNA strands of known sequence that act as probes [68] Currently, DNA chips called DNA micro array assays are used to analyze DNA. Passive (non-electronic) technologies can be slow, tedious, and prone to errors because of nonspecific hybridization of the DNA [69].

a)Nanochips:-A company called Nanogen has developed a product called the "Nanochip" that employs the power of an electronic current that separates DNA probes to specific sites on the array based on charge and size. Once these probes are on specific sites of the nanochip, the test sample (blood) can then be analyzed for target DNA sequences by hybridization with these probes. The DNA molecules that hybridize with target DNA sequences fluoresce, which is detected and relayed back to an onboard system through platinum wiring that is present within the chip [70].

b) Microfluidics (Lab-on-a Chip)

The newest technologies within nano-diagnostics involve microfluidic or "lab on a chip" systems, in which the DNA sample is completely unknown. The idea behind this kind of chip is simple: the combination of numerous processes of DNA analysis are combined on a single chip composed of a single glass and silicon substrate. The device itself is composed of micro fabricated fluidic channels, heaters, temperature sensors, electrophoretic chambers, and fluorescence detectors to analyze nano liter-size DNA samples. This device is described as capable of measuring aqueous reagent and DNA-containing solutions, mixing the solutions together, amplifying or digesting the DNA to form discrete products, and then separating and detecting those products. Using a pipette, a sample of DNA containing solution is placed on one fluid-entry port and a reagent containing solution on the other port. Capillary action draws both solutions into the device, but hydrophobic patches positioned just beyond the vent line in each injection channel stop the samples [71].

3) Nanotechnology in Drug Discovery: - Nanoparticles for Drug Discovery

Nanocrystals (QDs) and other nanoparticles (gold colloids, magnetic nanoparticles, nanobarcodes, nanobodies, dendrimers, fullerenes, and nanoshells) have received considerable attention recently with their unique properties for potential use in drug discovery. For example, QDs and magnetic nanoparticles can be used for barcoding of specific analytes. Gold and magnetic nanoparticles are key components of the bio-barcode assay, which has been proposed as a future alternative to the protein chain reaction [72].

4) Application of nano-biotechnology in various therapeutic areas:-

1) Oncology:-Nano-engineered particles have been developed to reach specific molecular targets on diseased cells and have been used in various experimental and clinical conditions. For cancer diagnostics nanoparticles have been engineered to optimize magnetic resonance imaging, ultrasound imaging and nuclear medicine imaging. The potential benefits of nanoparticle cancer treatment are highly selective and rapid tumor destruction with minimal damage to surrounding healthy tissue [73].

2) Neurological Disorder:-Nano-materials are delivered as a specific structure, or combination of structures, designed to deliver the therapeutic effect, directly to the site, requiring a much lower dose. These materials use very specific and deliberate molecular structures that can interact with neurons or protein structures inside the cells. A well-planned treatment spaced over time will produce functional return in the CNS. The four parts of CNS regeneration is a new framework for approaching CNS injury and evidence shows that nanotechnology is currently being used for stroke rehabilitation and, in several clinical trials, the treatment of scar formation blockade in the spinal cord. The four components are preserve, permit, promote, and plasticity [74].

5) Role of Nanobiotechnology in Based Drug Delivery in the Development of Nanomedicine:-

Nano-medicine is now within the realm of reality starting with nano-diagnostics and drug delivery facilitated by nano-biotechnology. Miniature devices such as nano-robots could carry out integrated diagnosis and therapy by refined and minimally invasive procedures, nano-surgery, as an alternative to crude surgery. Nanotechnology will markedly improve the implants and tissue engineering approaches as well. It offers the key to faster and remote diagnostic techniques including new high throughput diagnostics, multi-parameter, tunable diagnostic techniques, and biochips for a variety of assays. It also enables the development of tissue-engineered medical products and artificial organs, such as heart valves, veins and arteries, liver and skin. These can be grown from the individual's own tissues as stem cells on a 3-D scaffold, or by the expansion of other cell types on a suitable substrate [75].

6) APPLICATIONS OF NANOTECHNOLOGY IN PHARMACEUTICAL FIELD:-

A) Tumor Targeting Using Nano-particulate Delivery Systems

The rationale of using nanoparticles for tumor targeting is based on following characteristics:

1) Nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles [76].

2) Nanoparticles will reduce the drug exposure of healthy tissues by limiting drug distribution to target organ.

Studies show that the polymeric composition of nanoparticles such as type, hydrophobicity and biodegradation profile of the polymer along with the associated drugs molecular weight, its localization in the nano-spheres and mode of incorporation technique, adsorption or incorporation, have a great influence on the drug distribution pattern in vivo. The exact underlying mechanism is not fully understood but the bio-distribution of nanoparticles is rapid, within hour to 3 hours, and it likely involves mononuclear phagocytic system (MPS) and endocytosis/ phagocytosis process [77]. Such propensity of MPS for endocytosis/phagocytosis of nanoparticles provides an opportunity to effectively deliver therapeutic agents to these cells. This bio-distribution can be of benefit for the chemotherapeutic treatment of MPSrich organs/tissues localized tumors like hepato-carcinoma, hepatic metastasis arising from digestive tract or gynecological cancers, brochno-pulmonary tumors, primitive tumors and metastasis, small cell tumors, myeloma and leukemia [78].

B) Nanoparticles for Oral Delivery of Peptides and Proteins-

Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration. The surface area of human mucosa extends to 200 times that of skin [79]. The gastrointestinal tract provides a variety of physiological and morphological barriers against protein or peptide delivery, e.g,

(a) Proteolytic enzymes in the gut lumen like pepsin, trypsin and chymotrypsin;

(b) Proteolytic enzymes at the brush border membrane (endopeptidases);

(c) Bacterial gut flora;

(d) Mucus layer and epithelial cell lining itself. The histological architecture of the mucosa is designed to efficiently prevent uptake of particulate matter from the environment. One important strategy to overcome the gastrointestinal barrier is to deliver the drug in a colloidal carrier system, such as nanoparticles, which is capable of enhancing the interaction mechanisms of the drug delivery system and the epithelia cells in the GI tract.

C) Nanoparticles for Drug Delivery in to The Brain:-

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid-soluble molecules by the function of enzymes or efflux pumps. Consequently, the BBB only permits selective transport of molecules that are essential for brain function. Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with specific receptor-mediated transport systems in the BBB. For example polysorbate 80/LDL, transferring receptor binding antibody (such as OX26), lactoferrin, cell penetrating peptides and melanotransferrin [80].

D) Implantable delivery systems

Nanoparticles can act as the delivery systems by virtue of its size, controlled an approximately zero order kinetics, otherwise they may cause toxicity when compared to I.V. Carriers are liposome, ethosome and transferosome. These help in minimizing peak plasma levels and reduce risk of adverse reactions, allow for more predictable and extended duration of action, reduce the frequency of re-dosing and improve patient acceptance and compliance (Jain NK., 2002) [81].

E) Molecular diagnostics: (molecular imaging)

It is representing, characterizing and quantifying sub cellular biological processes include gene expression, protein-protein interaction, signal transduction, cellular metabolism. They are used in magnetic resonance imaging, optical imaging, ultrasonic imaging and nuclear imaging. Other applications are specific labeling of cells and tissues, useful for long-term imaging, multicolor multiplexing, dynamic imaging of sub cellular structures and fluorescence resonance energy transfer (FRET) and magnetic resonance imaging (MRI). MRI agents are replaced by nano-materials like dendrimer, quantum dots, carbon nanotubes and magnetic nanoparticles. They are very efficient, stable, intense, clearer image due to high

intensity, photo stability, resolution, resistance (Gupta P.k et al., 1987).Quantum dots, iron oxide nano-crystal and metallic nano-particles [82].

F) Biosensor and bio-labels:-

These tools are employed for determination of various pathological proteins and physiological-biochemical indicator associated with disease or disrupted metabolic conditions of body. Biosensor is a measurement system that consists of a probe with a sensitive biological recognition element or bio- receptor, a physiochemical detector component and a transducer to amplify and transducer these signals into measurable form. A nano-biosensor or nano-sensor is a biosensor that has dimensions on the nanometer size scale. Biosensors are used in target identification, validation, assay development, ADME, toxicity determination (Khopde AJ et al., 2001) [83].

NANOTECHNOLOGY BASED ON ENERGY BASED THERAPIES:-

There are some important points which are as follows:-

1) Nanotechnology has begun to be used as a tool to increase the resolution of thermal ablation treatment area [84], tumor visualization [85], and improve treatment effectiveness [86].

2) The most direct method used for the enhancement of thermal therapy [87] has been the systemic or local introduction of nanoparticles given concurrently with energy-based ablation treatments [88].

3) For hyper-thermic therapies, carbon nanotubes, gold nano-shells, and iron oxide nanoparticles have proven extremely useful for enhancing heating effects due to energy absorption by the nanoparticles during treatment [89].

4) Furthermore, the use of metallic or carbon nanoparticles as treatment adjuvants enables the treated region to be visualized through noninvasive means such as MRI and CT.

5) To overcome problems with systemic toxicity and enable target specificity, nano-capsule carriers with targeting moieties have been searched to preferentially deliver therapeutics to diseased tissue via cell surface receptors.

6) Some cell surface receptors help transmit messages from the extracellular environment to the intracellular environment, and in many cancerous cells are over expressed

7) In the early 1970s, Calcium phosphate (Ca-P) precipitates were used as transfection reagents of viral DNA as they are believed to be non-toxic [90].

8) Calcium Phosphate effectively protects the nucleic acids from enzymatic degradation and aided cellular delivery, but uncontrollable rapid growth of calcium phosphate crystals greatly reduced the transfection efficiency.

9) Also, biodegradable nanoparticles have been developed and have shown good potential as carriers for anticancer drugs with a spherical structure [91].

10) Thermally responsive nano-encapsulation systems have been developed using temperature sensitive carriers designed to deliver chemotherapeutic agents preferentially to tumor sites. During the temperature change associated with energy-based treatment [92], a conformational or structural change in the delivery vehicle causes the release of chemotherapeutics from the carrier [93]. Once released, therapeutic agents are free to diffuse away from their carrier and act on nearby targets with promising results [94].

11) Moreover, the delivery of metallic nanoparticles and chemotherapeutic agents simultaneously provide an approximated visualization of drug delivery localization and treatment area [95]. Therefore, this combined approach has the potential to reduce the total treatment area due to the energy absorbing properties of metallic nanoparticles [96], provide an increase to the complete kill zone from both targeted heating and chemotherapeutic agent delivery [97].

CONCLUSION

Through further investigation and clinical trials, energy-based therapy assisted by nanotechnology may bring about a developing shift in primary cancer treatment.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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