

Applications of Nanotechnology in Drug Delivery and Design - An Insight

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Abstract

Nanotechnological application is greatly important in the field of drug delivery because of its high specificity towards the target site, so it is able to reduce toxic side effects of drugs to normal cells. Reduce plasma fluctuation of drugs, high solubility, efficiency, reduces cost of products and enhancement of patient comfort are reasons that nanotechnology is used for drug delivery. The nanoparticle (NP) plays a vital role and it can conjugate with various drugs by different methods to deliver drugs to the target site. The NP surface is designed with ligands to get affinity towards specific cells and co-polymers to get protection from immune cells. The nanoparticles conjugated drug can eventually recognize the site and join to the target and enter to the cell by receptor mediated endocytosis. Then NPs are able to release drugs controllably to cure diseases. This review analyses the nanotechnology in drug delivery, discovery, nanoparticles and formulation, mechanism of drug delivery and applications.

Keywords: Nanoparticles, Nanoparticle formulation, history, Drug delivery system, mechanism of delivery.

Abbreviations

Acquired immunodeficiency syndrome (AIDS), Atomic force microscope (AFM), Blood brain barrier (BBB), Carbon nano-horns (CNH), Carbon nano-tubes (CNT'S), Drug delivery system (DDS), Elastomer-like proteins (ELP),

Genetic engineering method (GEM), Human immunodeficiency virus (HIV), Inosiazid (INH), Lipid drug conjugates (LDC), Metal nanoparticles (MNP), Multiple drug resistance (MDR), Nano structured lipid carriers (NLC), Nanoparticles (NP), National aeronautics and space administration (NASA), Polyethylene glycol (PEG), Poly-glycolic acid (PGA), Poly-lactic acid (PLA), Pyrazinamide (PZA), Rifampin (RMP), Screening tunneling microscope (STM), Solid lipid nano-particles (SLN), Tuberculosis (TB).

Introduction

National nanotechnology initiatives in USA, defined nanotechnology as "Science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers". The study, design, synthesis, manipulation, and application of functional materials at nanometer scale and one nanometer being equal to 1×10^{-9} m that is at the atomic and molecular levels (1).

Nanotechnology is recently developed science and it is able to create engineering functional materials or systems, devices with in the nanoscale. Nanomaterials have unique properties such as mechanical, optical, magnetic, electrical and biochemical with vast range of applications ranging from basic material science to personal care applications. Some recently developed applications of nanotechnology are energy storage production and conversion, agriculture productivity enhancement, water treatment and remediation, disease diagnosis

and screening, drug delivery systems, food processing and storage, air pollution and remediation, constructions, health monitoring using nanotubes and NPs, space science material production, chemical industry, information technology, textile industry, electronic consumer production, vector and pest detection and control, automobile industry. Nanotechnology produces new materials with the size of atomic scale/ super molecular scale/ nanoscale. This molecular scale is usually below 100nm in simple term it is one billionth of a meter. Nanotechnology is a field recently developed and it plays a vital role in science and technology field but yet it's not in the matured level (1, 2).

Nanotechnology uses in Medicine : National Institute of Health in USA, defined nanomedicine as “highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of disease”. This nanotechnology application in medicine also immature field and few methods already in action but some techniques only imagined while most of the techniques are under the research conditions (7). Nanotechnology is used in field of medicine for drug delivery, treatment, diagnostic & monitoring techniques, bio sensors, antimicrobial techniques, cell repair and control the biological system are some of applications (8). Fiber optic technology uses to monitoring diseases. Optical biosensors used to measurement physical parameters such as pH, blood flow rate, blood oxygen levels, radiation dosage. Endoscopy in next generation will extend its capability from imaging to diagnostics and therapy using nanofiber technology. Fiber optic sensors, endoscopes nano-scale bioprobes with the rapid advance of nanotechnology (9).

Drug Delivery : Drug delivery system (DDS) is defined by national institute of health in USA as, “Formulation of a device that enables the introduction of therapeutic substances in to the body and improves efficiency and safety by the control the rate, time and place of release of drug in the body.” The process of drug delivery can be mainly divided in to,

- 1) The administration of the drug or therapeutic product can be divided as non-invasive and invasive administration. Non-invasive administration such as oral, topical (skin), nasal, and inhalation routes. Invasive administration is injection or nanoneedle array.
- 2) The release of the active part of the drug by the product.
- 3) Transport active ingredients across the biological membrane to the target site to perform action.

DDS interface, between the patient and the drug and it may be formulation of the drug or device used to the deliver the drugs to the particular site (10, 11). The usual drug delivery systems are not up to the satisfactory level. There were many drawbacks include poor bioavailability, generate side effects, low drug loading capacity, poor ability to control the size range, plasma fluctuation of the drug levels, low therapeutic effectiveness, low in- vivo stability, low solubility, no control over the time, location and lack of target delivery to the site of action as well as some drugs are only active in a narrow range. If concentration is above the threshold level it becomes toxic, if it is low lack of therapeutic effect. These drawbacks put pressure on scientists to investigate more about new DDS and it control and determine the rate and location of drug release (12). Scientists developed NPs of the size of macromolecules such as DNA and proteins. The some developed nano-structures were smaller than diameter of a double stranded DNA (2nm). The smallest cellular form in the world is a bacteria named *mycoplasma*. Which has the size of 200nm but in comparison the largest NP is only 100nm in size. New DDS has the ability to deliver drugs to specific target cells in various areas of the body without degradation in the gastrointestinal track. It includes delivery and targeting of pharmaceutical, therapeutical and diagnostic agents by the help of NPs to the cells such as cancer cells. The ultimate goal of NP drug delivery is to improve the proper treatment diagnostics and prevention of disease (3, 7).

The NP used in DDS contains encapsulated, absorbed, dispersed or conjugated drugs and this were able to, provide lower toxic side effects, provide multi functionality targeting, delivery and reporting ability, have high saturation solubility, drug particles resistance to settling, provide improved therapeutically index, high efficiency of drug delivery, rapid dissolution, reduces plasma fluctuation level, reduces the drug dosage, The drug directly releases to site and it is in nanosize, ultimately cut down the cost of drugs (13).

Nanotechnology increases oral bioavailability of drugs as a result of their special uptake mechanisms such as absorptive endocytosis. The NPs are also able to remain in the blood for long period and release the drugs in controllable manner to the target tissue. The self-controlling system of drug releasing helps to reduce the plasma fluctuation and minimized the side effects. The drug is incorporated in to the NP which is in nanoscale and it is easily diffused through biological membranes and cells take up these particles for the efficiency in drug delivery to site of action (14). Nanotechnology improves performance effectiveness, safety, patient adherence as well as reduces the cost compare to traditional DDS. The nanotechnology successfully used in drug delivery in the treatment of cancer, asthma, and hypertension as well diabetics. There are hundreds of various ongoing researches in this field to improve efficiency of DDS (15). Nanotechnology capable of production biodegradable, biocompatible, targeting and stimulate responsive carriers such as liposomes, nanofabricated materials (fullerenes, carbon nanotubes, silicon, silica) metals (gold, silver, iron, platinum, quantum dots) and polymers (micelles, dendrimers). The nanoparticles can obtain different shapes such as spherical, rods, wires, discs, hemispherical and ellipsoidal (16). NPs are known as a successful drug delivery materials because of it contains several properties such as, high drug carrying capacity, higher stability for the drugs inside blood stream and can travel without sedimentation and

blockage, both hydrophilic and hydrophobic drugs can incorporate with the carrier, the drug conjugated NP can administration in to the body using various methods such as non-invasive and invasive administration, the drug releasing from the NP matrix can be control, NPs can easily penetrate in to the tissues such as cancer cells, NPs can take up by cell naturally via endocytosis. These properties of NP attached drug delivery method leads to improve duration of drug circulation, bio-availability of the drug and control drug releasing at the particular site. Ultimately NP with drug incorporation enhancing the ability to use highly toxic, poorly soluble, unstable drugs and maximizing patient comfort (17).

History of nanotechnology uses as drug delivery : First Generation-

This era basic mechanism of controlled drug release was established and most drug delivery formulations were oral and transdermal administration. The effectiveness and stability was low in these drug systems (4). More than 150 years ago, Michael Faraday prepared gold particles in nanometer scale. These colloidal gold particles were conjugated with antibodies for target specific staining known as immune-gold staining. This application of gold particle considered as a precursor of recent application of gold particles in nanotechnology. In 1960s, Liposomes and polymer micelles were first prepared, however it was never referred as nano-particles until 2000. In 1970s, NPs and dendrimers were first prepared without the knowledge of nanotechnological application. In 1980s, the period reported to be the successful development of micelles as drug delivery system. And in 1990s, Block co-polymers of polyethylene glycol (PEG), PEG-Polylysine have been invented by Kataoka (14). Prior to nanotechnology revolution, in past liposomes, polymeric micelles, nanoparticles, dendrimers, and nano-crystals used for drug delivery, but in the era nanotechnology, the terms were unknown.

Second Generation: The modern nanotechnology uses as drug delivery began when United States launched the national

nanotechnology initiatives, the world first program in the field of nanotechnology. There were various new methods introduced for drug delivery among them nanotechnology method became more efficiency and cut down drawbacks in ordinary DDS (4).

Current immature nanotechnology use microchips, carbon nanomaterials, micro needles based transdermal therapeutic systems, layer by layer assembled system and various microparticles produced by inject technology as well as previous nanocarriers were developed using co-polymers such as polyethylene glycol(PEG) and ligands. (14).

Nanoparticles : There are mainly 2 types of nanoparticles as, Organic nanoparticles {Polymers in DDS (polymeric miscalls, polymeric NPs, polymeric drug conjugates), dendrimers, nano crystals and lipid based NPs like liposomes, solid lipids} and Inorganic nanoparticles {Metal NPs (gold, silver, iron, platinum, quantum dots), Silica NPs (mesoporous, Xerogels)} (5, 16).

Liposome : Lipids are amphiphilic molecules; both hydrophobic and hydrophilic parts are included in same molecule. When it is contact with water, lipid bilayer forms as a result of unfavorable interactions by naturally or can make synthetically by mechanical agitation. A lipid bilayer will close in on itself; forming a spherical vesicle separating the external environment from an internal compartment such vesicles are named as liposomes. Liposomes are able to carry both hydrophobic and hydrophilic drugs incorporated in to their vesicle tails and heads/ aqueous core respectively. The liposomes are biocompatible, biodegradable, increase solubility of drugs; improve pharmacokinetic properties such as rapid metabolism, reduction of side effects, increase of an in-vitro and *in-vivo* anticancer activity and therapeutic index of chemotherapeutic agents (18).

The shape, surface charge, size and functional groups in liposomes can easily change according to the drug and target site. Liposomes

have high efficiency and low toxicity, so it can use to deliver DNA, si.RNA, proteins, antisense oligonucleotides both hydrophobic and hydrophilic chemotherapeutic agents. Liposomes can be prepared by methods such as mechanical agitation, solvent evaporation, solvent injection, surface solubilization method. Drugs are incorporated in to the liposomes by encapsulation method and it provides various size ranges, various physiochemical properties and prevents subsequent leakage from liposomes. pH, liposome composition, osmotic gradient, surrounding environment, magnetic field and radio frequency regulates the drug release to the target site (7,18,19).

Adsorption, fusion, lipid transfer and endocytosis are the various methods which can use to interaction of liposomes with cells. Liposomes are encapsulated with various drugs such as anticancer drugs, neurotransmitters, antibiotics and anti-inflammatory drugs as shown in table 1. (7)For instance doxorubicin is highly toxic compound, when treated to the cancer patients it have the ability to affecting tumor cells as well as heart and kidney, finally using liposomes it delivered directly to the tumor cells instead of accumulate in the heart and kidney.

The drawbacks include with liposomes as low encapsulation efficiency, quickly releasing of drugs, poor storage ability, lack of tunable triggers for drug release and it release drug in to the extracellular fluids. To overcome these problems scientists modified surface of liposomes using PEG and it is act as protection layer on the surface of liposomes and it can slowdown liposome recognition by macrophages. The liposomes attached to specific proteins, antigens, antibodies, ligands or other biological substances which helps to target cell recognition for target specific drug delivery (19).

Nanoparticles based on solid lipids: There are 3 main types such as solid lipid NPs (SLN), nano structured lipid carriers (NLC) and lipid drug conjugates (LDC). SLN are composed of pure triglycerides, complex glycerolaldehydes mixture

Table 1. Several drugs and treatment which uses liposomes.

Drug	Treatment
1) Amphotericin B	Fungal infections.
2) Doxorubicin	Ovarian cancer, Kaposi's sarcoma, breast cancer.
3) Cytarabine	Lymphomatous meningitis.
4) Daunorubicin	Kaposi's sarcoma
5) Comptothecin	Anticancer drug.
6) Vancomycin	Antibiotics drug.

or waxes stabilized by various surfactants. They are highly stable drug release in controllable manner, drug protection and good tolerability. The drawback is lower drug loading capacity and as a result NLC and LDC are modified. NLC produced by mixing both solid and liquid lipids and increase drug loading capacity and prevent drug deposition. LDC developed as lipophobic drug molecule and prepared by salt formation by covalent linking (18).

Nano-Crystals: The drug which needs to be injected in to the cell is produced in nano size and it can function as its own carrier. The drug particles readily water soluble as a result of its nanosize. The drug particle is reduced to the nanosize range and stabilized surface by polymeric macromolecules and nonionic surfactants. The size decreases means increasing surface area of drug. Ultimately solubility dissociation is increased and plasma concentration rises. The nanocrystals can reduce accumulation of carrier particles and directly drug can incorporate with target site. Nanocrystals become stable in aqueous dispersion without any stabilizers. These can efficiently take up by tumor cells (7, 20).

Polymeric nanoparticles-These are synthetic polymers and size ranging from 10-100nm such as polyglycolic copolymers, poly [-caprolactone, poly-acrylamide, poly-acrylate or natural polymers such as albumin, gelatin, alginate, collagen, DNA, chitosan, alginate.

Table 2. Several drugs and treatment which uses Nanocrystals.

Drug	Treatment
Rapamycin	Immunosuppressive
Megestrol	Anti-anorexia
Fenofibrate	Hypercholesterolemia
Aprepitant	Anti-emetic

These polymeric NPs may be biodegradable or non-biodegradable (21). These are produced using various methods such as solvent diffusion, emulsification diffusion, solvent evaporation, spontaneous emulsification and use of supercritical carbon dioxide and polymerization. Recently produced smart polymers and it stimuli to environment signals such as temperature, electrical mechanical strength, enzyme and biomolecules (22).

The various drug incorporating mechanisms use such as 1) Covalent bonding between drug and polymer carrier. 2) Hydrophobic interactions in-between drug and carrier 3) water filled depot for hydrophilic drug incorporation. The drug are released in to the target site by diffusion, desorption and NP erosion. The polymeric NP can deliver drugs to the site of action with minimum toxic levels and it is hydrolysis inside body to produce biodegradable metabolite monomers like lactic acid and glycolic acid (7, 18).

Table 3. Several drugs and treatment which uses polymeric NPs.

Drug	Treatment
Carboplatin	Ovarian, head, neck, lung cancer
Doxorubicin	Wide spectrum of tumors.
Lamivudine	Anti HIV drug
Clotrimazole	Antifungal drug

Polymer Drug conjugates: Protein and peptide drugs are conjugate with polymers such as polyethylene glycol(PEG), PEG-camptothecin and it can prevent protein drug degradation in stomach and also soluble in water hence increase the half life of drugs in plasma. White blood cells unable to recognize them as foreign particles because of it conjugated polymers. Recently developed brush polymer drug conjugates by ring opening metathesis copolymerization and it solubalized in water easily than polymer drug conjugates (7).

Table 4. Several drugs and treatment which uses polymer drug conjugates.

Drug	Treatment
L-asparaginase	Acute lymphoblastic leukemia
Adenosine deaminase	Adenosine deaminase enzyme deficiency
PEGylated IFN- α -2a	Hepatitis C

Polymeric micelles: It forms amphiphilic surfactants spontaneously associated in aqueous medium to form core shell structure. Inner core of micelle hydrophobic and surrounded by shell of hydrophilic polymers such as PEG. Hydrophobic core provide space for poor water soluble hydrophobic drugs while hydrophilic surface shell stabilizes core, prolongs circulation time and accumulate in tumor. Drug incorporated either by physical encapsulation or covalent attachment. For instance paclitaxel is drug which incorporated with polymeric micelles and use to delivery chemotherapy for cancer (7).

Dendrimers: Dendrimers are synthetic polymers with well defined size and structural branched chain. The chemical composition regulates the

biocompatibility and pharmacokinetics. The size ranging from 1-10nm while composed of core, dendrons and surface active groups. Core provides space to drug to encapsulate and it regulates the drug releasing rate. The branched monomers called dendrons are attached to the core and surface active groups determined the physiochemical properties. Dendrimers can be synthesized from core and after the layer called as divergent process. In convergent process synthesis starts at the outer surface and it stops at core region. In-vitro and In-vivo Cytotoxicity of the dendrimers is controlled by core materials and nature of dendrimers surface. Drugs can incorporate either to internal surface/core or dendrimers surface by covalent bonds and it decide by the drug and target site. High toxicity and poor soluble drugs encapsulated to core while amount of drug can control by surface attachment. Folic acid, antibiotics, cyclic targeting peptides, PEG can attach to get high activity and specificity. For example methotrexate, doxorubicin can deliver using dendrimers to tumors and ibuprofen, piroxicam as anti-inflammatory drugs (13,18).

Carbon nanomaterials: The nano-tubes (CNT'S), C-60-fullerenes and nano-horns (CNH) uses as carbon nanomaterials. Single walled CNT'S or multi walled CNT'S are produced using layer of graphite and it has higher electrical and thermal conductivity. The surface of CNT'S are covered by amphiphilic di block copolymers, PEG layer or hyaluronic acid matrix and it helps to increase biocompatibility of carrier. The drugs are attached to carrier by encapsulation drugs to CNT'S, chemical adsorption of drugs to surface and active agents into functionalized CNT'S. The CNT'S release drugs in controllable manner by electrically or chemically and it helps to protect drugs. CNH and C-60 fullerenes also have similar properties as CNT'S. They have several immobilization techniques to attach drugs as shown in table 5 (7). The drawbacks of carbon NPs is toxicity and it depends on geometrical structure and surface molecules like carbonyl, hydroxyl.

Table 5. Several drugs and immobilization method which uses in Carbon nanomaterials.

Drug	Mode of immobilization
Gemcitabine	Encapsulation
Doxorubicin	Adsorption
Amphotericin B	Conjugation
Pt (4) prodrug-FA	Covalent amide linkages
Dexamethasone	Encapsulation

Silica Materials: Xerogels and mesoporous silica NPs have higher biocompatibility, convenient functionalization and high porous matrix. Xerogels has highly porous and surface area and drug loaded by sol-gel technique. The drug releasing rate can control by changing synthesis conditions such as temperature, pressure, ratio of reagents. Phenytoin, cisplatin, nifedipine, doxorubicin, matronidazole, heparin are drugs incorporated with xerogels. Mesoporous silica nanomaterials have high surface area for drug absorption, homogenous structure. Anticancer drugs, antibiotics, heart disease drugs are delivered by mesoporous and drug releasing controlled by diffusion method (18).

Metal nano-particles (MNP): Gold, silver, iron, platinum, ceramic, quantum dots and super magnetic uses as NPs because of it shape depending optical, magnetic, electrical properties and size. Physical, chemical and green approaches uses to production of MNP's. Physical methods are evaporation condensation and laser ablation. It provides less solvent contamination and uniform distribution. Chemical method uses reducing agents such as ascorbate, sodium borohydride, tollens reagent. Biological approach uses bacteria fungi and plant species for production MNM. Magnetic NPs can control with help of external magnetic field so it able to same time reported and treated diseases (23).

Others

Nanoparticle formulation

1) *Nano-precipitation:* It is easy and quick method performed by adding an organic solution which containing polymer and lipophilic drug in to the aqueous solution in drop-wise manner under constant stirring. Co-polymer particles are highly flexible while it has both hydrophilic and hydrophobic surfaces. Inside water hydrophobic parts

Table 6. Several other NP

Other Nano particles	Description
Ethosomes	Carriers that enable drug to reach the deep skin layer/ systemic circulation
Aquasomes	Composed of nanocrystals and covered with polyhydroxyloligomeric film
Phamacosomes	Pure vesicles formed by amphiphilic drugs
Collidosomes	Bilayer structure made up of non-ionic surfactant vesicles
Nonemulsions	Submicron emulsions O/W or W/O (24)
Elastomer	Like proteins (ELP) are derived from elastin and having short hydrophobic domain with 5 amino acids. Series of ELP produce by changing temperature.
Electrospun nanofibers	Used to treatment diseases and membrane applied as topical or implanted DDS. These can orally administrate (25).
Hydrogel NP	Produced by cross-linked hydrophilic polymers. It has permeability, mechanical stability, swelling properties and network structure so control by physical conditions. These can use to transport high amount of drug to target site by external magnetic field (13).

goes inside and hydrophilic parts come outside and forms globular structure while hydrophilic drug attach to polymer outer surface and hydrophobic drugs penetrated in to core hydrophobic area. Finally this particle surface can design with ligands such as antibodies to targeting. The Size of NP can control by rate of polymer addition and by stirring speed.

- 2) **Emulsification based methods:** The organic phase contain drug and polymer are agitated/sonicated in aqueous phase to form emulsified droplets.

Emulsification-solvent evaporation: Polymer dissolved in volatile solvent like chloroform and emulsified in aqueous phase. Formation NP achieve by evaporation of solvent under reduced pressure. Adjusting solvent evaporation conditions such as temperature and pressure would improve quality but slower the process

Emulsification solvent diffusion: Polymer dissolved in pre-saturated partially water dissolving solvents like benzyl alcohol. It produces oil-water emulsion droplets. The dispersed droplets diluted by large amount of water containing stabilizers. Diffusion of organic solvents out from droplets lead to condensation and formation of nanoparticles.

Emulsification Salting out: Organic solvent use is totally dissolve in water. (Ex; acetone) Polymer containing organic solvent is emulsified in aqueous phase with high salt concentration. The saturated aqueous solution prevents acetone from mixing with water. Diffusion of emulsion droplets in large amount of water result in an abrupt drop of salt concentration of the continuous phase leading to extraction of organic solvents and precipitation of NP's.

- 3) **Layer by layer synthesis:** It makes electrostatic interaction between oppositely charged polyelectrolytes such as polylysine, chitosan, gelatin-B complex with sodium alginate, dextran sulfate, hyaluronic acid, heparin or chondroitin sulfate. Solid form of bioactive agents

is often use as core to grow the vesicular structure. A polymer layer is first absorbed on to the colloidal template by incubation in polymer solution, washed and transferred to opposite charged polymer solution. Repeat the cycle to multiple coating that can control the release kinetics. This method is used to manipulate bioactive agents such as vitamins, peptides, insulin and nucleic acid (14).

- 4) **Genetic engineering method (GEM):** It can control structural, functional properties of recombinant protein based drug carriers such as elastomer like proteins and silk like proteins. GEM can control molecular weight, hydrophobicity, drug conjugate site and secondary structure as well as provide higher transfection efficiency (14).

- 5) **Electrosprayed Technique:** The NP produce setup consist syringer pump with polymer solution connected to high voltage power supply. Metal foil collector placed opposite functions as ground electrode. Flow rate and applied voltage depend on type of solution used in process. Solid particles can produce by solvent evaporation. Electrosprayed particles can used to deliver directly drugs without polymer to the target site (26).

Mechanism of drug delivery using nanoparticles : The drug bullets are attached to NP and it contains ability to cure the diseases. The nanotechnology based DDS is only provide proper delivery of drug to target sites without any changes occurring in parental therapeutic particle. The drugs required special pH conditions, poorly water soluble or required high concentration of drugs in order to become therapeutically effective (11). Drug Polymer attachments are the encapsulation, non covalent complexation and conjugation to polymeric carriers via liable linker are the main methods use to attach drug to polymer. Size of polymer-drug conjugate plays major role and it should be control by adjusting the molecular weight of polymer. Drug-polymer attachment changes the drug solubility, hydrophobicity and

permeability (14). The NP's has drug loading capacity and it depends on matrix density. The drug loading capacity can increase by minimize solubility, increase ionic interactions between drug and matrix and by maximizing the absorption of drug load. Drug and polymer covalently attached via linkers and they are pH or enzyme sensitive (17,21). The drug attached NP can recognized by the immune cells and it can destroy. To overcome this problem the particle surface is decorated with biodegradable, hydrophilic copolymers to allow particles to circulate long period. The degradability could be control rate of the drug releasing rate. Polyglycolic acid (PGA), poly-lactic acid (PLA) and their co-polymers are widely used for decorating the surface. PEG-copolymers are greater interest due to their ability to condense nucleic acid in to nano-sized polyplex with protective and biocompatible PEG shell. Moreover PEG can resist serum protein adsorption, prolonging the systemic circulation of particles, reduce toxicity (11). Ligands also attached to the NP surface to get higher specificity drug delivery to the target site. Antibodies, protein, peptides, carbohydrates, lipoproteins, charged molecules. Nucleic acid ligands like DNA, si.RNA, m.RNA, are known as aptamers and have high affinity and specificity for target (27).

Oral, intravenous, arterially, dermal, transdermal and inhalation are methods use to enter NP to the body. The Drug-NP conjugate injected to circulation system and it can take up by the calls/tissues. Drug is delivered through blood by dissolving, dispersing and finally reached to the target site. Traditional DDS circulate drug in to all the cells in body while nanotechnology based DDS provide drug to target site by their ligand attraction process. The drug-NP conjugate should able to deliver drug to target site without degradation in gastrointestinal track, without reducing drug activity and volume. Secondly it should attack to target cells without harm to other cells and reduces side effects (14,28). The drug delivery to the cells can be of 2 types. 1) Passive targeting-The drugs are

diffused to the extra cellular matrix and diffused to the cell. It enhancing permeability and cellular retention effect of NP. Tumor vesicles are highly disorganized and presence of pores. So enlarge the gap junction in-between endothelial cells. These pores of tumor site allow NP to enter easily to tumor cells than normal cells. Passive targeting is not applicable to all tumors and normal cells, because some tumor cells are lack of pores. Diffuse of drugs out of NP decreases with decreasing concentration of reservoir (16,29). 2) Active Targeting - Affinity ligands, antibodies, aptamers bind to the specific receptor in the cell surface. Nanocarriers bind to the target cell through ligand-receptor interaction by the expression of receptors or epitopes on cell surface. These receptors are highly expressed on tumor cells than other cells (15,30).

The NP surface decorated by ligands and these ligands can attach with the specific receptors in the surface of targeted cell by bio-recognition. The NP's are entered to the target cells by receptor mediated endocytosis. In this endocytotic vesicle generated when segment of plasma membrane invaginate, enclosing with NPs. Thousands of NP's easily can enter to cell by this method. Inside the cell NPs are developed in to endosomes. Then endosomes merge with each other to form large endosomes or lysosomes. Finally therapeutic drugs can release in response to enzymes or acidic pH with controllable manner by degradation of polymeric NP shell (7).

Controllable drug releasing in particular sites can be control by different ways, 1) Polymers are biodegradable and it degraded in controllable manner to release drug to site 2) Pores within the polymer can be altered in the preparation method. So drug diffusion occurs more readily or slowly. 3) The distance of fusion and surface area of the NP can alter by changing size. The size of NP also plays major role, smaller size means larger surface area. Drug releasing and drug dissolve is faster and this can control engineering by changing size of NP. The drugs

are released by matrix by diffusion, swelling, erosion or degradation. The drug releasing control by osmotic pressure, mechanical pumping and through electro kinetic transport. Constant drug releasing can achieve by tuning the properties of nano-fluidic devices (16).

Nanotechnology uses in Treatments

Cancer treatment: The usual drug delivery to the tumor cells develop side effects in normal tissues such as nephrotoxicity, neurotoxicity, cardiotoxicity and multiple drug resistance(MDR) reduces drug concentration at target location, poor accumulation. MDR is mostly due to the increase efflux pumps in cell membrane such as P-glycoprotein. Paclitaxel loaded NP can pass drugs without disturbing by MDR (31). To overcome these problems NP based drug delivery system is used. The tumor sites forms new blood vessels to supply nutrients and oxygen rapidly. These newly formed vesicles are defective and have leaky vasculature allow NP to diffuse. The energy requirement increase and glycolysis occur. Ultimately acidic environment generated and the advantage of pH uses to drug releasing (11,32).

Nano X-ray nano-particle therapy

1) In standard radiotherapy X-ray able to hydrolysis water molecules to produce free radicals. It can ultimately damage DNA and other molecular structures in both tumor cells and healthy cells. Nano X-ray NP has self-protecting layer to minimize unwanted interactions and suspended in water. It is injected to cancer patients and it gets attached only with tumor cells by specific recognition. Nano x-ray NP attracts X-ray more readily than water. Finally it can damage both double stranded and single stranded DNA in Tumor cells to kill only tumors without harming healthy cells.

2) The NPs are attached with highly toxic cancer drugs like Doxorubin and NP surface decorated with PEG and target ligands to drug delivery to target site without harming to healthy cells (33).

3) Photothermal therapy-Au NP has optical

properties and that allow absorption of light near ultraviolet. Due to the increase temperature of cell above 42°C the viability of cells are lost. Following the irradiation of the body or under magnetic field, the NP gets heated up and that leads the irradiation of tumor cells. Angiogenesis inhibition-metal particles can inhibit phosphorylation of protein involve in the process angiogenesis by binding to the cysteine residues in heparin binding growth factor (34).

4) Cetureimab, fluorouracils are drugs attached with liposomes, hydrogels, crystals to treat oral cancers and overcome low solubility, permeability and poor bio-availability (35).

5) Most applications are still under research conditions, animal testing or only an envision. Researchers try to a) Improve blood circulation period of NP by coating their surface with red cell membrane instead of PEG. b) Reduce side effects by using gold NP's for platinum cancer therapy. c) Design different N.P's with different shapes, ligands and drug particles to treat tumors. d) Using photosensitive agents that accumulate in tumor and cause blood vesicles more porous to penetrate NPs more easily. e) Attach RNA to treat skin cancers (36). f).Spherical NP Coated with si.RNA to treated lung cancers (37). g) Monoclonal antibodies and vaccines are directed against tumor (38,39).

Heart Diseases: This is still under research. NP is a protein produced by translation and used to attach damaged regions of arteries as well as to break blood clots. NPs are tried to direct under magnetic field to deliver proteins to right place in arteries.

In Diabetics: Developed NP containing insulin attached to matrix. The enzymes are attached to NP, when blood glucose level increases enzymes stimulate insulin releasing and ultimately it can regulate blood glucose level for several days.

Ophthalmic diseases: a) polymeric NP, nanogels, liposomes, micelles, dendrimers, chitosan and protein NP's are investigated to treat several ophthalmic applications for back of the

eye diseases like diabetic retinopathy, retinoblastoma, retinitis pigmentosa. The drug and gene deliver to the target tissue for treatment of posterior segment disorders like choroid and retina, improving diagnosis and retinal prosthesis. b). to treated glaucoma nano-diamonds with drug (timolol maleate) embedded in contact lenses (40,41).

In Tuberculosis (TB): Treatment of TB required continuous and frequent drug supply to the cells. The NP attached with drugs such as rifampin (RMP), Isoniazid (INH)/Pyrazinamide (PZA) and covered with PEG to provide drugs sustainable manner to TB cells. Researchers try to improve bioavailability, reduce dosing frequency and drug administration methods in TB treatment (17).

Bone diseases: The calcium-phosphate based NP used in drug delivery to bone diseases without any toxicity to bone tissues. Arthritis, osteoarthritis, osteosarcoma and metabolic bone cancer treat using drugs such as bisphosphonates. Silica and magnetic NP success in bone regeneration (42).

Central nerve system diseases: NP can cross blood brain barrier (BBB) so it can use to deliver drugs to brain tumors, alzheimer's disease, inborn metabolic errors like lysosomal storage disease, infectious diseases and aging etc. Most therapeutic particles are unable to pass through BBB, blood cerebrospinal fluid barrier, or other specialized central nerve system barriers. Only a small class of drugs or molecules with high lipid solubility and low molecular mass can pass through BBB. NP has high affinity and able to specifically transport drug through BBB. Some transport molecules like growth factors, insulin and transferring can increase efficiency and kinetics of drug across range of tissues (43,44).

Other ongoing researches: 1) NASA developed bio-capsules to protect astronauts from effect of radiation. 2) Try to deliver antigens to the body to enhances immune system. 3). Improve dental implant by adding nanotubes to surface of implant matrix. 4)Try to attach RNA to NP surface to improve time of circulation (45).

Future opportunities : In future nanotechnology based DDS can improve to treat in the antitumor therapy, gene therapy, radiotherapy, delivery of proteins, antibiotics, vaccines, vesicles through BBB. Before human application mechanism and fate of NP-drugs should be study using animal models scientists will be able to develop drug loading, targeting, transporting, releasing, interaction with the barriers, low toxicity and safe conditions. The understanding of drugs, when delivered to sensitive organelles like nucleus as well as able to improve NPs to treat bone diseases and bone regeneration. Multi-functional NPs might be developed that are capable of detecting malignant cell, deliver different drugs at same time, visualize the location by imaging agents, killing cancer cells with minimum side effects and monitor and treat at the same time. (13,29,42,46). There is an ability to improve this particle to cure diseases like HIV, cancer and same nanoparticles can develop as robots to operations like heart diseases. The nanoparticles can combine with computer programming system to automatically regulate homeostasis in human such as blood glucose level, ca-level. We can also improve these NPs as powerful protectors in body towards foreign particles in future.

Discussion and Conclusion

Nanotechnologies as drug delivery systems are designed to improve the pharmacological and therapeutic properties of conventional drugs. The highly toxic and low selectivity drug are transported to the target site without accumulate in any place by using nanoparticles. The nanotechnology improves bioavailability of drugs, efficiency and selectivity as well as reduces the side-effects and toxicity. Reduction of plasma fluctuation and higher solubility also play vital role in drug delivery. Various nanoparticles are used to deliver drug such as polymeric miscalls, polymeric NPs, polymeric drug conjugates, dendrimers, nano crystals and lipid based nanoparticles like liposomes, solid lipids. Inorganic NPs like metal NPs (gold, silver, iron, platinum, quantum dots) and Silica NPs (mesoporous, xerogels).

The drugs are binds to the nanoparticle by help of different conjugations like encapsulation, non-covalent complexation and conjugation to polymeric carrier via liable linkers. After the polymer surface is covered by co-polymers like PEG to get protection from immune cells. Ligands are antibodies, proteins, charged molecules, carbohydrates, aptamers are attached to get high specificity towards target side. The drug conjugate NP enters to the cell by passive or active targeting, respectively by diffusion or by receptor mediated endocytosis. Finally nanoparticles can release drugs by controllable manner in response to enzyme or pH changes. NP based drug delivery still develop to cure diseases like cancers, diabetics, heart diseases and central nerve diseases are some of them. The nanoparticle based drug delivery can be further developed to cure most challengeable diseases like AIDS in future. Nanotechnology can be developed in future to treat all type of diseases in human at the same time by producing multifunctional nano-particles.

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