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Nanostructure-mediated Delivery of Therapeutic Drugs – A Comprehensive Review

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Abstract

The use of nanostructures especially as drug delivery agents comprises several benefits over traditional forms of drug delivery. Drug transportation to the site of action and its unwanted side effects on major body tissues can be reduced. Therapeutic drug accumulation is increased in the area being targeted and consequently, the required dose for specific treatment can be reduced. Controlled drug delivery systems (DDS) are modern forms of therapy and are most important when there is an inconsistency among the drug dose, concentration and its toxic effects or therapeutic results. Drug attachment to specifically designed carriers enable us cell-specific targeting. Several nanostructures comprising liposomes, polymeric, dendrimeric, silica, carbon, magnetic and biodegradable nanocarriers used as DDS are discussed in this review. Advantages of nanocarrier mediated drug delivery and its disadvantages are also discussed in this review.

Key words: Nanocarriers, Drug Delivery System, Targeting Therapy and Cell Specific Targeting

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1. Introduction

Biotechnology that deals with the synthesis and manipulation of numerous nanostructures by means of biological tools is called nano-biotechnology. Such structures that have dimensions less than 100 nm are manipulated in this technology [1]. Biomolecules are found suitable and reliable for the production of metal nanoparticles as it has highly controlled and hierarchical assembly properties [2]. For some time, there had been a rapid increase in conventional antibiotic resistant microbes. Bio-nanotechnology has appeared as incorporation between nanotechnology and biotechnology for inducing biosynthesis and environment friendly technology for synthesizing nanoparticles.

Nanoparticles are precisely regarded as cluster of atomic size 1-100 nm. Metallic nanoparticles are most favorable as they have outstanding antibacterial characteristics because of their great surface area to volume ratio. Current research has shown that microorganisms, plant extracts and fungi can produce nanoparticles through biological pathways [3]. They have exceptional properties that are unlike from large molecules of same element. Their electronic, optical and chemical properties are different from those observed in bulk compounds [4] than unpackaged or loose material. Metal nanoparticles e.g. gold and silver exhibit different colors because of their surface plasmon resonance (SPR) phenomenon [5]. They have an important role in the pharmaceutical and biotechnology industries [6].

Table 1: Nanostructures with their potential applications in the study of biological sciences

Nanoparticle Class	Materials	Applications
Biomaterials or their Derivatives	1. Chitosan 2. Dextran 3. Gelatin 4.Alginates 5. Liposomes 6. Starch	1. Drug delivery
Dendrimers	1. Branched polymers	1. Drug delivery
Fullerenes	1. Carbon-based carriers	1. Photo-dynamics 2. Drug delivery
Polymer Carriers	1. Polylactic acid 2. Poly cyanoacrylates 3. Polyethyleneimine 4. Block copolymers 5. Polycaprolactone	1. Drug delivery 2. Gene delivery
Quantum Dots	1. Cd and Zn-selenides	1. Imaging and in vitro diagnosis
Ferro-Fluids	1. Super paramagnetic iron-oxide nanoparticles (SPIONs) 2. Ultra-small SPIONS	1. Imaging (MRI)
Various	1. Silica nanoparticles 2. Combination of above	1. Gene delivery

In Table 1, some forms of chemical structures and chances for formulations of nanoscale ingredients that are utilized as carrier systems in pharmaceuticals. The basic aim of nanotechnology and nanoparticles is efficiency in drug delivery and active uptake of drug by the cell and also the reduced toxicity of these drugs for non-targeted cells [7].

For formulations of nanotechnology, management of matter on different scales including production, design, classification and application in medical field by nanoscale materials and in this way, several advances are being made in medical (nano-medicine) field. Drug delivery system related to nanostructures helps in primary detection of cancerous moieties and definite biomarkers of tumors and thus enhance efficacy of its treatment [8].

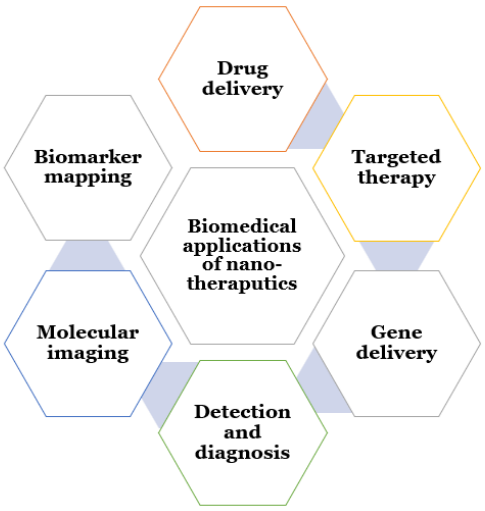

Fig. 1: Current biomedical applications of nano-therapeutics [9]

2. Nanoparticles in drug delivery systems

Main hurdle in many disease treatments is therapeutic drug delivery to the target site. Lack of selectivity, limited effectiveness and poor bio-distribution are the ways by which conventional applications of few drugs are characterized by drug delivery control, these drawbacks and limitations can be overcome. Drug transportation to the site of action via controlled drug delivery system (DDS), thus, its unwanted effects on vital tissues can be reduced [10]. Drug delivering system protects drug from clearance or rapid degradation and increases concentration of drug in target tissues [11]. This modified form of therapy has gained importance specifically when there is inconsistency between drug concentration and its therapeutic effects. By attaching specific drug to independently designed carrier, cell specific targeting may be achieved.

Such nanoparticles having molecular size less than 100 nm and have higher potential as drug nanocarriers. Nanoparticles show unique biological and physiochemical properties (an improved reactive area and also the ability to cross tissue and cell barriers) and are considered favorable material for drug delivery applications [12]. For example, if gold particles are used as drug delivery agents, they require capping agent's administration that is absorbed on the surface of nanoparticles. Gold nanoparticles can be formed in varied sizes by reduction of Au with diverse agents for examples those molecules having an aliphatic chain, a thiol group and charged group at end which can evade particle accumulation [13]. Moreover, this thick layer of stabilizing factors enhances a general alteration in surface charge of gold nanoparticles permitting ligand transfer with many other molecules and then increase the particle firmness in physical environment [8].

Gold nanoparticle-based delivery system is found to be based on its ability to bear several different functional groups it can form several non-covalent and covalent bonding by thiol-linker. The gold nanoparticles appear by its stabilization with thiolates if Au and thiol bonding is very strong. By this process, affinity of gold nanoparticles is increased for many types of ligands for example: nucleic acid (DNA and RNA), antibodies, polyethylene glycol (PEG), peptides and drug molecules of small size [14].

For targeted approach, basic issue is the choice of optimum targeting ligands, perhaps by equalizing their stoichiometry while comparing with antibiofouling upper layer of gold nanoparticles. More precisely, density and affinity are two significant ligand properties that may have very essential and basic role in targeting to the superficial membrane of nanoparticles. Equilibrium between entropic losses (flexibility, stretching and compressibility of nano-system) and enthalpic advantages (interaction of ligand and receptor) results into ligand binding affinity [15]. Furthermore, though uptake of gold nanoparticles normally increases with enhancing +/− ratio of charge of nanoparticles (in relation to zeta potential values), an extra positive charge can produce toxicity and enhances immunological reaction. Thus, the charge on the surface of gold nanoparticles and its optimum ligand density must be examined eventually [16].

Gold nanoparticles can be merged into bigger structures as liposomes or polymeric nanoparticles which deliver bigger payloads for increased applications in diagnostics, capably encapsulated drugs to add extra imaging labels or for synchronized therapy. That range of properties has led their way to biomedical fields, but recently in tactics where multifunctional AuNPs are utilized to several methods as synchronized therapy and diagnosis, also called theranostics [17]. Characterization relies on UV/V spectroscopy and transmission electron microscopy

(TEM) for measuring the optimal size of particles, surface plasmon resonance (SPR) for metallic gold and scanning electron microscopy (SEM) for classification of morphological features and absorption spectroscopy that counts the quantity of gold [18].

Biodistribution of gold nanoparticles can be examined before transfer of its payload that allows the formation of treatment plan [19]. The use of gold nanoparticles for in vivo imaging, in vitro diagnosis and therapy as DDSs accounts on their chemical firmness, great solubility in water, manageable morphology and restricted dispersion, greater surface to volume ratio, effortless synthesis and nontoxic behavior in biological system [20].

3. Nanocarriers as drug delivering agents

Nanoparticles are absorbed by cells more easily than those having large size because of their optimized biological and physiochemical properties so, for delivering bioactive compounds, they are very useful [21, 22]. Solid nanoparticles, liposomes, polymers, carbon or silicone materials, magnetic nanoparticles and dendrimers are some examples of nanostructures that present several benefits in drug delivery system. Important factors for targeted therapy are strategy of its targeting and way of conjugation with drug. Drug may be attached covalently to the surface of nanoparticle, encapsulated within nanoparticle or absorbed by it. Covalent linking enables precisely controlled amount of drug attached to nanoparticles, so, it has an advantage over other methods of binding of nanoparticles. By utilizing passive and active mechanisms, cell specific targeting may be achieved [23].

Attraction of drug is the first strategy, recognition ligands helps in conjugation to the effected site, low molecular weight ligands attaches to the conjugate antibody surface such as folic acid and peptides etc. By physical stimuli manipulation (pH, temperature and magnetism) its active strategy can also be achieved. A characteristic of tumor leaky tissues, electron paramagnetic resonance (EPR) or enhanced vascular permeability and retention, results into passive targeting. When nanocarriers conjugate reach diseased tissue, they release therapeutic agents by making physiochemical changes such as osmolality, pH, temperature or via enzymatic activity, controlled nanoparticle drug release can be achieved [24]. Biocompatibility (without giving negative effects or eliciting immune response and must be able to assimilate to a biological system) and nontoxicity are the properties required by nanoparticles to be used in medical applications. Hydrodynamic size, surface chemistry, reaction of immune system (granulocyte and phagocyte route of uptake), route of administration, shape, residence time period in bloodstream and number of nanoparticles may show undesirable effects [17].

Toxicological studies of every newly formed DDS formulations are required because there are number of particles that can influence the toxicity of nanocarrier. On the basis of size some generalizations can be made such as smaller structure are more reactive and have greater surface area and thus, more toxic. It is usually said that nanostructures having 10-100 nm hydrodynamic diameter present certain optimal pharmacokinetic characteristics for in vivo studies. Nanoparticles with small size are cleared by renal filtration and tissue extravasation but, on other hand, larger ones are readily opsonized and quickly eliminated from systemic circulation by macrophages of reticuloendothelial system [25].

4. Types of nanocarriers for drug delivery systems

4.1 Liposomes

Liposomes are the first nanostructures, studied as carrier for therapeutic drugs. They are 80-300 nm sized nano or microstructures which are spherical in shape, consists of steroids (cholesterol) and phospholipids, or surfactants that are synthesized spontaneously, when lipids came in contact to aqueous medium, liposomes are produced by several phenomena, such as sonication. Several recent studies have described liposomes as efficient drug carrier as they enhance the solubility and improve pharmacokinetics of the drug, particularly therapeutic index of medicine, reducing the harmful effects, rapid metabolism and enhancement anticancer effect for both in vivo and in vitro studies [26].

Drug encapsulation is the process of fusion of drug with certain liposomes as presented in Fig. 2. The delivery of a specific drug depends upon the osmotic gradient, liposome composition, surrounding environment and pH variability. Liposome interaction with adjacent tissues, may understood by adsorption, lipid transfer, endocytosis and fusion. Several liposomal formulations have been studied, for example, neurotransmitters (serotonin), anticancer drugs, antibiotics, anti-rheumatic and anti-inflammatory drugs. Recent studies have shown the side effects and clinical outcomes of photodynamic therapy using spray (0.5% of 5-aminolevulinic acid, encapsulated in liposomes), for the treatment of intense pulsed light and inflammatory facial acne [27].

Scientists compared safety and efficacy liposomal (lipid) and deoxycholate amphotericin B formulation (AMBF) to cure invasive fungal disorder in newborn babies. AMBF is a cost effective and efficient drug for the treatment of invasive fungal disease in newborn babies. This is a safer therapy and can be applied as first-line treatment if comorbid chances of nephrotoxicity are low. The

multifunctional liposomes, comprising specific antigens, proteins and/or other organic compound, may be manipulated to formulate drugs that are capable of selective targeting on a tissue. Hydrazine functionalized a polymer PEG/PE (polyethylene glycol/ phosphatidylethanolamine) capable of specific conjugation with triphenylphosphonium (TPP) as nanocarrier for drug encapsulation. They concluded, TPP/PEG-PE have potential for non-toxic targeting of specific drug [28].

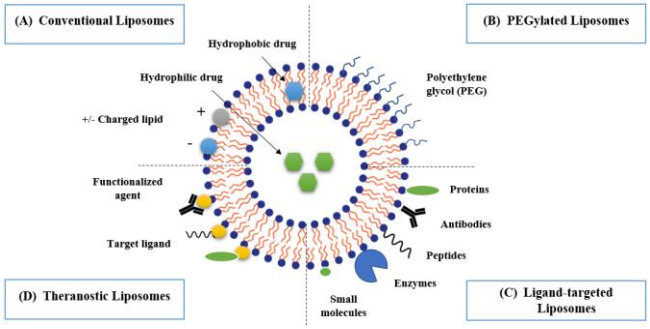

Fig. 2: Representation of various liposomal DDS (A) Conventional liposomes i.e. +/- charged or neutral lipids for both hydrophobic and hydrophilic drug encapsulation (B) PEGylated liposomes, polymer coating to induce desired characteristics (C) Targeted liposomes with various molecular targets i.e. proteins, peptides, antibodies, enzymes and other small molecules (D) Theranostic liposomal system consists of functional agent e.g. for PDT and target ligand

4.2. Solid lipid-based nanoparticles

Nanostructures such as NLCs (nanostructured lipid carriers), SLNs (Solid-lipid nanoparticles) and LDCs (lipid drug conjugates) are various types of nanocarrier bound on solid-lipid matrix, i.e., fats (lipids that are solid at the body temperature) as presented in Fig. 3. They have been utilized for rectal, parenteral, pleural, pulmonary, ocular and dermal delivery. These are such structures made up of solid lipids, for example, complex glycerides, wax stabilized by several surfactants or highly purified triglycerides [29].

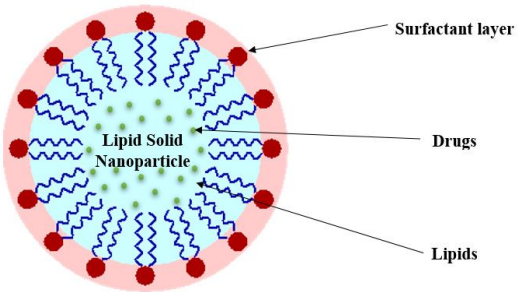

Fig. 3: Representation of solid-lipid-based nanostructure for drug delivery purpose

The major characteristics belonging to SLN comprise a controlled drug release, protection of encapsulated drug from chemical/biochemical degradation, good physical stability and good tolerability. Lipid drug conjugates (LDC) and nanostructured lipid carriers (NLC) are other types of lipid-conjugated nanocarriers that have been synthesized to overcome the limitation associated with the use of conventional SLNs. The production of NLC requires mixing of solid lipids with liquid ones that leads to the formation of distinct nanostructure presenting improved drug payload [30]. Some distinct types of NLC e.g. imperfect NLCs (overall inadequacies in nanostructure for incoming molecules) and amorphous NLC (drug expulsion by the crystallization) have been reported by research studies [31]. LDC was synthesized to improve applicability of lipophilic transporters to lipophobic drug conjugates. These conjugates are insoluble and can be organized by covalent bonding or salt forming followed by homogenization.

4.3. Polymeric nanoparticles

The polymeric nanoparticles are obtained from conventional polymers e.g. polyacrylate and poly-e-caprolactone, polyacrylate, or biopolymers like gelatin, chitosan, DNA and albumin. On the basis of in vivo performance, these nanostructures may be categorized into biodegradable, i.e., polyglycolide (PGA), and poly(L-lactide), non-biodegradable, e.g., polyurethane poly(L-lactide) [32]. Polymeric NPs are generally covered with surfactants to decrease immunological attachment (e.g., opsonization with CD8 T-lymphocytes) along with intermolecular bonding among the chemical groups present at the surface (e.g., hydrogen bonding, hydrophobic interaction or Van der Waal's interactions).

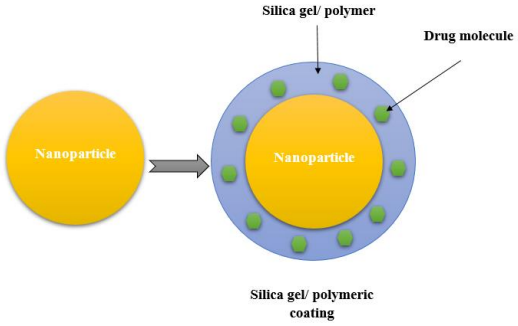

Fig. 4: Surface modification of Gold NPs, the coating of polymer/ silica gel for efficient drug attachment

Drugs are immobilized on the surface of PNPs or encapsulation on nanostructure using different polymerization reactions. Among the above-mentioned applications, the most interesting one is the retinyl acetate immobilization on ethyl-cellulose that advances photo-stability and aqueous stability of drug molecules. In a study, in vitro tests were performed on mice skin, a complete

absorption of retinyl acetate after 1 day has been studied. The important thing is chitosan-g-poly(N-vinylcaprolactam), which is a thermo-responsive and biodegradable polymer, utilized to transport 5-fluorouracil on tumor cells. The hypothesis of controlled release of 5-fluorouracil from PNPs was swelling by the conformation alteration during low critical solution temperature (LCST). In vitro drug transportation presented a remarkable difference than LCST. The cancer cell accumulation with increased toxicity was detected as compared with normal body tissues [33]. Polymeric, drug-biodegradable nanocarrier conjugates utilized for drug delivery are firm in blood, non-thrombogenic and non-toxic. They are non-proinflammatory as well as nonimmunogenic, and they neither activate neutrophils nor affect reticuloendothelial system in the body [34, 35].

4.4. Dendrimeric nanostructures

These are polymers with distinct structure and particle size. Dendritic construction is most widely studied in all living systems. Few examples of dendritic nanostructure comprise glycogen, amylopectin and proteoglycans [36]. In dendrimer structure, in contrast to linear one, following elements may be observed: dendron, surface active groups and a core (Fig. 5). The dendrimer core is basically an atom or a group of atoms, to which dendrons develop interactions. Dendrimer arms are molecules that attach with the core, building consecutive generations (having spatially limited growth). Physicochemical and biocompatibility are analyzed by the presence of functional groups at the surface [37]. Surface functional groups, type of monomer and selection of a core determine their use in health purposes [38].

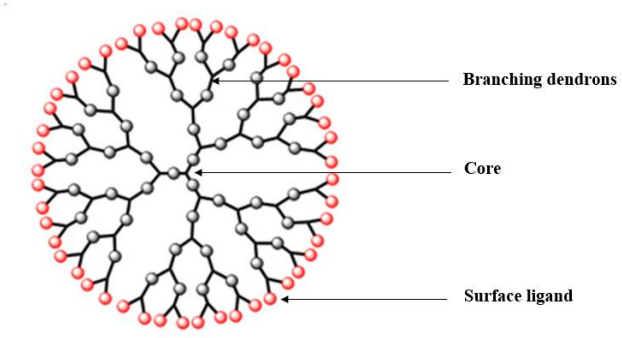

Fig. 5: General representation of dendrimeric nanostructure basically consisting of core, the branches – dendrons and surface ligand molecules

Drug either encapsulated in interior of dendrimeric structure or it may be absorbed physically or chemically attached on the surface [39]. Chemical attachment increases the drug regulation on the surface of dendrimers by regulating chemical bond numbers. Selectivity of the strategy may be improved by folic acid or epidermal growth factor. Surface delivers a platform for precise ligand attachment that may include, cyclic antibody targeting peptides. Choice of immobilization process relies upon the specific characteristics that a drug bears. Encapsulation is done when drugs are acid silver salts complexes antimicrobial agents, selective A3 adenosine receptor, or polyethylene glycol (PEG). Compounds attached can advance surface activity along with physical and biological characteristics of dendrimeric nanostructures. Poly(amidoamides) are often used in biomedical applications.

Anticancer drugs, including anti-inflammatory drugs are important examples of assimilation in PAMAM, (piroxicam, ibuprofen or indomethacin), methotrexate, doxorubicin, 5-florouracil, e.g., piroxicam, ibuprofen or indomethacin. Dendrimers presenting positive charge, entered into circulation interact with blood machineries producing cell lysis and destabilization of cell membranes. Kesharwani et al. [40] said that PAMAM-dendrimeric structures trigger decline in feasibility of cell, although, that have not found immunogenic in experimental models. Dendrimers can moderate chemokine and cytokine release. This is a positive aspect for in vivo therapy, but it may also pose serious health issues.

The production of 3,5-glucosamine dendrimers starts the production of pro-inflammatory chemokines, e.g. maximum intensity projection (MIP)-1h, MIP-1a, and cytokines TNF (tumor necrosis factor)-a, IL (interleukin)-1h, IL-6, IL-8 in macrophages and dendritic cells, that shows an immunomodulatory effect. Researchers studied the subsequent parameters: feed intake, animal behavior, body weight, protein, lipids and carbohydrates metabolism, hematological parameters, cell viability and histopathology. They experienced no effect on other biochemical parameters (apart from the reduction of glucose concentration in body during high-NH2 circumstances) and hematological (excluding red blood cells, hemoglobin and hematocrit) along with organ weight, feed intake, and body. Furthermore, the histopathology presented a toxic effect on kidneys and liver. PEGylation of dendritic systems is another way of reducing general toxicity [41].

4.5. Silica nanomaterials

Silica materials are also being utilized in controlled DDS are categorized as mesoporous silica nanoparticles (MSNs), e.g., SBA-15, mobile composition of matter (MCM-41), and xerogels. They present numerous benefits as drug carrier molecules with extremely porous structure and ease in terms of functionalization and biocompatibility. From these inorganic nanostructures, silica materials are carriers of drugs that are most frequently chosen especially for in vivo studies. Silica xerogels comprises an amorphous

structure with increased surface area and high porosity [42].

Specific porous structure of nanoparticle (shape and dimension) relies upon synthesis parameters. Silica xerogels that are loaded with drugs are, therefore, made by sol-gel technique. During controlled drug release, properties of xerogels can be altered by modifications in conditions for production, like temperature, pressure of drying and ration of reagents. By this technique many drugs have been incorporated into xerogels such as heparin, nifedipine, phenytoin, diclofenac, metronidazole and doxorubicin. MCM-41 is a renowned kind of mesoporous silica nanomaterial having a hexagonal symmetry of SBA-15 along with proper hexagonal system of pores and mesopores. On other hand, MSNs possess lower polydispersity, greater surface area for adsorption and more homogenous structure for diagnostic and therapeutic drugs [43].

By either physical or chemical adsorption, drug is loaded into mesoporous silica material. Various kinds of drugs have been entered into MNSs such as anticancer drugs, cardiovascular drugs and antibiotics by this method. In photodynamic therapy, potential application of mesoporous silica and silicates has been studied. For many biomedical and pharmaceutical application MNSs properties has proved as an excellent material. Gene transfer, adsorption of DNA and incorporation of large and small molecules is enabled by structure of MNSs. By this, it is may be possible to use these nanomaterials for combined therapy. It has been indicated by some data that SNPs or nano-sized particles have effective potential for therapeutic and diagnostic application in the field of medicine and are biocompatible. Though, recent studies have discovered certain hazards of utilizing nanosalica as in vivo and in vitro toxicity [12].

Effect of nanoparticle on red blood cells has been shown in recent studies depending upon their structure, surface properties and size. Such RBCs that uptake large silica particle showed high level of local membrane deformation that leads to internalization of particles, speculations of RBCs and finally, hemolysis. By contrast, small particle adsorption does not affect morphology of RBCs and membrane. Thus, toxicity has much to do with size of nanoparticle. Several researchers stated that inhaling silica nanoparticles can cause the pulmonary tract inflammation, damage of myocardial ischemic and atrioventricular blockage. Additionally, they noticed an increased concentration of fibrinogen in blood. However, silica nanoparticles that were organically modified, accumulate in every organ and there were no associated symptoms of toxicity. Nishimori et al. [44] observed a considerable hepatoxicity while assessing severe toxicity of amorphous silica particles. Liver fibrosis was caused by nano materials during chronic administration in experimental animals.

4.6. Carbon nanomaterials

Carbon nanomaterials (CNs) are utilized in DDS and is further differentiated into nanohorns (CNHs) and nanotubes (CNTs). CNTs are distinguished by exceptional architecture designed by multi-walled carbon nanotubes (MWCNTs), and/or single-walled carbon nanotubes (SWNCTs), with vast surface area and outstanding thermal/ electrical conductivity. Biocompatibility of carbon-based materials can be improved by chemical modifications. The modifications may include covalent attachment of various PEG layers and PAMAM dendrimers on the surface of CNTs, amphiphilic deblock copolymers or by scattering inside a matrix of hyaluronic acid. Because of their mechanical strength, SWCNTs can be used as support e.g., non-polymeric or polymeric composites [45].

During encapsulation, drug is made safe from degradation during transport towards cell and is released in specific conditions, and these characteristics make encapsulation valuable over conventional methods. Carbon nanotubes released drug can be controlled both chemically and electrically. Open ending of CNTs are closed with polypyrrole (PPy) to avoid undesired release of drug. To improve drug delivery system selectivity, homing factors such as epidermal growth factor and folic acid are attached. A kind of single-wall nanotubes, nanohorns shows similar characteristics to nanotubes. They can be early synthesized with high purity and at very low cost because their synthesis does not require any metal catalyst [46].

Adsorption of drug on nanohorns wall or drug nanohorns may cause its immobilization. Nano-precipitation has an advantage (about 3-fold enhancement in nanohorns entrapped molecule number) over adsorption. Exceptional and defined geometric structure also gives rise to the carbon nanomaterial toxicity. Increased level of ROS caused by impurities such as amorphous carbon and residual metal, give rise to oxidative stress within cells. Resemblance in carcinogenic potential between asbestos and CNT has been figured out by recent studies. Alterations in cell morphology and apoptosis and necrosis of macrophagic cell line have figured out to be caused by carbon nanotubes. Radomski et al. [47] studied effects onto human platelet aggregation of engineered carbon nanoparticles such as SWCNT and MWCNT by both in vivo and in vitro vascular thrombosis.

4.7. Magnetic nanoparticles

Magnetic nanoparticles (MNPs) present various remarkable characteristics that make them extremely suitable candidate for therapeutic drug delivery. These

properties include ease in administration by outside magnetic field, probability of manipulating active and passive targeting approaches, ability of magnetic resonance imagining using MNPs and improved uptake by marked tissue subsequent in operative treatment at therapeutically optimum doses. Though difficulty in obtaining these goals or objectives is appeared where magnetic nanocarriers are used. It occurs mostly due to inadequate magnetic system or unsuitable characteristics of these nanomaterials. Magnetic nanocarriers may lose specific characteristics associated with their smaller dimensions making difficult their physical handling because they use to assemble into large sized clusters. Moreover, magnetic force cannot be powerful enough to combine together the magnetic drugs just at target site and to compete the force of blood [48].

Magnetic delivery systems of drugs require consideration of many features e.g. magnetic characteristics and particles size, magnetic field strength, capacity of drug loading, place of target tissue accessibility or blood flow rate. Food and Drug Administration (FDA) only approved one type of MNPs for clinical purposes, iron oxide, because of their favorable features. These features are: being chemically stable in all physiologic conditions, chances of chemical modification various shell coating on iron oxide such as polymeric, dendrimeric, golden or silane and synthesis in single step by alkaline corporation of Fe^{3+} and Fe^{2+} [49].

Iron oxides such as maghemite and magnetite are found naturally in human liver, spleen and heart and this feature indicates their nontoxicity and biocompatibility at physiological concentration. MNPs and drug association can be achieved by electrostatic interactions, encapsulation process, covalent bonding or adsorption. MNPs-drug conjugates targeting (MTDDS or magnetic targeted drug delivery system) could be done through active and passive mechanisms to diseased tissues depending upon their surface chemistry and size. Synchronized use of magneto-fluorescent or magnetic resonance imaging and targeted therapy (by targeting moieties conjugation) can increase efficiency of cancer therapy [50].

For the treatment of thrombosis, MNPs have also been utilized as carriers. Ancient thrombolytic therapy is affiliated with adverse side effects like hemorrhagic complication. A protein that dissolves blood clot called tissue plasminogen activator (tPA) is covalently attached to chitosan-modified nanoparticles to eliminate these tissues. Initial studies have indicated that these conjugates can enhance clinical prospective of thrombolytic therapy and can be beneficial for magnetic targeted destruction of thrombosis [51].

Mechanism of MNP biodistribution and internalization is strictly attached with their hydrodynamic sizes and surface chemistry. Magnetic nanocarriers may be readily opsonized via plasma proteins, removed and recognized by macrophages of reticuloendothelial system from blood stream. The highest overall commitment of nanocarriers can be seen in spleen and liver. MNPs covered with polymers of long C-chain, are lesser toxic than shorter polymer chain coated MNPs of similar type (with expressively lesser viability). Magnetic nanocarriers enhance activation of phagocytic functions and cytokine-release from macrophages. Temporary increase of serum alanine aminotransferase (ALT), alkaline phosphatase (ALP) and aspartate aminotransferase (AST) is also caused by MNPs. Without countable effects and histological changes in main organs, many reports have found that iron oxide accumulate in tissues [52].

It is admitted that by over production of ROS, oxidative stress can be induced by iron nanoparticles. The reply of defense elements tends to improve expression of antioxidant enzymes like heme oxygenase and superoxide dismutase. Proinflammatory responses such as chemokine, cytokine and matrix metalloproteinase or MMP form this stage and guide its way to mutagenesis and apoptosis. Neuronal damage and enhanced BBB permeability can be caused by increased activity of MMP in nervous system. Cell death and injury is caused by oxidative stress and appropriate dose of MMP can avoid it [53].

5. Benefits of nanoparticles as DDS

The chief goals for nano-biotechnologies research in drug delivery comprise; biocompatibility and greater safety, additional specific drug delivery and targeting, faster growth of novel safe medicines, lessening in toxicity while preserving therapeutic effects. The basic issue in search for suitable carriers as systems for drug delivery relate to subsequent topics which are main fundamentals to project a new material. They include knowledge on (i) targeting and biodistribution (ii) functionality (iii) biocompatibility (iv) drug encapsulation and release (v) shelf life and formulation stability. In count, when used exclusively as carrier, probable hostile effects of enduring material after drug delivery should be thought as well. According to this, biodegradable nanoparticles having limited life span as far therapeutically desired would be optimum [54]. Engineered nanoparticles are a significant tool to understand its applications. Nanoparticles usually have large surface area that can easily absorb, bind and take away compounds like drugs, probes and proteins [55].

6. Conclusion

Nanostructures are designed to enhance therapeutic and pharmacological applications of drug delivery system.

Nanocarrier can protects the drug from biodegradation and provides controlled drug delivery at target site. Having small dimensions, nanoparticles can cross blood-brain barrier and function on cellular level. Nanocarrier mediated drug delivery system is efficient and selective that traditional forms of drug. They can reduce the side effects of drug on other tissues by accumulating drug at targeted area and required drug doses are lowered. Use of nanoparticle in drug delivery comprises some drawbacks as well. For example, drug conjugates may cause severe toxic effect or phagocytosed by body's internal metabolism and/or their small size may cause aggregation in organs, causing hurdles in physical handling of drugs. Other problems include small drug loading efficacy and decreased capacity of size distribution control. Despite limitations, nanocarrier mediated DDS which cause slight alteration in body's internal environment, present a potential alternative to conventional drug delivery issues.

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