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Recent Developments in Nanomedicines for Management of Various Health Issues Via Metabolism and Physico-Chemical Properties

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Abstract: During the last decade the nanotechnologists began research on applications of nanomaterials for medicine and therapeutics. Various nanoparticles (nanomedicines) are being used worldwide for the diagnosis and management in a number of disorders including cancer and neurodegenerative disorders. The successful non-viral gene therapy is now possible with the advancements in nanotechnology. Mostly nanoparticles are divided into two main classes: organic and inorganic nanoparticles. Diverse features of nanomedicines with surface modification help to make them biocompatible with addition of varying polymer that facilitates targeted delivery of drug and its controlled release into the cells, tissues and organs. Liposomes, quantum dots, silver and gold nanoparticles are the most common examples of nanomedicines.

Keywords: Cancer, gene therapy¸ liposomes, nanomedicines, neurodegenerative disorders, quantum dots, silver and gold nanoparticles.

INTRODUCTION

Nanomedicine is the product of nanotechnology, with the aim to facilitate site-specific, targeted way of treatment with minimum side effects, imaging methodologies for early diagnosis and/or monitoring of disorders as well as control of biological system. It is actually the control of matter (approximately, 1-100nm) in the biological system dealing with pathological state in the body. Exclusive physico-chemical properties are associated with nanomedicines like very small size, large surface area to mass ratio as well as high reactivity as compared to other bulk materials of the same composition. Three important aspects are related to the mode of action, metabolism, fate of the particles and other functionalities including toxicities such as 1) size of the nanoparticle, 2) shape of the nanoparticle and 3) surface chemistry of the nanoparticles.

Various types of nanoparticles are being employed for the development of nanomedicines for the management of various health issues. Nanoparticles are classified usually into two major groups; a particle with major building material is organic molecule and other in which inorganic elements are in core, such as metals. In organic particles, dendrimers, liposomes, emulsions, carbon nanotubes are included having general structural components like lipid membrane, polyethylene glycol (PEG), human albumin and drug of interest. On the other hand, inorganic nanoparticles also share the common features such as a central core: for fluorescence, electronic, magnetic as well as optical characteristics of particle and shielding coating are organic in nature. The outer organic layer protects the core from degradation in physiological environment of biological system and can produce covalent and/or electrostatic bonds with positively charged components and biological molecules that have basic functional groups like thiol and amines.

Various nanoparticle based medicines and diagnostic tools have been developed for the management of a number of disorders like cancer, pain, allergy, diabetes and so on [1, 2]. Nanoparticles provide therapeutic delivery system because they facilitate targeted delivery of a drug and its controlled release. Moreover, nanoparticles provide diagnostic tools for the detection of precancerous cells, viral fragments and disease markers [3, 4].

A number of nanoparticle based medicines have been approved for clinical use. Moreover, multiple forms of therapeutics are in clinical and pre-clinical trials [5]. Among these therapeutics, liposomal and polymer-drug conjugates are two dominant nanoparticle based medicines. Other forms of nanoparticles (Table **1**) are micelles [6-8], nano-shells [9], dendrimers [10, 11], metallic nanoparticles [12, 13], viral nanoparticles [14, 15], polysaccharide based [16, 17], ceramic nanoparticles [18, 19] and albumin based nanoparticles [20, 21].

The emerging nanomedicines are usually given by intravenous injections, while orally administered medicines are in preclinical trial [22] for the delivery of drugs both hydrophobic and hydrophilic in nature. Moreover, the imperative aim for the drug is bioavailability at the target site in the biological system. A prodrug nanomedicine approach has been investigated for a hydrophilic peptide, and leucine (5)-enkephalin, to the brain via oral route [23]. Mitoxantrone poly (butyl cyanoacrylate) nanomedicine produced fruitful outcomes in hepatocellular carcinoma (HCC) patients. It accumulates into the macrophages of spleen and liver [24]. Nanoparticles containing the metal core coated by the dextran or any other polymer coating help to produce magnetic resonance imaging (MRI).

Nanoparticles have also been explored in respect to their potential to produce the small signaling molecules in response to immune

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Table 1. Multiple nanoparticles and their uses in management of disorders.

Nanoparticle	Therapeutic	Use in	References
Micelles	Antibody-directed enzyme, Daunomycin, Doxorubicin, Docetaxel	Various cancers including ovarian, prostate, and brain	[1, 6, 7, 94]
Nano-shells		Tumors	[9]
Dendrimers	Methotrexate, Chloroquine phosphate, Efavirenz, Camptothecin	Various cancer including epithelial, HIV, malaria	[10, 11, 95, 96]
Metallic	Thermal and photothermal therapy, mitoxantrone	Breast cancer, brain tumor and tumor angiogenesis	[12, 13]
Viral	Phototherapy, gene therapy	Tumor	[14, 15]
Polysaccharide	Doxorubicin	Tumors and breast cancer	[16, 17]
Ceramic (silica)	Imaging agents, photodynamic therapy and chemotherapy	Cancers and imaging	[18, 19]
Albumin-based	NC-1900 vasopressin fragment analog, Doxorubicin and methotrexate	Scopolamine-induced memory deficit and cancers including breast cancer	[20, 21, 97]

system as certain nanoparticle preparations promote cytokines release from endothelial cells. As far as cancer is concerned, nanomedicines have proved to be a better tool in the field of diagnostics and improved management of disorder. Most of the cancerous cells exhibit a protein called epidermal growth factor receptor (EGFR) on the surface of their membranes, while non-cancerous cells have less expression of EGFR. The combination of gold nanoparticle with an antibody for EGFR (anti-EGFR) has been employed for binding of nanoparticles to the cancer cells, hence, manifesting various light absorptions and scattering spectra as compared to benign cells. With the help of this malignant cells can be determined easily in biopsy samples [25].

Supermagnetic nanoparticles having a core of metal could be conjugated with antibodies against Erbb2 have exhibited fruitful outcomes both *in vivo* targeting of breast cancer and molecular imaging simultaneously [26].

LIPOSOMES

Liposomes are bilayered membrane structures (spherical lipid vesicles) consisting of synthetic or natural amphiphilic lipid molecules having unique properties. Liposomes are used as carriers for medicines because of encapsulation of both hydrophobic and hydrophilic drugs with high effectiveness; encapsulating the drug from external conditions of biological system; functionalization with specific ligand to target the desired cells, and coating with biocompatible polymer like polyethylene glycol (PEG). Hence, half life of liposomes is enhanced to circulate in the biological system [27] and decreased spleen and liver capturing [28] as well as resistance to serum degradation [29]. First liposomal drug formulation (Doxil) was approved for the treatment of AIDS associated with Kaposi's sarcoma by Food and Drug Administration (FDA), USA in 1995 [30].

Doxil has prolonged the doxorubicin half life in circulation as well as drug deposition in the site of interest such as tumor area. Moreover, liposomes are cleared from blood rapidly by phagocytic cells of reticuloendothelial system. Such drawback can be overcome by coating the liposomal surface with biocompatible and inert polymer like PEG. The coating of the polymer facilitates with protective covering to the liposome and reduces liposomal recognition by opsonins [31]. Another strategy can be employed in which antibodies, small-molecules like transferrin or folate and peptides are attached to the liposomal surface and can be used for drug delivery to the specific site [32]. By incorporation of oleyl alcohol, phosphatidyl ethanolamine or dimethyl dioctadecylammonium bromide make the liposome stable in blood while facing the phase transition of endosomal pH [33]. Liposomal uptake by tumor cells mainly depends on the enhanced permeability and retention (EPR) effect [30].

To enhance the drug accumulation in the cancer cells, liposomes must combine with a small size targeting ligand to differentiate between the cancer as well as supportive cells, and more important for internalizing moiety for intracellular drug delivery and enhancing the long circulation time to reach the target site (tumor cells). Thus, PEG chains are coated for long blood circulation. PEGylation provides multivalent binding and shows flexibility, with respect to ligand. In this way, such nanomedicines facilitate with best therapeutic activity in contrast to PEGylated liposomes without ligand [34, 35]. Various types of ligands including peptide, protein, antibodies and small molecules have been used for targeted drug delivery with the help of liposomes. *In vitro* toxicity and *in vivo* antitumor activity of PEGylated liposomes were investigated in the animal model [36]. Antibodies like anti-HER2 and anti-CD19 have been studied for HER-2 receptor on cancer cells, and CD19 receptors are found to be over-expressed in B cell lymphoma [37, 38].

Dual drug-loaded liposome (daunorubicin and cytarabine) being investigated for the treatment of acute myeloid leukemia is under phase II clinical trial. HL-60B human leukemia cells showed a median survival time of forty-three days from the 30-days of saline treated mice [39]. Similarly, liposomes (floxouridine and irinotecan) used for the treatment of colorectal cancer are under the phase

II trial and have shown better drug efficacy results as compared to liposomal floxouridine or irinotecan alone treatment [40]. Other examples can be observed from Table **2**.

POLYMER-DRUG CONJUGATES

Anticancer chemotherapeutic agents have two unfavorable features such as short half-life in biological system and non site-specific targeting leading to side effects. The conjugation of anticancer agents with nanoparticles can improve the undesired side effects. Polymer-drug conjugates are able to enhance the circulation time for several hours as well as decrease cellular uptake to the endocytic way. As a result, passive delivery of drug to the desired tissue is enhanced in tumors and atherosclerotic plaques [41, 42]. *In vitro* and *in vivo* studies related to combination cancer therapy with polymer-drug conjugates are under investigations. For example, doxorubicin and gemcitabine (*in vivo*) for prostate cancer [43], doxorubicin and phosphatidylinositol-3 kinase inhibitor (*in vitro*) for breast cancer [44], doxorubicin and combretastatin (*in vivo*) for lung cancer and melanoma [45], paclitaxel and Bcl-2 targeted siRNA (*in vitro*) for breast cancer [46] and paclitaxel and VEGF siRNA (*in vitro*) for prostate cancer [47].

NANOFIBERS (NFS)

Nanofibers provide the platform for bone tissue engineering [48], with the help of 50% bead free silk-fibroin (SF) and 50% of chitosan (CS) composite nanofibers. Moreover, nanofiber based wound dressings (NFDs) have made progress in drug delivery vehicle in the form of hyperbranched polyglycerol NFD [49], regulation in release of dual drugs [50], combination of ZnO with sodium alginate nanofibers to increase antibacterial action [51] and silica NFD combination with silver nanoparticles used in recovering the wound cover [52].

CERIUM OXIDE NANOPARTICLES (CONPS)

Cerium oxide nanoparticles (CONPs) have different abilities that attracted the scientists' intention as therapeutic agent to manage various diseases, including cancer. The antioxidant ability of CONPs and/or protection from free radical, particularly reactive oxygen species (ROS), shows that these nanoparticles may be used to treat many human diseases that are associated with the production of ROS. Studies show that CONPs exhibit imitative activities of superoxide dismutase (SOD) [61] and catalase [62] that neutralizes the superoxide ion (O_2^-) and hydrogen peroxide (H_2O_2) in the biological system. Similarly, CONPs show scavenging ability for nitric oxide (NO) [63] and hydroxyl radical (OH^-) [64]. In contrast to these investigations CONPs also reflects the direct oxidant action in the biological system. It could be inferred from the research that pH is one of the few crucial factors that direct the particles whether CONPs act as oxidant or antioxidant [65, 66].

Polymer coating of CONPs enhances the aqueous solubility and shows both cytotoxic and anti-invasive properties in tumor-stroma interactions [67]. Treatment of CONPs before giving the radiation therapy exposure alleviate the radiation therapy-induced damaging and death of cells in normal tissues of breast [68], head and neck [69] and lung [70].

GOLD NANOPARTICLES (GNPS)

Gold nanoparticles (GNP) are considered to be promising agents for cancer therapy. Moreover, GNPs are being explored as contrast agents, photothermal agents, and radio-sensitizers as well as drug carriers. GNPs show various physic-chemical characteristics such as surface plasmon response (SPR) and ability to bind with thiol and amine groups, facilitating surface modification, hence, fruitful in applications of biomedical sciences [71]. The exact mechanism for entry of GNP into the cell is unknown; therefore, one of the most suitable mechanisms could be non-specific receptor mediated endocytosis (RME) [72]. Tumor targeting, with respect to GNPs, may be achieved by binding the tumor-recognizing molecules such as transferrin, epidermal growth factor (EGF), monoclonal antibodies or folic acid [73, 74].

As far as the drug carrier is concerned, GNP is covalently bound to gemcitabine (as payload) and cetuximab (targeting agent) in pancreatic cancer [75]. Up to 60% of EGFR is over-expressed by pancreatic cells and combination of these two molecules has been studied in phase II trials [76]. Citrate-coated GNPs were produced and bound with multiple trastuzumab antibodies to facilitate the targeting in SK-BR3 breast cancer cells [77].

Table 2. Multifunctional nano-carrier uses following combination of drugs.

Drug	Disease/cell line	Status	References
Vincristine	Acute lymphoblastic eukemia	Approved	[98]
Paclitaxel	Solid tumor	Approved	[99]
Daunorubicin and cytarabine	Acute myeloid leukemia	Phase I	[100]
Floxouridine and irinotecan	Solid tumor	Phase I	[101]
PKN3 siRNA	Pulmonary metastasis	Phase I	[102]
Doxorubicin	Colorectal cancer	Phase I	[103]
Doxorubicin	B-cell non-Hodgkin's lymphoma	Preclinical	[34]
Paclitaxel	Breast cancer	Preclinical	[35]
Vincristine	B lymphoma cells	Preclinical	[99]

QUANTUM DOTS (QDS)

Quantum dots (QDs) are inorganic fluorescent probes, used for multiplexed imaging and detection and long circulating time. QDs have several advantageous features in fluorescence characteristics in biological applications as compared to the normal organic dyes. 1) broad excitation spectra, 2) narrow and symmetric emission spectra, 3) large molar extinction coefficients which enable them to absorb more photons (10-50 times) than organic dyes and 4) much more stability with considered photobleching. The bare QDs are considered not suitable for biological purposes because they are insoluble in water. To make them use in biological system due to their optical properties, the surface modifications are necessary. Multiple surface modifications are employed in case of QDs for their use in biological system. The binding of thiolated PEG polymer helps in the biocompatibility, water solubility and decrease in non-specific cellular uptake [78]. Other polymers are also used with varying length of chain and number of binding dentates like dendrimers [79], phosphine polymers [80] and PEGylated dihydrolipoic acid [81, 82].

NANOPARTICLES AND NEURODEGENERATIVE DISORDERS

With the advancement in the nanoparticle technology it is now achievable to target the drug to specific, cells and/or tissue successfully with less toxic outcomes in biological system. The importance of medical implications of nanotechnology products is evident in various disorders linked with central nervous system [83]. Various particulates have shown successful gene transfer in brain and neuronal tissues [84-86]. A successful cure and management of various neurodegenerative disorders are not possible, at present. Such disorders are characterized by protein accumulation as well as neuronal degeneration. Moreover, the number and type of damaged neurons vary from disease to disease in nervous system. Degenerating cholinergic neuritis, amyloids plaques with amyloids-beta (Aβ) fragments and anomalous combination of hyperphosphorylated tau protein in neurofibillary tangles are the main characters of Alzheimer's disease (AD) [87]. The possible biomarker for AD is amyloids-beta derived diffusible ligands (ADDL). Association between cerebrospinal fluid (CSF) and ADDL levels may be helpful for the better diagnosis and early treatment for AD. This could be possible by the biding of ADDL-specific monoclonal antibodies with nanoparticle based detection technique, known as biobarcode amplification (BCA) [88]. However, the evaluation of toxic effect of nanoparticles is most crucial before treating any disorder related to CNS. Another important nanoparticle, organically modified silica (ORMOSIL) nanoparticle have been used as a non-viral vector for *in vivo* gene transferring and its expression in the brain region using animal model [89].

NANOPARTICLES, IMMUNE RESPONSE AND NANOTOXICITY

Current investigations have been reported that nanoparticles are responsible for the elicit of immune responses because every particle that is entered into the body, is recognized by the immune cells that cope with the foreign invader through various mechanisms including release of signaling molecules that are accountable for immune response. The immune system shows two types of immunity; adaptive and innate. Adaptive immunity refers to the adaptation of immune system over time to identify the specific pathogen or foreign invader more efficiently. While innate immunity is responsible for facilitating the immediate protection against infection. Due to the electrical, optical and biological properties of nanoparticles, they have attracted considerable attention of researchers with a number of applications including drug delivery.

Studies reflect that the nanoparticles are pro-inflammatory in nature, such as very small size proteoliposomes [53], gold nanoparticles [54] and silica nanoparticles [55]. In contrast to these nanoparticles, silver nanoparticle (Ag@tiopronin) did not show pro-inflammatory impact on macrophages and differentially inhibited the interleukin-6 (IL-6) secretion mediated by specific Toll-like receptor (TLRs) [56]. In the case of other cell types, silver nanoparticles strongly inhibited the production of IL-5, interferon-γ (INF-γ) and tumor necrosis factor-α (TNF-α) by the peripheral blood mononuclear cells (PBMCs) [57] and IL-6, 8 and 11 by the human mesenchymal stem cells (hMSCs) [54].

Silver nanoparticles have the ability to bind the bacterial cell wall and cell membrane and are responsible for halting the process of respiration. These particulates can interfere with sulphur containing proteins present in the bacterial membrane and phosphorous containing molecules such as DNA to prevent replication mechanism [58]. Antimicrobial activity of silver nanoparticles has been explored against *Escherichia coli* (Gram negative) and *Staphylococcus aureus* (Gram positive). In case of *E. coli* bacterial growth was inhibited [59] while *S. aureus* showed mild inhibition in growth [60], suggesting that antimicrobial effect may be associated with the differences between the cell wall and membrane (Gram negative and positive) of bacterial including chemical nature, thickness and extensive cross linking.

Various studies have shown the cytotoxicity in the biological system by the nanoparticles [90-92]. The risk of toxicity depends upon the uptake mechanism, inflammation, transport within the body and exposure rate of the particulates. The term non-toxicity for nanoparticles in controlled standard cell culture medium during cytotoxic experiments does not mean that they are completely harmless. They may produce toxic effects in a tissue, disturbing normal physiology of body, without rapidly or significantly killing the cells. The toxicity idea related to nanoparticles is linked with the presence of metallic surfaces without coating by biocompatible material. The particulates covered with organic layer or coatings are relatively much less toxic. However, nanoparticles coated with starch exhibited production of reactive oxygen species (ROS), reduced ATP contents, cell cycle arrest, mitochondria dysfunction as well as DNA damage [93].

CONCLUSION

Nanomedicines show variations in their physico-chemical properties and are being investigated for management of various health issues throughout the world. Various pharmaceutical companies are working for the manufacturing of multiple types of nanomedicines which are on the stages of clinical trials Table **3**. Researchers are hopeful by collecting the data from animal models and predicting nanomedicines as a better option for management of various disorders.

Table 3. Various nanoparticles (nanomedicines) in different phases*.

Company	Product	Nanoparticle	Effect/use	Surface chemistry	Status
Pharmaceutical's Acti-coat™	SILCRYST™	Nanocrytals	Antimicrobial activity	Biocompatible surface	-
Nanopartz™	Ntherapy™ Ntracker™ Nsense™	Nanorods	Photoacoustic imaging, optical coherence to-mography (OCT)	Amine, carboxyl, neu-travidin	-
Nanopartz™	Gold nanobeads™ Accurate™ Microgold™	Nanobeads	Diagnostics and imag-ing	Biocompatible surface	-
Nanopartz™	Gold nanobeads™	Gold colloid with polymer-cage nanoparticles		Methyl, carboxyl, amine, biotin or neutravidin	-
Nanopartz™	Accurate™	Spherical gold nanoparticles	Conjugate with most antibodies and DNA	Methyl, carboxyl, amine, biotin or neutravidin	-
Nanopartz™	Microgold™	Largest gold nanomaterials	Labeling in electron microscopy and as sensors	-	-
CytImmune Sciences Inc.	Aurmine™	PEGyalted colloidal gold nanoparticles	Target drug delivery to tumors	Tumor killing agent, recom-binant human TNFα	Phase I
CytImmune Sciences Inc.	AuriTol™ (CYT-21001)	PEGyalted colloidal gold nanoparticles	Target drug delivery to tumors	Chemotherapeutic drug, Paclitaxel	Phase I
CytImmune Sciences Inc.	AuriTol™	PEGyalted colloidal gold nanoparticles	Target drug delivery to tumors	TNF with Paclitaxel	-
CytImmune Sciences Inc.	AuriCin™ (CYT-31000)	PEGyalted colloidal gold nanoparticles	Target drug delivery to tumors	TNF with Doxorubicin	-
CytImmune Sciences Inc.	AuriCin™ (CYT-41000)	PEGyalted colloidal gold nanoparticles	Target drug delivery to tumors	TNF with Interleukin-12 (IL-12)	-
CytImmune Sciences Inc.	AuriCin™ (CYT-51000)	PEGyalted colloidal gold nanoparticles	Target drug delivery to tumors	TNF with Interleukin-2 (IL-2)	-
BioDelivery Sciences Inc.	Bioral™	Encapsulated nanochelate	Oral drug delivery	Biocompatible surface	Phase I
NanoBio™	NanoStat™	Nano-emulsion	Antibacterial, antiviral, antifungal,	Biocompatible surface	Phase III
NanoXray™	Nbtxr3™	Inert and inactive core	Cancer therapies	Biocompatible surface	Phase I
NanoXray™	NanoMag,	Magnetic nanoparticles	Diagnosis and treatment of cancer	Biocompatible surface	-
NanoXray™	NanoPDT	Magnetic nanoparticles	Treatment of cancer	Biocompatible surface	-

* Further detail can be access by using following URLs
www.nucryst.com; www.ncbi.nlm.nih.gov; www.nanopartz.com; www.cytimmune.com; www.understandingnano.com; www.nanobio.com; www.nanobiotix.com

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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