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Therapeutic Nanoparticles: Advantages and Toxicity

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Abstract: ***The present review focused on various advantages and hazardous aspects of therapeutically used nanoparticles. Therapeutic applications of nanoparticles have been covered in cancer diagnosing and therapy, surgery, bio-detection of disease markers, molecular imaging, implant application, tissue engineering, and devices for gene, drug, radionuclide, and protein delivery. Many therapeutic nanotechnology applications are still in their beginning stages. However, promising applications are being developed especially in the field of cancer therapy. Nanoparticles are proficient as carriers for chemo-therapeutic drugs and enhance their therapeutic index. These NPs act as therapeutic agents in gene and photothermal therapy. Furthermore, they function as molecular imaging agents to distinguish target cells and monitor cancer progression. Finally, the generations of toxic biological responses of these nanoparticles are mentioned based on detailed explanations of NPs toxicity assessment. Evaluation of potential toxicity of NPs are mainly comprises of its physicochemical properties, inclusive particle characterization (such as size, shape, specific surface area, agglomeration, solubility, element impurity etc.), function of cellular and non-cellular in vitro toxicity assessment and animal supported toxicological measures.***

Keywords: ***Therapeutic Nanoparticles, Drug Therapy, Targeted Delivery Vehicles, Nanocarriers, Nanoparticle Toxicity.***

I. INTRODUCTION

Nanoparticles (NPs) in the size rangingfrom1to100 nm have been developed as novel, unique, and specific therapeutic and diagnostic agents. Their unique physical and chemical properties such as large surface area to mass (or volume) ratio and extremely small size that enable bioengineers to modify fundamental properties such as improvement in solubility, higher diffusion ability and hydrophilicity, reduced immunogenicity and enhanced therapeutic index to defeat with the difficulty related to use of traditional mode. Since the conventional chemo-therapeutics dispersed throughout the body, where they impact both cancer and normal cells, NPs due totheir increased permeability and retention (EPR) phenomenon exhibit preferential accumulation into tumors [1]. Numerous NP-based therapeutic and diagnostic modalities have been successfully introduced for treatment and signal detection of cancer, pain, communicable disease and allergens [2].

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As therapeutic agents, these NPs enabled invasive routes of administration, targeted delivery of drugs more precisely, controlled released of therapeutics, improved solubility, extended half-life, improved therapeutic index and lower systemic toxicity. As diagnostic agent NPs have given rise to detection at molecular level, aid in identifying abnormalities (like virus fragments, malignant tumor cells, and specific disease factors or markers, which cannot be identified with conventional medical forte) as well as drastically improved the sensitivity and specificity of nuclear image, magnetic resonance image, optical image, and ultrasonic image [3].

The most frequent NP platforms now a days include liposomes, polymeric NPs, dendrimers, gold NPs, magnetic NPs, carbon nanotubes, silicon oxide NPs and quantum dots. These NPs are known as ‘therapeutic nanoparticles’ and remarkably use as carriers for drug molecules. Therapeutic applications of nanocarriers are include exploitation of nanomedicine, surgery, nanorobots, tissue technology, improved diagnosis, bio-detection of disease markers, diagnostic and therapeutic drug carriers, and as biosensor, biomarker, advanced molecular imaging devices, implant engineering, antimicrobial coating for medical devices, bio-active surfaces and devices for drug, protein, gene and radionuclide delivery.

Many therapeutic nano-technological applications are quiet initiatory phase (Figure 1). However, promising applications are being developed particularly in tumor therapy, for example, nanoparticle-based diffusion across the blood-brain obstruction could qualify an effectual treatment for brain tumors as well as other central nervous system CNS-diseases like Alzheimer’s and Parkinson’s [4].

Some of the examples of nano-materials and devices used in drug-delivery applications includes in nano-polymer based gene delivery process, nano-needles for cell surgical operations and moleculardeliveryto the cell nucleus, incorporation of nano-crystalline silver NPs with anti-bacterial agentand haemostatic properties to wound care medicines, microchip-mediated programmable medicine release plans, and nano-porous drug elution coating on stents. Several novel nanoparticles are respond to externally applied physical stimuli in ways that make them suitable therapeutics or therapeutic delivery systems. For example, magnetic Fe_2O_3NPs, gold-coated silica nanoshells, and carbon nanotubes (CNT) can alter electro-magnetic energy to heat energy that increase temperature of tumor cells and have lethal effects. Slight enhancement in the magnetic field or using irradiation of external laser-infra red light at the tumor cell localization where these CNT are bound to or inside the tumor cells can enhanced the temperature [6].

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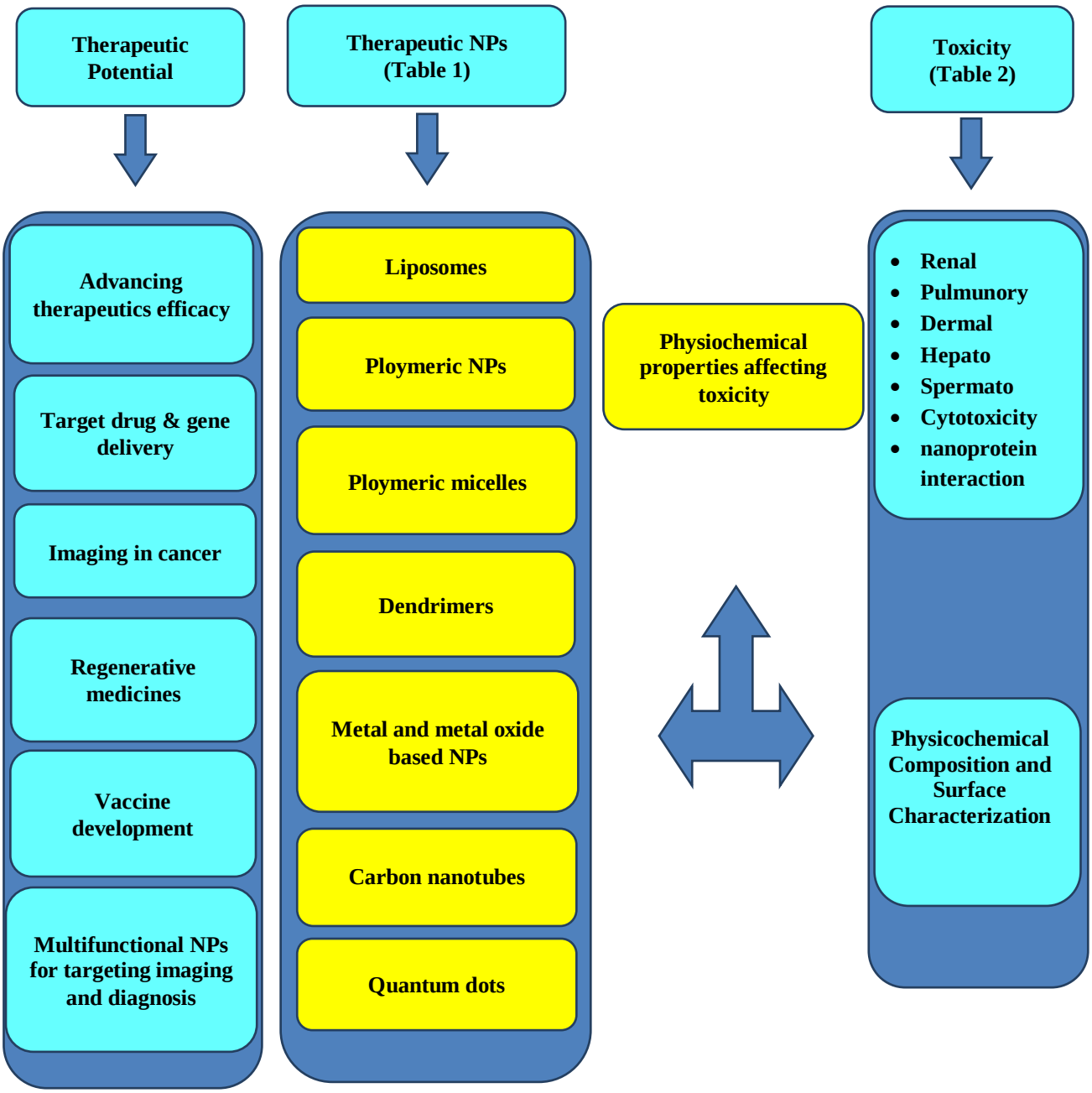

Figure 1: Graphical Representaion for Therapeutic Applications and Toxicological Aspects of Nps

II. THERAPEUTIC APPLICATIONS OF NANOPARTICLES

(i) Drug delivery and diagnosis

Nanotechnologies mediated drugs, are also known as nano-medicines or nano-drugs. They are nano-sized materials assembled with natural / synthetic polymers and have been formulated and assessed for diagnosis and curative applications. The major applications of nanodrugs include prevention or treatment of various cancer types, drug delivery, and use in biotechnology, healthcare, pharmaceuticals, skincare etc. Natural/synthetic polymers including liposomes, dextrans, polylactic-co-glycolic acid (PLGA) and dendrimers have been prepared as nano-carriers for delivering therapeutic and imaging agents. Similarly, other nanostructures such as metal based (gold and silver NPs / nanoshells), CNT, quantum dots (semiconductor based NPs) and metal-oxide based (super-magnetic) NPs are also utilized for different clinical applications. Nano scale complexes for drug delivery and diagnosis are being developed using the NPs as the drug carrier and as the chemo-therapeutic medicine [6]. The drug could be dissolve, adsorb, or disperse onto the NP-complex or attached to the NP surface co-valently. The chemo-therapeutic drugs can also be developed at a nano-scale horizon with the use of engineered NPs for drug delivery [5]. When the conventional preparations compared with the NP-based developement of the drug paclitaxel reveled enhanced both cytotoxicity effects on cell line culture and therapeutic ratio in live animal model [7].

Thus the nanoparticle formulations have distinctive feature of higher bio-accessibility and prolonged sustainable remedial time, which permits the drug density to persist above the minimal effectual value for longer period.

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In addition, the NP-mediated drug solved the issues related with the existing conceptualization of paclitaxel, such as less water- solubility and severe side effects related to attached adjuvant Cremophor EL. The hollow cavity of several nano-fabrication has been helpful for the encapsulation of drugs like anticancer, chemo-therapeutic, immuno-therapeutic or nucleic acids. Successful core level encapsulation in various nano-assemblies like spherical,rod-shape, genetic and chemical modified are more suitable for drug delivery applications. The major challenge to deliver drugs into tumor cells include heterogeneous blood supplying, vascular permeability, unequal interstitial penetrations, intracellular diffusion obstruction, restricted movement of hydrophilic drugs across the cell envelopes, and in across the nuclear membranes. Moreover, numerous specific issues can also be considereddуring the handling of drug delivery process, like administration path, drug transportation into cells and tissues, drug resistance,clearance from the body, drug density distribution, gross drug accumulation in side the targeted tissue, toxic and antigenic properties of drug, and dosage, dose proportion and time programme of drug administration. Recently, the nano-assembly in use of drug release system include the pH-respondent polymeric micelles as nanocarrier process depends on the alteration in pH that allow the controlled drug delivery [8]. Another form of intracellular stimuli applied for drug release method is the variation in higher redox potential between the reducing intracellular space and the oxidizing extracellular space. Song et al., (2011) [9] prepared, redox-respondent polymeric NPs with incorporation of disulphide bondcomprising redox-sensitive polymer, poly(ethylene glycol)-b-poly(lactic acid). The reducing situation of the cellular cytoplasm initiate the constant liberation of the paclitaxel drug in to tumor cells resulted in marked cytotoxicity. However, it is necessary to observe the entry of targeted drug, changes in nano-assembly during i*n vitro* drug delivery, and *in vivo* assays with both pH- and redox-respondent polymeric NPs. Multi-stage NPsare able to alter their size, in the beginning these NPs are 100 nm in diameter after assembly with proteases they disperse into small size of 10 nm NPs, which are extremely expressed in the tumor cell cytoplasm. The small size of NPs permits for higher diffusion rate into the tumor cells and also deeper penetration throughout the tumor tissues [10]. Photo-sensitive NPs are another category of smart nano-carriers; they utilize the knowledge of physics, chemistry and biology [11]. Hybrid spiropyran / lipid-PEG NPs could altered their size from 150 to 40 nm when illuminated with UV radiations. These alterations are reversible type that permits the spatio-temporal control of drug delivery, better tissue penetrations, which is beneficial for cancer and many other disease treatment. Doxil (≈100 nm PEGylated liposomal form of doxorubicin) and Abraxane (≈130 nm albumin-bound paclitaxel nanoparticle) are the representative drug for Food and Drug dose Administration-approved NP-based therapeutics for solid tumor treatments. These NP-based drugs are specifically accumulated into tumor cells due to their improved permeability and retention time therefore, reduced the normal cell toxicity. In the following section, the properties and significance of the major NP platforms applied as drug delivery systems are discussed in details.

(ii) Cell targeting of therapeutic drug

Cell targeting is intended to achieve higher intake of therapeutic drug and/or diagnostic agent in a discriminatory localization for example, a tumor and solid tumor to blood/normal tissue for quantitative relation. Therefore, it could reduce possible side effects and improved therapeutic/diagnostic efficiencies and make the drug advantageous for handling of tumor and other diseases.Cell targeting has been accomplished with change in the physiochemical characteristics of the nanoscale assemblies as well as receptor-mediated endocytosis [2]. The cell targeting of therapeutic nanoscale assemblies can be carried out by change in its surface topography and charge that facilitate their intracellular release. Cell targeting could also be established by peptide,protein (e.g. antibodies), nucleic acid (e.g. aptamer), carbohydrate and vitamin. The attachment of these molecules with target drug could specify the receptor mediated endocytosis in the targeted cells. Virus are species and host cell specific and these natural affinity could be explore for tumor cell target treatment. For instance, bacteriophage MS2 virus like particles werecovalent coupled to peptides (SP94), which adhere to human hepatocellular cancer cells. Thus, virus-like particles are suitable for the privilege transfer of NPs, chemotherapeutic agents, protein toxins and siRNA conjugated drugs to human hepatocellular cancer cells [12]. Currently, the covalent conjugations of human epidermis growth factor (EGF) to simian virus SV-40 helped in cell targeting. Simian virus SV 40 holding significant advantage in gene delivery systems because of their low-level toxicity and higher stability in the blood [13]. In the cell-targeting field, the discovery of targeting ligands is required for enhancement of cellular uptake. A novel strategy was formulated for selected cell-uptake in separation of specific prostate cancer intrinsic aptamers [14]. Aptamers are tiny DNA or RNA oligonucleotides, configured in three-dimensional arrangement and having higher specificity and binding capacity.

(iii) Regenerative nanomedicine:

Reported by National Institute of Health (NIH)-USA the regenerative medicine and tissue engineering is multidisciplinary field of research and clinical application involving life sciences, physical and engineering sciences that focused on formulation of functional cell, tissue and organ substitute to repair, replace or enhanced biological function that has been impaired due to disease, congenital abnormalities, trauma, injury or ageing. Fundamentally, nanomedicine has dissimilar paradigm for medicine, it uses nanometer scaled tools utilizes cell regenerative and repair perspective working at the single cell level rather than at the organ level. The regenerative nanomedicines are revolutionized with the designing of novel grafts/scaffold systems that significantly increase regenerative characteristics of cell and/or tissues like cartilage, bone, teeth, nerve, skin, liver, myocardium, and eye. Since, the nanoscale level cell-matrix and cell-cell interaction takes place at the biological organs, which altered the cytoplasmic and cellular function in a more required manner to simulate the native tissue or organ.

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(iv) Bioimaging

Nano-scale formulations predominantly nanobio-assembly, provided excellent platform for *in vivo* or *in vitro*bioimaging with incorporation of fluorescent dyes or different nano-probes due to their higherspecific surface area, shape and size. The fluorescent dyes or probes could be bind onto the surface or inter space of the nanoassemblies thus, higher localized concentration of the dyeand/or probe have received for bioimaging. Moreover, any level of fluorescence quenching could be avoidable when the dyes are incorporated in a precise order and structure mode. Chemical modifications are required for conjugation of the dye or probe to the formulation of polymeric nanoassembly. However, in case of development of nanobioassemblies the chemical or genetic alterationsare required for bioconjugation of fluorescent dyes or probes. Other importance of nanobioassembly preparation using virus like particles for bioimaging is due to their bio-compatibility [15]. For example, a nanobioassembly with inert nature small plant virus CPMV (cowpea mosaic virus) have used for bioimaging [16]. Cowpea mosaic viruswas fluorescent conjugatedwith a fluorescent dyes using N-hydroxysuccin imide ester at higher concentrations with no measurable quenching. The fluorescent cowpea mosaic virus was injected into the embryos of mice and chick,give rise in exceeding luminous particles with *in vivo* scattering characteristic that allow high-resolution internal bio-imaging of vascular endothelium for time periods of 72 h (Figure 2). Furthermore, the fluorescent labelled cow pea mosaic virus NPs resulted a visual image of the vascular and blood flow rate up to 500 mm depth as well as allowed the long-run vascular mapping of tumors. The potential applications of M13 bacteriophage in bioimaging and drug delivery was demonstrated by Li et al., 2017 [17]. This rod-like virus NPs displayed potency in cell imaging when labelled with cell-targeting agents, like folic acid and fluorescent dye. Another alternative to fluorescent labelled nanoscale formulations are quantum dots (QDs) that have colloid nanocrystals with specific optical properties. The novel developments in QDs have promise for in-depth study of intracellular functionalities at the molecular horizon, higher resolution of cell imaging, long-run *in vivo* observance of cell processes, tumor therapeutics, and diagnostics [18].

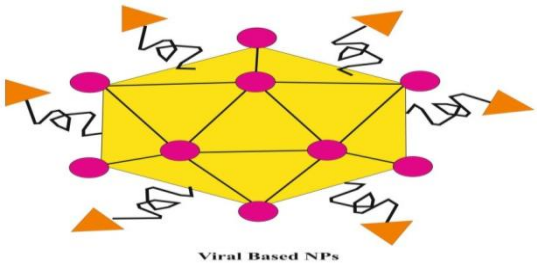

Figure 2: Schemetic representation of viral based NPs

(v) Vaccine development

In the literature, the various classes of nanoscale formulations such as liposomes, polymers etc. have been applied for development of new vaccine delivery systems. The targeting and adjuvant properties of nanocarriersalong with their size range from 200-300 nm could be suitable candidature for vaccine technologies [19-22]. The use of vaccines that generate auto antibodies to denature the infective protein effectively against non-transmittable acute diseases including rheumatoid arthritis, hypertension, Alzheimer's and Parkinson's sickness as well as vaccines for drug addiction.Virus-like particles (VLPs) are efficient and frequently considered for such vaccine applications because they are considered safe.Therapeutic vaccines or immunodrugs are developed by VLPs covalent coupled with antigens to that induce immunoresponses against the disease. These VLP based vaccines could be design in two- or multi-fold mode to generate antigenic B-cell humoral and cell-mediated, or immuno-modulating responses [23]. Although, live attenuated vaccines (or inactivated live virus vaccine) has no risk of infection in vaccinated individuals due to non existence of genomic matter required for replication and spread of viruses. However, the use of VLP based vaccine have some limitations including their mass productions, needed antigen size regulation for their conjugation to VLP for vaccine efficiencies. Some of the worldwide currently commercial VLP-mediated vaccine are Merck and Co., Recombivax HB (HBV) and Gardasil (HPV) and GlaxoSmithKline's Engerix (HBV) and Cervarix (HPV). The VLP-based vaccines have immunodrug nature and function to treat acute diseases or cases of drug addiction, which are differ traditional vaccines. The VLP-mediated vaccines are developed by covalent conjugation of self-antigen to virus like particles to produce autoantibodies. For example, vaccine for hypertension i.e. angiotensin II has been tried for clinical trials and was based on VLP vaccine delivery systems. A protein copied from angiotensin II was chemically synthesized and covalently conjugated with the RNA bacteriophage Qb VLP capsid. The synthesized angiotensin II vaccine was injected to spontaneous hypertensive rat and outcome showed the decrement in blood pressure [24].

These vaccine can have advantage for treatment in human beings for improved patient compliance, and no need of daily dose. Nanoparticles prove great potential as powerful vaccine prospect because they are voluntarily accepted by the antigen presenting cells of the immune response system. The nanomaterial size, distribution and the denseness of the B cell epitopes represented on the particle surface can significantly influence the quality responses of the humoral immune system. Self-assembling polypeptide nanoparticles (SAPNs) have huge potency as repetitive antigen presentation system for the vaccine synthesis. SAPN molecules are designed based on coiled-coil structural motifs and protein folding pattern. α-helical coiled coils are known to oligomerize and are able to form highly stable oligomerization domains [25]. The original SAPN constructs consisted of a pentameric coiled coil and a trimeric coiled coil joined together by a linker [26]. The coiled coils in each subunit join together through non-covalent interactions to create an assembly with a minimum of 15 subunits. Due to its trimeric and pentameric coiled coil structure, the assembly has contain a 3-fold and 5-fold axis of symmetry that overall can lead to an icosahedral symmetry [27]. An icosahedral structure in its smallest form consists of 60 subunits. Many viral capsids also contain this icosahedral symmetry. The SAPN subunits will each have an antigen of choice attached to the core and this antigen will be displayed on the surface of the SAPN.

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Because ideally 60 subunits come together, the SAPN molecules are repetitive display systems [28]. The repetitive antigen display and icosahedral symmetry both lead to an increase in immunostimulation, which is idealistic for vaccine candidates. Yang et al., (2013) [29] have utilized coiled-coil arenas as basic aggregation to engineer self-assembling polypeptide nanoparticles (SAPN). Such peptides were synthesized by genetically engineered cells and lengthenboth at the N or C-terminus by addition of suitable amino acid moiety. If the antigen of known protein sequence is used for NP assemblies, this will produce the repetitive presentations of that antigen and could be use for development of suitable and efficient vaccines for treatment of diseases like malaria,influenza, HIV, as well as SARS.

(vi) Photothermal Therapy

Hyper-thermaltherapy of cancer employs heating system of tumors using magnetic fields, microwaves, radio-frequency (RF) or ultrasound to cause irreversible cell destruction by damaging cell membranes and denature plasma proteins leads to cell death. The limitations of thermal therapy include the damage caused to normal surrounding tissue and the issue is overcome via photothermal therapy (PTT) with the application of photothermal agents. These photothermal agents could attain further controlled and distinguish heating of the targeted cancerous cells thus restricting it to the tumor. Efficacy of photothermal agents are defined as increased light absorption and proficient light-to-heat conversion. Natural chromophores and external dyes (indocyanine green) are traditional photothermal agents that suffer from low absorption and photobleaching respectively. The carbon nanotubes and metal NPs like gold nanoshells, nanorods, nanocages and nanospheres have absorption potential in the NIR regions of the electromagnetic spectrum as well as enhanced depth penetration of light and could solve these problems. Moreover, nanoparticles in the size range from 10-100 nm exhibit an improved light-to-heat conversionsin comparison with traditional dyes thus,offering reduced optical energies to attain target cell damage. However, consequences of their incomplete clearance and high accumulation within the RES have been reported. Hence, further studies should be directed towards the synthesis of sized metal NPs that can self-aggregate at tumor site and evade the RES [30].

(vii) Nanoparticles as Theranostic Agents

Nanoparticles are known as theranostic agents due to its simultaneous application in diagnosis and treatment of tumor cells. Thus a multi-functional NP should be developed for diagnosis, targeted drug delivery as well as observance of issues related to the therapy in respective incorporated manner. Improved polymerization and emulsification processes could directly create NP with hydrophilic and hydrophobic surfaces which enables their loading with different active materials (i.e. a hydrophobic therapeutic drug and a hydrophilic contrast drug and vice versa) [31-32]. The examples of potential NP as theranostic agents includes SPIONs used for MRI are coated with chemotherapeutic drug or cross-linked and conjugated with DNA (detail described later), carbon nanotubes and gold NPs those are applied for optical and phototherapeutic imaging could also be utilize in photothermal therapy.

III. THERAPEUTIC NANOPARTICLES FOR DRUG DELIVERY IN CANCER

The field of nanotechnology achieved a significant progress to resolve issues related to conventional anticancer drugs and allow a potential and efficient option for cancer treatment. The conventional tumor therapy consider as surgical intervention, radiation therapy and chemotherapeutic drugs are subjected to non-specific mechanism of action, larger doses are demanded, lack of selectivity to target tumor cells and inadequate bio-accessibility of these drugs to tumor tissue, often enhanced frequency of multiple drug resistivity that also destroyed the surrounding non cancerous cells and produced toxicity to the patient. Therefore, it created an enormous interest in the research and exploitation of novel cancer therapies predominantly; tumor-targeted nanomedicines and application of nanocarrier drug delivery systems. The suitable stages nanocarrier or nanovehicle between 10-100 nm in size are perfect for intracellular uptake, higher drug releasing capability and selectivity to target tumor cells when configured for efficient drug delivery. The NPs are also reasoned as a potential tool for the release of insoluble and highly sensitive therapeutics, offering discriminate and programmed drug delivery system at target tumour cells and also protecting them from degradation. Thus, offer great potency to solve the issues related to chemotherapeutic drugs and make them suitable candidate for target drug delivery system. Moreover, the traditional chemotherapeutic agents are rather tiny molecules and quickly clear out from the blood as well as from body and decrease their efficient amount within the cancer cell. Conjugation of chemotherapeutic agents with suitable nanocarriers, enhanced their blood circulation time, providing sufficient concentrations of drug to reach to the tumor site. Likewise, they prolonged the drug accumulations at tumor site hence, reduce the drug amounts in healthy cells and lower the toxicity. Thus, use of nanotherapeutic have enhanced anti-tumor efficiency at similar timeline and reduced their consequent toxicity and side effects [33]. Cancerous cells proliferate faster and uncontrolled manner in comparison to healthy cells and creating distinguish physiological features of tumor tissue such as increased vascular permeability to macromolecules, impaired lymphatic drainage and acidic tumor microenvironment. The rapid dividing tumor cells display an enhanced metabolic rate that demands more of oxygen and nutrients to acquire extra energy by glycolysis and creating an acidic environment. The abnormal multiplication of endothelial cells produce an impaired structure for freshly defined microvascular system at the tumor site. Furthermore, the new tumor blood vascular system existing as disorganized and twisted architecture, with larger space in between the endothelial cells, generating a permeable and porous microvascular network resulted into high vascular leakage of macromolecules. In addition, dividing tumor cells are able to break intratumor lymph vessels by compression, reduce the function of lymph vessels to the outlying tumor. The dysfunctional lymphatic leakage, along with disorganized permeability of new defined tumor blood vessels, are recognized as a phenomenon named enhanced permeability and retention (EPR) effect.

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The EPR effect is a significant process by which NP-conjugated therapeutic and other macro-molecules upto 50 KDa size could be accumulate within the tumor tissue.
NPs used as drug carrier should able to conjugate with various therapeutic agents like tiny hydrophilic and/or hydrophobic molecules, proteins, peptide-based drug, and nucleic acid. After encapsulation of drug moiety within the nanovehicle, solubility and stability of the drug increased and could be release from nanocarriers in a defined mode with time. Thus, the nanocarriers can hold the drug amount within a therapeutic framework and their delivery could be trigger by any stimuli specific to the tumor site. Furthermore, the drug delivery process must be continue in the blood vessels for longer time with minimum loss of drug loading or drug activities. They should be obscure from macrophages of the reticular-endothelial system (RES), liable for ingesting, assimilating and killing newly appeared molecule. Thus, the nanotherapeutic drug size and their surface properties are two specific factors that affect uptake by tumor cells and recognition by the RES. In general, 10 to 100 nm is considered to be the suitable size for nanoparticle drug vehicles. If the drug nanocarrier size is less than 10 nm, the particles will be rapidly eliminated by nephritic clearance (thresh hold < 6 nm). When the nanocarrier size are greater than 100 nm, the possibility of ingestion by the RES will significantly increase [34-35].
A precise surface coatingsare required for the stability and higher retention of nanoparticle-mediated drug delivery system. Nanovehicleshaving hydrophilic coatings exhibit longer circulation times in the blood vessels due to reduced nephriticclearance by RES.For example, a hydrophilic polymer, poly(ethyleneglycol) (PEG), used for modifying the surface of nanoparticles. The PEG coatings on the NP surface inhibit the opsonin binding due to loss of interaction with proteins thus, increased the colloidal stability and suppress the ingestion by the RES, prolonged their circulation time and hence their accumulation at the tumor site [36]. Surface charge and shape of the NP are other cause affected the cancer cell internalization and intracellular trafficking [37].moreover, the positive charged NPs can be simply accepted by cells, and generates immune responses. Thus, for the clinical concerns, neutral or negatively charged NPs are desirable candidates.
NPs used for anticancer drug vehicles have been developed made from various materials such as polymeric NPs, polymeric micelles, polymer-drug conjugate NPs, dendrimer, liposome, virus, CNT, and metals NPs likeFe_2O_3 and Au. Several of them have been in proper clinical applications but some are still in clinical and pre-clinical trial stages. NPs have qualified as suitable resolution for the various issues associated in drug delivery systems for examples, drug solubility and stability, improved circulation time, and reducing the toxicity to healthy tissues.
Some of the definite criteria to be fulfill by the nanoparticle conjugated drugs for their effective delivery to the targeted tumor cells are as follows:

- The NPs should be conjugated or attached to the desired drug(s)
- The nanocarrier should be < 100 nm in size are suitable for cell uptake, higher drug loading capability and selective target to tumor cells for efficient drug release
- The nanoparticle-drug complex should have stability in the serum to perform controlled drug delivery
- The nanoparticle must be competent to deliver the drug at the tumor site
- The nanoparticle-drug conjugates should be specifically released to target cells via receptor-based transports and/or by the EPR effect, thus decreasing the toxicity to healthy cells
- The residual nanocarriers has to be of biological origin or biological inert material with a narrow life-span that allows safe denaturation
- In case, if a non-biodegradable material is applied, it should not be lethal at higher required doses and have easy renal clearance ability

Table 1 summarizes the several types of nanoparticle used for drug delivery systems.

Table 1: Various Types of Nanoparticles for Drug Delivery System

Type of NPs	Shape	Size (nm)	Structural feature	Characteristics	Example of NP-drug formulations	References
Liposomes	Globular	25-1000	Self-associated lipid bilayer surrounds a central aqueous space closed colloidal structure	1. Amphiphilic, 2. Encapsulate water soluble drugs, Assemble hydrophobic drugs at lipid interface, 3. Biocompatible, 4. Ease of modification, 5. Targeting potential	1. IHL-305 (Irinotecan encapsulated in PEG-liposomes) 2. PEG-liposomal doxorubicin 3. Doxil® 4. Myocet® 5. CPT-11, 6. CPX-1, CPX-351 7. Thermodox™	33, 38-40

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Polymeric NPs (Polymer-drug conjugates)	solid, Globular	50-1000	Drugs are conjugated to the side chain of linear polymer with a linker (cleavable bond)	1. Water soluble, biodegradable colloidal system, nontoxic 2. Drug can either dissolve, entrapped, adsorbed, attached or encapsulated in to the NPs 3. Surface modification (Pegylation) 4. Selective accumulation and retention in tumor tissue (EPR effect) 5. Specific targeting of cancer cell-receptor -mediated targeting with a ligand	1. Paclitaxel(Abraxane AB-007) Albumin bound NP (nab) 2. Docetaxel-PNP 3. CRLX101(Cyclodextrin-PEG NPs) 4. CALAA-01 (Cyclodextrin-PEG-transferring- NPs) 5. BIND-014 (Docetaxel + PEG-PLGA NPs) 6. HPMA-DOX	41 42 43, 44 44
Polymeric micelles	Spherical	10-100	Amphiphilic block copolymers assemble and form micelle with a hydrophobic core and hydrophilic shell	1. Appropriate carrier for water insoluble drugs developing particle suitable for i.v. administration 2. Biocompatible, longevity, high stability, Self-assembling, Biodegradeble 3. Functional modification 4. Targeting potential	1. Genexol-PM® (Paclitaxel + PEG-PLA micelle) 2. NK911, NK105 (Doxorubicin / Paclitaxel + PEG-PAA micelle) 3. NC-6004, NK012 (Cisplatin/SN-38 + PEG-PGA micelle)	45 46 47,48 49,50
Solid lipids	Spherical	50-1000	physiologically tolerated lipid components with solid shape	1. Suitable carrier for water insoluble drugs to develop the oral bioavailability 2. high & improve drug content 3. control release of drug 4. ease of scaling up and sterilizing 5. enhanced bioavailability	1. ALN-VSP (Lipid conjugated antiKSP & antiVEGF, siRNA 2. C-VISA BikDD (Lipid + plasmid-C + BikDD) 3. Atu027(Lipid + antiPKN3)	33 51
Dendrimers	Globular polymer	15-200	Hyper-branched synthetic polymer with regular pattern and repeated units. Accurately controlled structures	1. High structural and chemical homogeneity 2. Ease of functionalization, high ligand density 3. Biodistribution and PK can be tuned 4. Non-covalent encapsulation & covalent conjugation with cleavable linkers 5. Hydrophobic & hydrophilic drugs 6. Control degradation	1.PAMAM-MTX 2. PAMAM- platinate 3. G4-PAMAM 4. G6-PAMAM	52-54
Metal and metal oxide based NPs	Different shapes, Spherical rod, plate film layer	10-250	NP contain a metal core covered by a shell (metal or metal oxide)	1. Easily synthesized and functionalized 2. Tunable surface feature 3. Controlled release of drug 4. Stability in *in vivo* conditions 5. Low cytotoxicity	Preclinical stage of drug delivery system	55-57
Carbon nanotubes	Cylindrical	1-1000	Molecular scale tubes or cylinders of graphitic carbon composed of benzene ring	1. water soluble, biocompatible using chemical modification (organic functionalization) 2. thermal and electrical conductivity 3. high mechanical strength 4. good stiffness as well as flexibility	1. CNT-MTX 2. CNT-amphotericin B	58-60
Viral NPs	Hexagonal or Octagonal	50-500	Protein cages (capsid), Multivalent, self-assembled structures	1. Defined geometry and uniformality 2. Enhanced multivalency using surface modification by mutagenesis or bioconjugation 3. specific tumor targeting 4. Biological compatibility and inert nature	1. HSP-DOX 2. CPMV-DOX (canine parvovirus (CPV) + DOX) 3. Rexin-G (Retroviral vector-dnG1 plasmid DNA)	61-63

Abbreviations: PEG, polyethylene glycol; PAA, poly-(L-aspartate); PGA, poly-(L-glutamate); PLA, poly-(L-lactide); PAMAM, poly(amidoamine); PLGA, poly (D,L-lactic-co-glycolic acid); HPMA, N-(2-hydroxypropyl)-methacrylamide copolymer; DOX, doxorubicin; MTX, methotrexate; PK, pharmacokinetics; EPR, enhanced permeability and retention; CNT, carbon nanotube; HSP, heat shock protein; CPMV, cowpea mosaic virus.

IV. VARIOUS TYPES OF NANOPARTICLES FOR DRUG DELIVERY SYSTEM

(i) Liposomal nanoparticles

Liposomes are round shape lipid carries with a phospholipid bilayered membrane arrangement contains either natural or synthetic amphiphilic lipid molecules. Liposomes were the first NP carriers used in drug release conjugation since Bangham represented them in 1961[64]. Liposomes are synthetic vesicles with globular character composed of self-associated lipid bilayers (amphiphilic phospholipids and cholesterol) surrounds a central aqueous space. Liposomes may vary in size (diameter varies from 25nm to 2.5mm), lipid composition, proportion of drug delivery and biodistribution [40]. The liposome assemblies can enclose water-soluble drugs at the core level of the phospholipid bilayer while hydrophobic drugs can be assembled at the lipid bilayer interface. Liposomal formulations are capable in cellular drug delivery by fusion response or endocytosis, and any type of drug depending on its solubility can be encapsulated in it (Figure 3).

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Based on their surface charge, the liposomes are classified into anionic, cationic and neutral NPs [65-66].

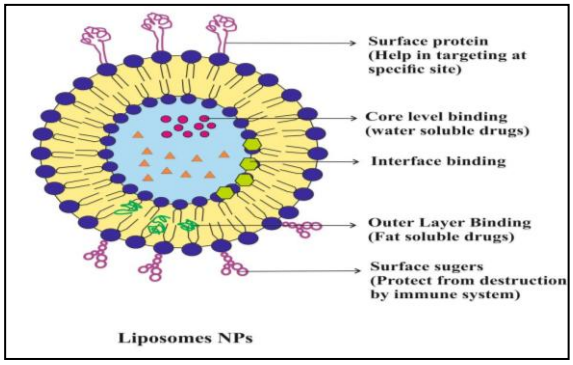

Figure 3: Schemetic representaion of Liposome

In the past decade, the most important breakthrough in rapid development of liposome has achieved for new pharmaceutical applications. Improved liposomes have been constructed for therapeutic delivery, that enhanced the permeation rate of drugs provisionally and deliver the desired target drug in a controlled time and limited mode to the tumor site. Assembly methods also play significant part in ultimate liposome properties, such as efficacy of encapsulation and drug delivery profile. Thus, as a drug delivery system, liposomes recommend numerous benefits like self-assembly competence, biocompatibility, capability of carrying large drug loads, and broad variety of biophysical and physicochemical properties that can be modified to control biological characteristics (Sercombe et al., 2015, Zylberberg et al., 2016, Khosa, et al., 2018) Presently, numerous categories of cancer drugs have been entrapped into nanoliposomal assemblies with different formulation processes. For example, liposomeassemblies having anthracyclines doxorubicin (Doxil®, Myocet), daunorubicin (DaunoXome®), and DepoCyt® are authorized for the treatment of metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi's sarcoma [4]. Nab-paclitaxel (Abraxane) resolved the solubility issues of the drug paclitaxel, and was lately approved by the US Food and Drug Administration (FDA) for activated metastatic breast cancer patients [41]. Moreover, some of the liposome drug conjugates have in various clinical trial stages. Among them, nanoliposomal CPT-11 is a multiple constituent liposomeassembly includes a camptothecin derivative and a topoisomerase-I inhibitor (in a Phase I study), SPI-077 (liposome cisplatin for solid tumors), CPX-351 (cytarabine: daunorubicin for acute myeloid leukemia), Lipoplatin (cisplatin for larger cell lung cancer), ThermoDox (a thermo-sensitive doxorubicin for hepatocellular carcinoma, and other advanced cancers), and Stimulax (an anti-MUC1 cancer vaccine for larger cell lung cancer). In addition, Yakult Honsha Co., Ltd. developed IHL-305, a PEGylated liposome entrapping irinotecan (in a phase-I study for advanced solid tumors) [38,67]. As drug vehicles, nanoliposome is capable to enhance the bioavailability, drug solubility and stability *in vivo*, and reduced the binding of drug with proteins or other biomolecules, thus decreased the toxicities and side effects to the healthy cells [66]. Nanoliposomes also have benefits of reduced toxic side effects, easy to altered their size and surface properties (hydrophobic or hydrophilic), biocompatible, biodegradable and having renal clearance. Therefore,modification and improvement in liposome formulations strategy have shown significant enhancement in their solubility, stability, circulation time, reduced nephritic clearance by reticulo-endothelial system; RES, and increased accumulation in tumors [5,40, 68].

To encourage the accumulation in target tumor tissues, liposome surface can be conjugated with ligand molecule able to recognize and bind to specific group of cells for example, the antibodies herceptin / trastuzumab that target the Her-2 antigen and explicit by definite breast cancer cells, folic acidspecifically received by folic acid receptors that are present at higher numbers in set of ovarian tumor cell, and/or RGD to target integrins that are over expressed by multiplying endothelial cells of the tumor tissues [67]. Cationic liposome are efficient nanocarriers for delivering DNA or siRNA into mammalian cells. Mechanistically, the cationic liposomesinteract and adhere with negative charge cells and deliver loaded DNA or siRNA into cells. The adsorption-mediated endocytosis mechanism is also pertinent for cationic liposomal gene delivery [69, 70].

Cationic liposomes are suitable candidature as nanovehicle flexible, highergene transport efficiency and stipulate pairing locations for conjugationwith aptamers, ligands or antibodies [71]. Other important features of cationic liposomes as gene delivery vehicles includes simple formulation and transfection modes, higher rate ofliposomal-aptamer conjugation, lack of size restriction, not necessary to protein encapsulation forgene, capable to transfer in various cell types with higher transfection efficacy, lack of immunogenicity, allowing safe and repeated administration and its commercial availability.

The neutral liposomes are clinically applied for siRNA delivery because of non toxic to normal fibroblasts or hematopoietic cells [69, 71, 72]. Neutral liposomes developed via 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC) successfully released siRNA into cancer cells in comparision to cation liposome (DOTAP) or non-targeted siRNA [73]. Intraperitoneal or intravenous injections of DOPC nanoliposomes-siRNA complex reported with significant decrease in IL-8, EphA2, Bcl-2, neuropilin-2, FAK and tumor size reduction in mice model. Systemic administration of DOPC nanoliposomes - siRN Aassembly (140-150 µg per kg of body weight, i.v.) targeted to EphA2 combined with paclitaxel (5 mg per kg of body weight) efficiently suppressed ovarian tumor tissues in comparison to free siRNAs or paclitaxel alone [74, 75].

(ii) Polymeric nanoparticles

Polymeric NPs are solid, biodegradable, colloidal particle and characterized by their polymer compound, chemical nature and structural size and the drug molecule adhere/adsorbed either on the surface or entrapped/encapsulated into the nanostructure. [76]. Generally, the polymeric NPs belong to a hydrophobic core in which the therapeutic agents can conjugate and a hydrophilic shell that stabilized the NPs in aqueous medium (Figure 4).

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The major advantages of polymeric NPs are known to form well-defined repetitive chemical motifs, stable in acid and base environments, can be autoclaved, having various functional groups for derivative formulations amenable to chemical manipulation, capability of controlled release of drug, capability of active or passive target system, and minimum biodegradation in blood vessels [68, 77]. Both natural polymers (such as heparin, dextran, albumin, gelatine, alginate, collagen, and chitosan) and synthetic polymers (polyethylene glycol (PEG), polyglutamic acid (PGA), polylactic acid (PLA), polycarprolactone (PCL) and N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA) have been employed for preparation of these nanoparticles [34]. The reported polymeric NPs assemblies available for medical use of breast cancer are the Abraxane®(ABI-007), an albumin-conjugatedNP assembly of paclitaxel (nab-paclitaxel) [41].

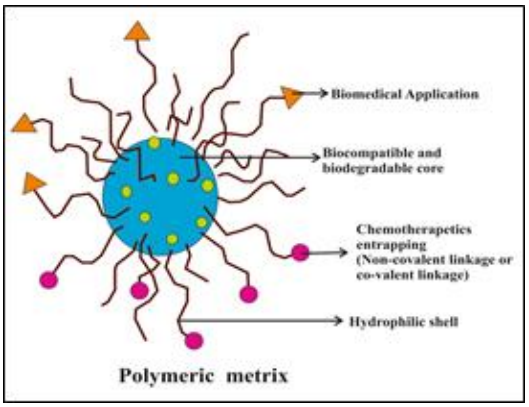

Figure 4: Schematic representation of Polymeric matrix

Several other polymeric nanoparticles entrapping different chemotherapeutics are in various phases of clinical and preclinical development. Such as, incorporating docetaxel, include BIND-014 (PEG-PLGA NPs) or Docetaxel- PNP are in a phase-I trial, CRLX101, contains camptothecin complexes with cyclodextrin-PEG polymer further the self-reorganized and develop the nanoparticles (in a phase-II trial) [42]. CALAA-01, a cyclodextrin-mediated NP incorporating anti-RRM2 siRNA, PEG to stabilize their preparation and the ligand transferrin for targeting the tumor cells, is in a phase-I clinical trial stage. The small interference RNA (siRNA) has been promising means for tumor therapeutics because of its capability in silencing gene manifestation. The siRNA genes advantages of endurance, penetration, multiplication, maturation, metastasis, necrosis inhibition or genes causing resistivity to chemo- or radiotherapy. However, siRNA has some disadvantages including enhanced biodegradation, lower cell uptake and fast renal clearances which prevent its applications as drug delivery [43, 72].

(iii) Polymeric micelles

Likewise, the spherical construction of liposome, micelles also have agglomerations of surfactant or natural/synthetic polymer distributed in an aqueous matrix, however they do not contain the inner hydrophilic phase which present in liposome. The structural characteristic of micelles includes amphiphilic aggregation of polymer molecules, the hydrophobic core domain provides area for hydrophobic drugs and the hydrophilic shield domain strengthen the hydrophobic center and makes the polymeric micelles soluble, suitable for i.v. injections. The therapeutic agents can either be conjugated with the aqueous domain or encapsulated in the hydrophobic center of the polymeric NPs (Figure 5). Polymeric micelles have certain advantages like they protect the drug from biodegradation and enhanced their blood circulation time. They are broadly evaluated as suitable nanovehicles for various applications, like symptomatic imaging, controlled release of therapeutic and/or gene.

Various favorable properties such as biocompatibility, longevity, high stability, ability to effective dissolution of a verity of less-soluble drugs, easy to alter their drug liberation pattern and enhanced the drug retention time in the target tumor cells due to the permeability circulation time, reduced nephriticclearance by reticulo-endothelial system; RES [45, 46, 78].

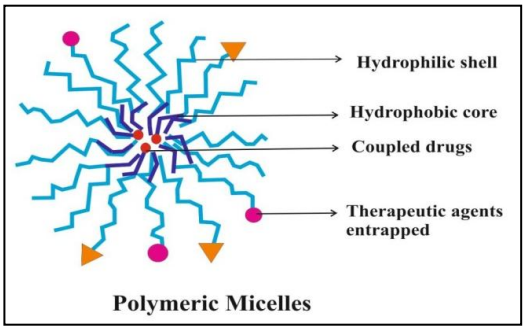

Figure 5: Schematic representation of Polymeric Micelles

The phase-I trial and pharmacokinetic studies have been performed in the patient of advanced recalcitrant malignancies, Genexol-PM® displayed fundamental antitumor activities and enhanced maximal dose toleration, permitted the administration of high dosage of paclitaxel. Moreover, when Genexol-PM® has been conjugated to other therapeutic agents, reveled enhanced efficiency but they exhibited some toxic side effects [47-50].

Other polymeric micelles containing PGA (poly glutamic acid) were formulated, NK012, NC-6004, NC-4016, incorporating SN-38, cisplatin, oxaliplatin respectively. Similarly, the block copolymer PAA (poly aspartic acid) used for preparation of polymeric micelles such as NK911, NK105 and NC-6300/K912 with entrapped drug doxorubicin, paclitaxel and epirubicin respectively. Additionally, SP1049C has been developed with copolymer pluranic L61 and F127 and drug doxorubicin.

All are mainly in phase-I trial, and a phase-II study of clinical evaluation [45].

(iv) Dendrimers

Dendrimers differ from traditional polymer; they are synthetic macromolecules repeatedly branched, roughly large spherical structures polymer. Dendrimers could develop from macro-organic compounds include poly (*N*-isopropylacrylamide)-polystyrene and poly(ethylene oxide)-poly(β-benzyl-L-aspartate) and possess perfect nano-architecture . Dendrimers have a spherical three-dimensional morphology conjunctive of three different parts;

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a central point, repetitious chains of numerous layers of inner shell, and an outer shell with multiple peripheral functional groups [52, 69]. Each region can be formulated in step-by-step mode from branched monomers that shows capability to regulate some of their molecular properties (like configuration, size, shape, dimension, number of branches, polar properties and capability to incorporate several surface and/or core level functional groups) and different functionality including solubility, thermal stability, modification of different chemical component for various application and controlled degradation (Figure 6). Thus, dendrimers exhibited tremendous potency in cancer therapy,controlled drug release, gene delivery, imaging for therapeutic purpose, bacterial cell killing and as sensors. Approximate fifty different kinds of dendrimers are in commercial applications including, polyamidoamine (PAMAM) and poly (propylenemine) (PPI) have been used extensively as anticancer drug nanovehicles, gene delivery, for NP sentrapping, diagnostic imaging etc. [34, 80].

Dendrimer designing for anticancer drugs delivery or encapsulation of hydrophobic compounds requires conjugation of particular chemical species on the dendrimer surface. Terminal ester groups (4^{th}, 8^{th}, and 16^{th}) of dendrimers were reformed to hydroxy- groups that was capable of encapsulate benzoate and 2,6-dibromo-4-nitrophenol with 1:1 and 2:1 (drug : dendrimer) ratios while non-acidic tioconazole drug did not form complex. Hence, the therapeutic doxorubicin formed covalent linkage to dendrimer as an acid-reactive hydrazone structure. The doxorubicin showed 80–98% reduced hemolytictoxicity and the therapeutic was significantly accepted by cancer cell lines [81]. Bhadra et al., (2003) [82] developed and explored, PEGylated 4.0 G PAMAM dendrimers entrapped with therapeutic agent 5-fluorouracil on carboxymethyl PEG5000 surface units exhibited higher drug load, limited release rate and decreased cytotoxicity in comparison with non-PEGylated dendrimer. The use of such PEGylated dendrimer can function as nanoparticle depository kind of arrangement for drug release.

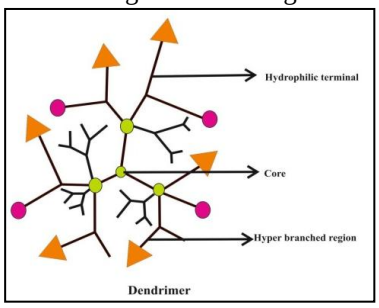

Figure 6: Schematic representation of Dendrimers

Dendrimers are act as vectors, in gene transfection. PAMAM or PPI dendrimers were applied as non-viral gene delivery systems, which enhanced the insertion of DNA by endocytosis [83]. Activated dendrimers with transfection reagent called Super FectTM can hold higher quantity of gene materials than viruses. PAMAM dendrimers conjugated with cisplatin resulted in high accumulation, reduced release rate and minimal toxicity at solid tumors as compared to cisplatin alone. In another example, amino terminated PAMAM dendrimers conjugated with silver salt showed antimicrobial activity against Gram-positive bacteria [54, 84]. PAMAM dendrimers coupled with the folate molecule and fluoresceine isothicyanate for targeting the cancer cells and diagnostic imaging, respectively [53]. Gadolinium (Gd) paramagnetic the deferential agents for MRI have been conjugated to PPI dendrimer unit for contrast enhancement [85].

(v) Metal and metal oxide based nanoparticles

Metal NPs of various shapes, dimension, porosity and sizes range 10 to100 nm are being studied as diagnostic and drug carriers for cancer therapy. Most frequently applied metal and metal oxides NPs as nanovehicles include Au, Ag, Gd, Ni, iron oxide, zinc oxide, and titanium dioxide NPs etc. They displayed specific characteristic including higher specific surface area, broad optical characteristics, simplepreparation steps, easily produced in large quantities, and facile surface properties and functional potential for the cancer treatment. They could be easily prepare in large amount of different size, shapes, porosity and reproducibility. They could be simply coupled with ligands and could easily evade the RES for targeting tumor therapy and/or for chemotherapeutics tumor therapy. Furthermore, these metal-based NPs are more stable at broad range of pH and temperatures than liposomes and solid lipid NPs (Figure 7). However, the associated problem of slow dissolution rate and biodegradation raises concern and uncertainty for their toxicity [30, 86-88]. Additionally, a crucial portion of the NPs could be retain in the body partsafter administration, and the accumulation as well as aggregation of metal NPswith subsequent administration can lead to cytotoxicity. Hence, the most of investigations on metal NPsmediated drug delivery systems are in the preclinical stage [68].

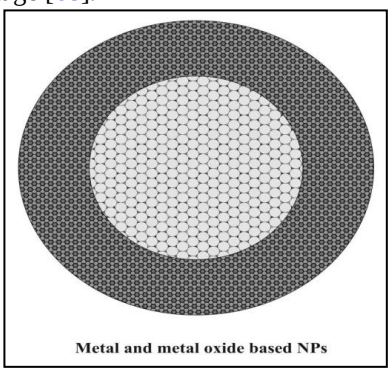

Figure 7: Schematic representation of Metal and Metal oxidebased nanoparticles

Gold and silver nanoparticles (noble metal NPs) are easily conjugated with different chemo- therapeutics like gene, antibodies, proteins and peptides, to target specific cells [89] along with natural or synthetic polymers (e.g., polyethylene glycol and PAG) to make them biocompatible and extend their circulation time for drug and gene delivery applications [90]. Additionally, they could easily alter the light or radio-frequencies into heat, therefore, enable thermal surgery of targeted tumor cells [91-92]. The metal / metal oxide NPs represent advanced optical characteristic, which could be easily tuned to desired wavelengths depending on their shapes (e.g., nanoparticles, nanoshells, nanorods, etc.), sizes (e.g., 1-100 nm), and arrangement (e.g., core/shell or alloy noble metals), capable of diagnostic imaging and photothermal applications in cancer therapy.

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Metal nanoparticles are effective photothermal agent because of their strong absorption in the near infrared domain of the electromagnetic spectrum (specially at 650 to 900 nm) and efficient light-to-heat conversions. Spherical gold NPs have maximal surface Plasmon resonance (SPR) absorption peak in the visible range at 520 nm [93].

Qian et al.,(2008) [94] established the applications of gold-mediated nanovehicles in human cancer cells and in transplant tumor mouse models. They demonstrated the function of bio-compatibility and nontoxic PEG-gold nanoparticles for *in vivo* tumor target systems, which could be detected by surface-enhanced Raman scattering (SERS). Superparamagnetic iron oxide nanoparticles (SPION) contain an iron oxide core covered by either silica/gold or some of the organic materials (polysaccharides, proteins, fatty acids, phospholipids, polymers) or surfactants [95]. Therapeutic use of SPION has been progressively increasing and is used for MRI imaging, for radiotherapy, drug and gene delivery, magnetic hyperthermia based treatment, for detection of solid tumor metastases, and metastasis in lymph nodes. For example, Fe_2O_3 or Fe_3O_4 metal oxide NPs (20 nm) have been applied for thermal surgery in cancer treatment and MRI imaging [96]. The particle conjugated to antibodies were applied for breast cancer targeting and imaging [97]. Iron NPs within water (i.e. magnetic fluids) have high surface to volume ratio of magnetic elements and excellent absorption efficiencies that make them more appropriate for candidate for specific internal heating of tumor cells.

Magnetic fluid hyperthermia has displayed hopeful outcomes in models of various cancer types malignant glioma, prostate (phase-I clinical trial stage), breast and brain (phase-II clinical trial stage).However, at present, they cannot be attained with systemic administration of iron oxide NPs [98-101]. Iron oxide NPs in water with externally applied oscillating magnetic field generated heat when administer straight into tumor cells [102]. SPIONs applied for MRI have been broadly described as potential theranostic drug (ability of NPs to perform duel functions of diagnose and therapy). They were outercoated by therapeutic agents (like methotrexate, trastuzumab, temozolomide), that have concerted hydrophilic and hydrophobic therapeutic drugs in a double-emulsion capsule (i.e. doxorubicin and paclitaxel), or entrapped with chemo-therapeutic drugs (cisplatin) for improved therapeutic benefit and controlled drug release [55-56, 103]. SPIONs are also capable to combine with p53 cancer suppressor gene for prompt gene delivery and nanovehicle which can be diagnose by MRI [9]. Polymeric liposomal carriers can co-encapsulate SPIONs for imaging and doxorubicin for tunable drug delivery [1]. SPIONs have also been radiolabeled with ^{64}Cu (for combined imaging PET/MRI), coupled with doxorubicin (for chemotherapy), and function with RGD for targeting tumor cells [104]. However, at present these nanoassemblies have been well-tried within cell culture and their promising results need to be effectual in living animal models.

(vi) Quantum Dots

Quantum dots (QDs) are tiny 2 to-10 nm in size, colloid mixture, fluorescent semiconductor based nanoparticles, in their composition it contains a metalloid crystalline center (element usually systematized of as alone or in combination of cadmium selenide, cadmium telluride, and indium phosphide or indium arsenide) and a shell chiefly of zinc sulfide. QDs are essentially applied for biomedical imagings because of emitting fluoresce in different colors that depend on component size and constituents. Their properties like specific surface area,size, shape, could be design and modify to find out significant absorption and light emission [105-106]. Due to their unique optical and electronic properties, semiconductors QDs have been investigated as a NP probe for molecular, cellular and *in vivo* imaging [108]. For instance, fluorescent QDs could be couple to receptor ligands molecule / aptemer / antibody for effective evidence of tumor cells, analysis of signal systems in tumors, measurements of peroxisomes activity and determination of cell membrane receptors.

Quantum dots have also been conjugated to therapeutic agents and can applied for targeted gene therapy and drug delivery [109-112]. QDs have been rising as a novel category of fluorescent marker in cancer therapy. Their comparability with organic dyes and fluorescent proteins, they hold specific optical and electronic properties, with controlled size and shape, emitting fluoresce light in multiple color and brightness, better signal emission, resistivity to photobleaching, and wide absorption spectra for synchronous excitation of different fluorescence pattern. Researchers got significant success in applicability QDs for *in vitro* imaging [113], labeling fixed cells [114] and tissue specimens [115], and for imaging membrane proteins on live tumor cells [116]. However, imaging of plasma protein molecules present inside the tumor cells using QD probes are difficult. The researchers have achieved limited success due to unavailability suitable techniques for release of monodispersed (i.e. single) QDs into the cytoplasm of live cancer cells. A major issues is that the QDs get aggregated inside the living cells, and are frequently captured by endocytotic vesicles such as endosomes and lysosomes. Monodispersed QDs have been generated and enclosed in stable polymers with variable surface properties. These nanoparticles are brilliantly fluorescent, suitable as imaging probes both *in vitro* and *in vivo* [117]. The advance improvement in the synthesis processes and alteration in their surface properties of QD nanocrystals, for application as imaging probes for live cells and animals as well as their integrated application in imaging and therapy have been detail reported by Smith et al., (2008) [108]. Moreover, they identified QD biodispersion, pharmacological kinetics, toxicity, and the limitations and possibilities of processing NP drug for *in vivo* imaging, diagnosis and therapy.

V. TOXICITY OF THERAPEUTICALLY USED NANOPARTICLES

The field of nanomedicine mainly involves the use of incisivelyengineered drugs / agents at nano level scale to produce effective therapeutics and diagnostic assemblies. NPs hold specific physico-chemical characteristic like nanosize, larger specific surface area to mass (or volume) ratio, and higher responsiveness, in comparison to microscale materials of identical formulations. To resolve the challenges, drawbacks and side effects (toxicity to surrounding normal cells) of traditional cancer drugs the nanomedicine have been successfully applied as therapeutics and diagnosis.

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Nanotoxicology' is rising as acrucial sub-discipline of nano-engineering. This is also projected as a new subdivision of toxicology that addresses the harmful conditions generated by nanoassemblies. Nanotoxicology refers to the focus on physiological and biochemical changes generated after the interaction of nanomedicine with biological processes. It also describes the quantity and the duration of cytotoxic biological responses generated due to theiroccurrence and specific dimension (such as surface properties, sizing, composition, configuration, aggregation and accumulation behavior) of nanotherapeutic applied for drug delivery systems [118]. People are in continuous exposure to airborne nanosized particles, and now a day's such exposures have increased due to research and development activities, formulations of various NPs, patients administration with nanotherapeutic, or human utilization of NP incorporated products. These exposures occur through superficial adherence, dermal contact, respiratory organ, and the gastrointestinal system. The common mechanism of cytotoxicity of therapeutically used NPs could be induced in following manner- (i) entry of natural or antropogenic NPs to the body by various path: Oral administrations, skin adherence, aspiration, Intra-venous, hypodermic and intra-peritoneal injections; (ii) absorption and relationship between NPs and biological components (i.e. tissue, cells, proteins, lipid membranes etc.); (iii) distribution to different body organs and can persist in the same composition, be altered, or metabolized; (iv) get into the living cells or organ tissues,accumulated and retained for undefined period of time before their renal clearance. Due to their tiny sizing, NPs can easily enter into the blood circulation and lymph system, and finally reached to tumor cells and target organs. Moreover, the NPs can attached to cellular proteins and directly enter into the target tissues where bigger molecules cannot reach for example NPs can enter into the cell nucleus or easily cross the mother's placenta of pregnant mice to pups, therefore, they poses adverse and toxic effects to target cells and also to*in vivo* surroundings [119-120]. *In vitro*, they interrupted DNA helical, break up gene expression, protein synthesis, and mitochondrial disturbance via oxidative stress mechanism [121-124]. *In vivo*, they cause inflammation, redness and induce or suppress the immune responses [125-127] (Table 2). However, a proper knowledge of NPs associated toxicity has yet to be achieved. Thus, studies should also directed on the challenges and disadvantages related to synthesized therapeutic nanoassemblies, minimization or eliminationof associated cytotoxicity even before their comprehensive applications. Some of the literature reported on the consequences of individual type nanoparticle to specific cell lines for a limited incubation time period, therefore, a generalize comparison of adverse effects between different investigations arenot possible. However, the safety of nanoassemblies for therapeutic applications and their influence to cell lines remain obscure. Recently, the focus on nanotoxicology has enhanced and much reports on cytotoxic pattern of NPs have been immersed. However, the categorization of nanoparticle safety is complicated because of different varieties of: (1) kind of nanomaterials, (2) coating and stabilizing compounds, (3) physico-chemical conditions of the NPs (specific surface area, size, shape, porosity, charge, surface morphology), (4) incubation time and concentration, (5) studies on type of cell lines, (6) assay method or (7) potential involvement of the NPs with the assay output signal. The factors influencing cytotoxicity are not completely interpreted and necessitate advancement is require for standard processes to assess proper toxicity. Fundamental explanations required to evaluate potential toxicity of NPs comprises of its physicochemical properties, inclusive NPsparameters (like sizing, shape, specific surface area, agglomeration, solubility, element purity etc.), Application of cellular and non-cellular *in vitro* toxicity assessments and animal model cytotoxicity measurements [68]. Detail methods NPs toxicity assessment comprises (i) surface property characterization and chemical composition of NPs includes NTA, BET, DLS, DFM, NMR, ESR, AFM, FT-IR, SEM, TEM, EDAX, XRD, XPS (ii) NP evaluation under physiological conditions.

(also needed for potentiality as pharmacological agents) (iii) Sterility and pyrogenicity determination (iv) cellular and non-cellular *in vitro* toxicity assays incorporate biocompatibility test, ROS production test, hemolytic and platelet aggregation test, immune system activation tests, geno-toxicity assay (v) NP mediated toxicity assessment in animal model consist of dose range finding, tolerance test for single and multiple dose, acute cytotoxicity measurement, tissue dispersion and renal clearance assays, deposition and degradation of NPs and immune toxicity of NPs.

Table 2: Nanotoxicity and Health Hazards of Therapeutically Used Nanoparticles

S. No	Type of Nanotoxicity	Effects on Human Health	Reference
1	Neurotoxicity	Reduced neuro viabilities, Increase cytoskeletal disruption, Decreased intracellular content, Diminshed ability to form neuritis in response to nerve growth factor (NGF)	128 129
2	Hepatotoxicity	Generation of reactive oxygen species (ROS), Mitochondrial dysfunction, Glutathione (GSH) depletion, LDH leakage , Abnormal cell morphologies	130
3	Renal toxicity	Necrosis, Swollen glomerulus, Dwindling in lumen Bowman's capsules, Glomerulonephritis, Deterioration of metabolic alkalosis	131
4	Pulmonary toxicity	Inflamation, Granuloma formation, elevation of blood pH	131-133
5	Spermatotoxicity	Sperm fragmentation, Necrosis, Apoptosis male sterility	134-135

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6	Nanoprotein interaction	NP act as haptens and modified protein structures, Altered protein function and representing them as antigen, Raising protein potential for autoimmune response	136
7	Dermal toxicity	Affect cell morphology, Inhibit keratinocyte proliferation	137-138
8	Mammalian germline stem cell cytotoxicity	Drastic reduction in mitochondrial function, Increase membrane leakage, Necrosis, Induction of apoptosis	139

The toxicological effects and limitations associated due to therapeutics applications of each category of nanoparticles are discussed in the paragraphs below. Nanotechnology-based drugs (nano-drugs) are mainly applied in drug delivery, pharmaceuticals, healthcare, biotechnology and skincare. Various biomedical applications use nanocarriers for delivering therapeutic and imaging agents. Examples are liposomes, dextrans, poly(lactic-co-glycolic acid) (PLGA), dendrimers, carbon nanotubes (CNTs), metal and metal oxide NPs (gold and silver NPs /nanoshells), superamagnetic NPs and semiconductor based nanoparticles such as QDs.

(i) Liposomes toxicity

Liposomes are lipid mediated nanovehicles that have been applied for drug and gene delivery to reduce the survival of cancer in kidney, lung, liver, prostate and skin. They have several specific benefit include preserving therapeutics or siRNA from biodegradation, selective target through ligand peptide or antibody conjugation and less toxicity to the surrounding cells [140]. For instance, Liposomal doxorubicin (FDA authorized drug) has resulted in inhibition of some taxane- and platinum-sensitive and resistant perennial ovarian tumors [141]. Liposomes do have inherent difficulties hindering clinical efficacy, including: (i) Release of water soluble therapeutics with existence of blood constituent (ii) aggregation and miserable retention constancy, (iii) low encapsulation efficiency, (iv) relaibility and reproducibility, (v) disadvantage of scale-up for clinical assessment, and (vi) cytotoxicity [69, 105, 142]. Toxic side effects can fall out principally because of liposomes arrangements, and compositions, shape, size and charge of the particle. For instance, cationic liposomes could show some similarity with blood lipoproteins (LDL, HDL) and other serum proteins and can interact with the extracellular substances. Due to their interaction, aggregation or delivery of loaded therapeutics before reaching the target tumor cells nanocarriers can lead to systemic cytotoxicity. Other chemical constituents in the cationic liposomes act as surfactants that cause membrane solubilization, cell lysis and generate toxicity. Quaternary amines are more toxic than tertiary amines and result in potential inhibition of PKC (Protein Kinase C) activity [143-144]. Furthermore, cationic liposomes have generated reactive oxygen species that cause cellular influx and inflammation of lungs. They could also exert macrophages based toxicity due to continuous exposure of more than three hours. Positive charge of cationic liposomes and their systematic application for several weeks in mice resulted in liver damage that can be reduced by controlling dose of agents [145-146]. Therefore, neutral liposomes formulation is better for systemic applications and uptake of targeting drugs at the site of action.

(ii) Dextrans toxicity

Dextrans are glucose polymers (with α-1,6-glucopyranosidic linkages) and are able to make well-defined repetitive unit pattern applied for a broad spectrum of therapeutic utilization. Various physicochemical properties of dextrans includes hydrophilic and lipophilic nature, molecular size, shape, surface charge, adaptability and biocompatibility, which can influence its pharmacokinetic behavior. For example, dextrans with <70 KDa size result in rapid elimination (one hour after injection) as compared to dextrans between 70 to 250 KDa size that exhibit prolonged circulation. Dextrans are able to conjugate in irreversible or reversible mode with drugs, imaging molecules, growth factors, hormones, proteins, and peptides. For example, the pharmaceutical agentssuch as aspirin, nicotinate, naproxen, ketoprofen, ibuprofen, diclofenac and indomethacin can combine with dextran by esterification method, for sustained release. Periodate oxidation, carbamic acid esterification, and cyanogen bromide activation are the known methods used for conjugating drugs to dextrans. These dextran based drugs and enzymes can improve solubility and stability that leads to effective target delivery [147-148]. Development of non-toxic drug delivery vehicles and effective delivery method for efficient delivery of therapeutic agents are major difficulties associated with pharmacological agents for clinic use. Therefore, dextran conjugated drugs have been formed that enhance the target delivery into thetumor cells. A dicarboxy methyl-dextran conjugated with cisplatin showed stronger inhibitory effects and prolonged self-life in colon tumor cells than free cisplatin [149]. Furthermore, the dextran-based drugs reduced toxicity due to delayed excretion by the kidneys as well as prolonged plasma circulation time. The nonsteroid anti-inflammatory drug (Flurbiprofe, that initiated peptic ulceration, gastrointestinal perturbation and GIT hemorrhage) when conjugated with dextrans decreased gastrointestinal associated toxicity due to improved physicochemical modifications [150]. However, some side effects like anaphylaxis, platelet dysfunction, volume overload, pulmonary oedema or cerebral oedema associated with dextran have been reported that can become serious in future [148]. An uncommon but serious interference of dextran mediated osmotic pressure has been also reported that leads to acute renal failure [151]. Therefore, the treatment using dextran-based drugs is not advisable for patients suffering from renal insufficiency, diabetes mellitus, or vascular disorders. Normally, the toxicological aspects of dextran-based drugs are considered as minor and their advantages compensate for the issues.

(iii) Poly (lactic-co-glycolic acid) (PLGA) toxicity

PLGA is a common degradable, non-toxic, biocompatiblepolymer in humans that has been used since the 1970s. It is FDA authorized elastomeric polymer for therapeutic delivery as it biodegradable, biocompatible, and ease of processing [152-153].

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The general toxicity related to PLGA conjugated NP for therapeutic applications are low-level and their degradation products are metabolized by the Krebs cycle and are easily release by renal clearance.

PLGA is frequently exploited in the assembly of therapeutic delivery, and vascular tissue engineering devices, like grafts, sutures, implants and prosthetic medical devices [154]. The PLGA based nanoparticle delivery system enhances accumulation of diagnostic and therapeutic agents because of its enhanced permeability and circulation retention time. PLGA as drug delivery has been explored for treatment of various diseases, like arthritis, diabetes mellitus, bowel syndrome, brain and tumor imaging, because of their biodistribution and biodegradability [152-153]. For instance, Lupron Depot® is a commercializedtherapeuticdelivery device having PLGA used for the management of progressive prostate tumors. PLGA mediated NPs can be used to conjugate paclitaxel to attain programmed release of drug to the luminal surface and inner part of ePTFE vascular grafts [155]. PLGA NPs have evidenced as a safe nanovehicles. Cytotoxicity measurement taken over in Balb/C mice displayed no change in the tissue damage or histopathology. However, oral doses of PLGA NPs assemblies reveled 40% accumulation in liver cells [44]. Thus, poly(lactic-co-glycolic acid) based NPs have significant potential in several biomedical applications. However, modification in their physicochemical parameters can lead to significant reduction of accumulation in the liver cells [68].

(iv) Dendrimers Toxicity

Research and development on dendrimers recommended that they could be suitable as nanovehicles for the controlled release of anticancer drugs, gene delivery and encapsulation of hydrophobic compounds. The physiochemical properties such assolubility in aqueous medium, monodispersity, encapsulation capability, and huge amount of surface functional groups, can formulate these NPs as efficient drug carrier. Common example of dendrimer is the polyamido-amine or PAMAM[84, 156-158]. They could also cause toxicity similar to other NPs. Surface functional groups mainly positive charged moietyof dendrimers can disrupt and weaken the lipid bilayer that leads to cell lysis. The amino-terminal end of PAMAM dendrimers were caused cell necrosis on human intestineadenocarcinoma Caco-2 cells and haemolysis and cytotoxic effects, on the solution of RBCs [158-159]. However, the plasticity of the dendrimer molecules after chemical pretreatment could resolve some of toxic apprehension that may occurred. Fischer et al. 2003 [160], reported that amino-terminated PAMAM dendrimers revealed little cytotoxicity than the much flexible amino-functional linear dendrimers. The researcher suggested that level of substitution and the kind of functional amine were significant; the secondary and/or tertiary amines were lesser toxic in compare to the primary amines. Cytotoxicity of cationic dendrimers can be reduced by surface functional group alteration by exploitation of four PEG chains or six lipid chains on PAMAM. Hydroxy- or methoxy-terminated dendrimers injection (10mg/kg PAMAM) to mice did not establish acute or long-term toxicity [158-159]. Thus dendrimers can be more suitable to variety of biomedical applications. Moreover, the molecular flexibility and simple chemical modifications can resolve its toxicity issues.

(v) Carbon nanotubes toxicity

Carbon nanotubes are non-metal based NPs. They are graphic carbon molecular tubes in nano-scale with large surface area, strong thermal and electrical conductivity, high mechanical strength, superior stiffness as well as flexibility. Carbon nanotubes can be conjugated with drugs, inhibitors and/or imaging agents useful for cancer diagnosis and treatment applications [58-59]. Due to their large size and fiber like structures, carbon nanotubes cause cytotoxicity with inflammation, morphological changes in cells (in bronchial epithelium cells and keratinocytes), platelet aggregation, mitochondrial dysfunction and DNA damage. It can also generate reactive oxygen species (ROS), lipid per-oxidation and oxidative stress that leads to cell death [161-166]. These potential toxic and degrading effects can decreased the use of CNTs for therapeutic exploitation.

(vi) Metallic nanoparticles toxicity

Metal and metal oxide mediated nanoparticles have a center and a shell. Both core and covering could be either an inorganic or a metal oxide. Metal colloid of gold and silver NPs have been exploited as carrier for imaging agents, gene delivery, to enhance fluorescence imaging, to improve optical sensing and are biocompatible and stable. Nanometals present in metal nanocarriers couldreact with fluorophores to enhance fluorescence, advancement in photo-constancy and lessen quenching. Colloidal gold and silver NPs are produced by different physical, chemical and biological processes and are commercially available in different shape and size ranges [167-171]. Gold NPs conjugated with anti-EGFR antibody have been safely applied for identification of the EGFR expressing cells [172]. During studies on photothermal surgical treatment in mice model of colon carcinoma, intravenous injections of PEG coated gold nanoshells showed no toxicity [57]. Although gold NPs have been used for cancer drug delivery, this exercise was hampered by complexities related to formation of stabilized and nontoxic structures. Gold NPs might cross mother's placental barrier resulting harmful toxic effects to the developing fetus [173]. Gold NPs can interact with serum proteins as well as can transform cellular proteins structure causing autoimmune related toxicity. It can also generate ROS that induces cell death [174]. Currently, to prevent theseissues, stable, nontoxic gum arabic coated NPs have been tested that in form of injection or oral administration [175]. Thus, gold NPs can safely be applied for photoablation therapy. Silver NPs have been used as nanomedicine for treatment associated to injury, burns, wounds and catheter related infections and commercialized for antimicrobial activity [176]. Furthermore, their therapeutic potential is applied in treating various diseases like acquired immune-deficiency syndrome, retinal neovascularization, and as anti cancer and anti tumor properties.

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The toxicity aspect of silver NPs are that they cause blood brain barrier destruction, brain edema and neuronal degeneration by generating reactive oxygen species (ROS), dysfunction of mitochondria and glutathione depletion in liver cells [177]. They are also reported for alteration in the membrane composition and impairment of the bacterial cell wall due to attachment of sulphur integrated peptides. Thus, usage of silver NPs as drug nanocarrier for humans could be restricted. Technological advances are required that would reduce their toxicological effects in animal model. Silver NPs have been successfully applied for controlling bacterial infections. Superparamagnetic iron oxide nanoparticles (SPION) are globular nanocrystal of 15–20 nm of size with a Fe^{2+} and Fe^{3+} center molecule generally encircled by dextran or PEG particles. Their magnetic behavior are suitable as the marker bio-units in assays, as well as MRI differentiation molecules. Likewise, they are responsible for superficial functionalization for operational target *in vivo* or for *in vitro* diagnosis. SPION particles have desirable magnetic characteristics, and with the existence of an externally used AC magnetic field they facilitate targeting of the NPs in a defined location, which is known as magnetic drug targeting. The method is effective in releasing drugs to the preferred target area as well as retaining it at the tumor cells during restricted drug delivery and reduces the systemic toxicity of drugs [178]. Superamagnetic nanoparticles have least toxicity in the human body. An investigation compared numerous metal oxide NPs illustrated that iron oxide NPs were non-cytotoxic and safe at below 100 mg/ml concentrations [179]. However, intravenous administration of higher dose resulted in potential accumulation to the targeted organ which can produce inflammation, homeostasis imbalance, oxidative stress and DNA impairment, [180]. Thus, SPION particles can be safely and effectively applied in humans in controlled concentrations (< 100 mg/mL) and retention intothe tissues needs to be observed that avoid excess iron. Furthermore, specific precautions must be paid to the release of iron (Fe^{+3}) ions during monitoring which can otherwise interact with H_2O_2 and generate free radicals such as hydroxyl radicals.

(vii) Quantum dots (QDs) toxicity

Quantum dots (QD) are nano sized fluorescent semiconductor nanocrystals, which have size-tunable optical and electrical characteristics. They are coated with polyethylene glycol that can conjugate with targeting molecules like antibodies or ligands. QDs distribution, absorption, biodegradation, renal clearance and cytotoxicity rely on number of factors resulting from constitutional physiocochemical characteristics and environmental conditions. Research related to examine QDs cytotoxicity are fewer. QDs core metal components become toxic after degradation or removal of the coating material. Dissolutions of polyethylene glycol further leads to other toxicological effects that could be diminished by pretreatment with N-acetylcysteine [107]. Quantum dots core containing metalloid Cd or Zn when exposed to acidic or oxidative conditions results in degradation, and subsequent release of metal into the cytoplasm produced toxicity [106]. QDs with specific optical dimensions are normally imperturbable of cadmium containing semiconductors. Cadmium has hazardouspotential, and cytotoxicity of these types of QDs to cell-lines, and human beings require systematic investigations. Although, QDs have been useful for characterizing cell and drug diagnosis, referredas imaging probe or protein signaling but it would be hard to resolve the toxic effects of these nanoparticles that would limit their application in cancer therapy.

VI. CONCLUDING REMARKS

Therapeutic use of nanoparticles much specific as drug delivery that primed to dispersed quickly and to minimize cytotoxicity in normal surrounding cells. Moreover, in drug delivery system NPs are applied as nanovehicles, they would either adhere / conjugated the drug superficially or enclosed/ encapsulated the drug and provide protection from dissociation, biodgradation or denaturation. Currently, numerous novel and potential NPs are in research and exploitation stage, probability of more and new treatment methods can be hoped to be available in future. Systematic physiochemical characterization as well as immunological, pharmacological and FDA approved clinical trials will be required for all newly developed NPs to be deemed suitable for use as drug delivery, therapeutic agents, photothermal therapy or imaging probes. Furthermore, NPs enclosed with polymer coating and ligand formation their load distribution need to be analyzed. The allocation of nanoparticle size, shape, uniformity and consistency of its synthesis in different batches must be maintained. The toxicity aspects and safe exploitation of nanoparticles in therapeutic applications remains an unsolved issue. In the last decade, the significance attention is given in nano-toxicological aspects and more information on cytotoxicity of NPs have been reported in the literature. Studies focus on to recognize the consequence of NPs on cells is essential and the proper correlation with intracellular accumulation and extracellular NP distribution and their associated cytotoxicity or the intracellular degradability of NPs would provide new discovery and directions on the reduction in normal cell cytotoxicity. Although, some progress has been made with *in vitro* systems, translation to animal and human patients has thus far been limited. The animal and human body complexity and distribution variability, pharmacokinetics and toxicity of NPs, brought only by slight change in the particle's physicochemical properties present as enormous challenge that must be overcome. In addition, studies related to short and longer duration toxicity would also be needed in both cell-line culture and live animal models before they could get FDA acceptance for clinical phase trials.

DECLARATIONS LIST OF ABBREVIATIONS

NPs: Nanoparticles, FDA: Food and Drug Administration, RES: Reticulo-endothelial system, EPR: enhanced permeability and retention, ROS: reactive oxygen species, CNT: carbon nanotubes, SPION: Suparparamagnetic iron oxide nanoparticles, QDs: Quantum dots, EGF: epidermis growth factor, PLGA: polylactic co-glycolic acid, PEG:

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polyethylene glycol, NIH: National institute of Health, CPMV: Cowpea mosaic virus, VLPs: Virus like particles, SAPNs: Self assembling polypeptide nanoparticles, PTT: photothermal therapy, RF: radio frequency, SPR: surface plasmon responses, SERS: Surface enhanced Raman Scattreing.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

COMPETING INTERESTS

The author has declared no conflicts of interest for this review article.

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AUTHORS' CONTRIBUTIONS

LR formulated the conceptual thought and planned the write up. The author reviewed literature, outlined, wrote, edited the manuscript and prepared all the figures and Tables.

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