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NANOPARTICLES FOR CANCER

Nitish Chugh*, Mahesh Kumar Kataria

Department of Pharmaceutics, Seth G.L. Bihani. S.D. College of Technical Education, Gagan Path, Sri Ganganagar (Raj.) 335001, India.

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ABSTRACT

Despite the "battle on cancer" is today in its fourth era and contemptwidelydevelop has been made in sorting the environmental origins and cellular and molecular biological basis for this dreaded disease, we yet do not have anexactperceptive of the variationsamong a cancer cell and its normal equivalent. If we do not recognize cancer, we cannot handle, take control, and exclude it. The accomplishment of the human genome sequence and its consequent enhancements in the succession data are essentialstages to totallyunderstand cancer cell biology. Nanotechnology, anoriginal, novel emphasis of explorationdevelopedcommencing the convergence and coalescence of severalassorted scientific regulations and as a usual term for the conception, operation, and function of structures in the nanometer size range. In this article, Nano medicine expressions of nanotechnology will be frazzled and will includeregionsfor instance drug delivery systems and new drug therapies as they convey to cancer.

Corresponding author
Nitish Chugh
M.Pharm. (Pharmaceutics)
Research Scholar,
Department of Pharmaceutics, Seth G.L. Bihani,
S.D. College of Technical Education,
Gagan Path, Sri Ganganagar (Raj.) 335001, India.
chughnitish880@gmail.com

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INTRODUCTION

Cancer is one of the prominentinstigates of mortality around the globe. Around 70% of the world's death occurs in Asia, Africa and Central and South America due to cancer. 22 million new cancer cases will emerge within the next two decades[1]. Cancer the unrestrained propagation of cells where caspase-mediated cell death is prominentlyvanished, have need ofmanydenseprocedures of remedy, due todifficulty in genetic and phenotypic levels, it demonstrates clinical diversity and therapeutic resistance [2]. Nanotechnology and Nanoscience research have occurredswiftlythroughout the earlier years in a wide-ranging of product domains. It impartsprospects for the growth of materials, together with those for medical applications, where conventional methods may reach their boundaries [3]. The foremostobjectives in designing nanoparticles as a delivery system are to constraint particle size, surface properties and release of pharmacologically active agents in order to attain the site-specific action of the drug at the therapeutically ideal rate and dose regimen [4]. Nanoparticles (NPs) are regarded as nanoentities whose size ranges from 10 to 1000 nm. Attributable to their smaller size, they present much complex specific surface area, since the total surface area of a particle is inversely proportional to its diameter[5]. The reason behind nanoparticles is attractive is established on their exclusive and essentialaspects, such as their surface to mass ratio, which is much bigger than that of other particles and materials, their aptitude to adsorb and bring other compounds [6]. Polymeric nanoparticles established on synthetic polymers or natural polymers have fine biocompatibility with great loading of therapeutic drugs [7].

General Principles:

1. Passive targeting implies to the collection of drug or drug-carrier system at specificlocation due to pharmacological factors. Penetration of the tumor vasculature rises to the place where particulate carriers for instance nanoparticles can erupt from blood circulation and locate in the tumor tissue [8].
2. Active targeting is generally gotten by coupling the nanoparticle to a targeting moiety, thuslettingbettercollection of the drug in the tumor tissue, insidespecific cancer cells, intracellular organelles or precise molecules in cancer cells [9].
3.Nano-sized inorganic particles of either simple or complex nature, show unique, physical and chemical properties and signifyaprogressivelyeminent material in the growth of novel nanodevices which can be used in many biological, biomedical and pharmaceutical properties [10].
4.Dendrimers are nano-sized artificial macromolecules which composed of a numeric no. of functional groups with a compact molecular structure and the biological properties including polyvalence electrostatic interactions, solubility [11].
5. Improving designs of clinical trials involving nanotherapeutics [12].
6. Informatics techniques are considered to be important tools for the progression of cancer nanotechnology research. This diversity is linked to combinatoricallyenormous numbers of mechanisms by which the chemical configuration of nanoparticles can be altered [13].
7. Liposomal nanoparticles can conjugate with either antibodies or ligands for discerning drug delivery. They havecertain advantages that they are biodegradation, nonantigenic and have transport rate [2].Linking anti-cancer operational constituents with imaging molecules in order to achieve a real-time assessment of the in vivo competence of the drugs[14].

Types of nanoparticles

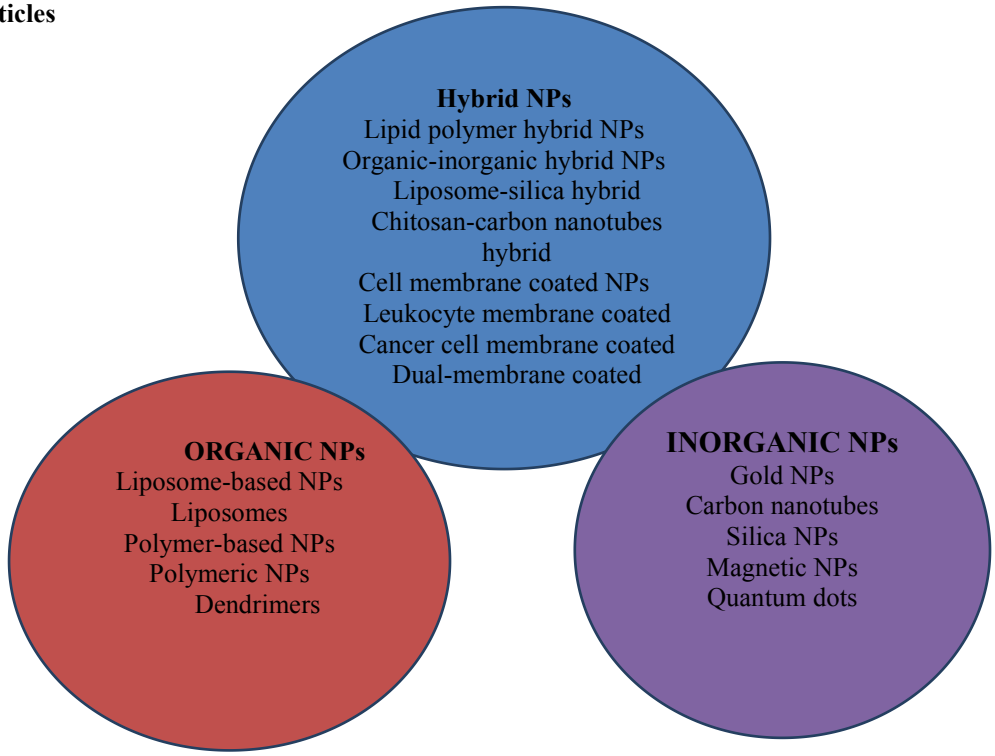


Figure 1: Variouskinds of nanoparticlesfor cancer therapy [15].

DDS (DRUG DELIVERY SYSTEM)

Polymeric Nanoparticles (NPs):

Drugs can be entangled, encapsulated to polymeric NPs in the form of a nanosphere, nano capsule. Nanospheres are colloidal particles that entangle the drug inside their matrix by physical scattering or by adsorption on the particle surface, though nano capsules are systems involving of a core action with acompressed drug and polymeric shell enclosing it. Polymeric capsules can be designed by the conjugation of targeting ligands that increase discrimination for cancer cells and progress intracellular drug delivery, as well as demotingvarious side effects and drug toxicity.

Targeting ligands of polymeric capsules are commonly mAbs, aptamers, peptides and small molecules such as folic acid, which are conjugated to shell developing block. These ligands are preciselycombined to antigens or receptors that are overexpressed on the cancer and they allow cellular discrimination and intracellular delivery of polymeric micelles. The efficiency of polymeric carriers altered with targeting ligands be contingent on the ligand properties, for instance their density and binding affinities to receptors, which can improve receptor incorporation and the biodistribution of drugs. Drug-conjugates have a drug that is chemically attached to the polymer across a linker/spacer.

The bond drug linker/spacer is a common breakage-point when the drug is discharge at the target site. Natural polymers can be linked with synthetic molecules across the chemical alteration of their functional groups and so-called semi synthetic polymers can imitate human tissue components. In formulation of controlled DDS, synthetic polymers enticeextraconsideration than bio polymers due to the substantialability for the design of their structure and alterations of their physicochemical properties.

The encapsulation of cancer drugs in polymeric micelles with alterations for cancer targeting and triggered discharge results in more effective drug delivery [16].

Magnetic Iron Oxide Nanoparticles (NPs):

One of the highly expansivelydiscover classifications of nano systemsappropriate for drug delivery are inorganic nanoparticles (INPs). One category of INPs that is extensively used in DDS are superparamagnetic iron oxide nanoparticles (SPIONs). They can be organized in several sizes (which may be defined in terms of hydrodynamic size or core size), are extremely biocompatible and have a broadervariety of curious and intricate properties that are suitable for drug delivery than another INPs such as carbon or silica nanoparticles.

The main advantage of SPIONs as DDS originates from their magnetic conduct. This lets them to act as a contrast agents magnetic resonance imaging (MRI), which is presently one of the veryadmired and extensivelyaccessible medical imaging techniques. It concedes them to be guided and detained in a chosen location by magnetic fields and to persuade local heating in tumor regions by magnetic fluid hyperthermia. This can be used to generate the release of a loaded drug or to bring about cell death by temperature-induce apoptosis. These properties provide SPIONs anextensive range of potential applications as advance theranostics agents (i.e., medicines that are helpful for both therapy and diagnosis) and nano carriers for drug delivery.

For instance, they could possibly be carried to tumor tissues by region-specific magnetic targeting, where they would release the loaded/attached drug on need while allowing the wholemethod to be observed by MRI. Though, the magnetic properties of SPIONs also represent certainproblems and challenges; particularly, they rise the particles' propensity to aggregate. Thus, SPIONs are very usually united with biological or synthetic polymers to form nanostructures such as magnetic nano clusters, SPIONs entangled in organic stimuli-responsive matrices, magnetic micelles amid others.

The polymers avert accumulation and facilitate secondary functionalization with drugs, radionuclides and compounds that can guard the carrier against identification by the immune system (i.e., compounds that increase carrier's identification time). Such polymeric coatings make SPIONs acquiescent to both covalent and noncovalent drug-loading approaches, providing them access to a broad range of drug release profile and mechanisms involving release stimulated by external stimuli or changes in physiological situations in the area of tumors.

Approaches that exploit the essential magnetic properties of SPION-based drug carriers depend on their strong magnetic response to small applied magnetic fields[17].

Passive and Active Targeting

Passive Targeting:

It is currently a well-known fact that under particular circumstances (inflammation/hypoxia, which is usual for tumors), the endothelium of blood vessels turns out to be more penetrable than in the healthy state. The lack of standard lymphatic drainage in tumor provides to the NPs retention. This unique feature, however, is not applicable to small molecule drugs which have almost short circulation time and rapid washout from the tumor.

Therefore, the encapsulation of small-molecule drugs in nanosized drug carriers increases their pharmacokinetics (prolonged systemic circulation), givecertain tumor selectivity and lowers side effects. This type of tumor targeting called **Passive** depends on carrier features (size, circulation time) and tumor biology (vascularity, leakiness) but does not have a ligand for precise tissue or organ binding,

Active Targeting:

It is significant that the active targeting is necessary for the delivery of drugs, genes and theranostics to the site of interest ignoring the normal tissues and thusdevelops the therapeutic efficiency and restrict the side effects. Active targeting is capable to expressivelyrise the amount of drug conveyed to the target cell compared to free drug or passively targeted nanosystems.

After addition in the tumor area, the drug efficiency can be stillenhanced by the so-called active targeting. This is attainedamong the decoration of the nanocarrier surfaces with ligands combining to receptors over-expressed against the tumor cells. This approach will enhance the affinities of the nanocarriers for the surface of cancer cell and thereforeimprove the drug penetration.

Among the classical targets, we can refer to the transferrin receptors (TFR) or nicotinic acetylcholine receptors that let the reach the environment of brain tumors. In this situation, the mechanism concerns targeting if endothelial cells, that is vascular targeting. smeared to target glioma, for drug delivery or biomedical imaging, transferrin ligands were attached on solid lipid nanoparticles (SLNPs), micelles, dendrimers and superparamagnetic iron oxide NPs (SPIONPs)[18].

Silicon-Based Structures:

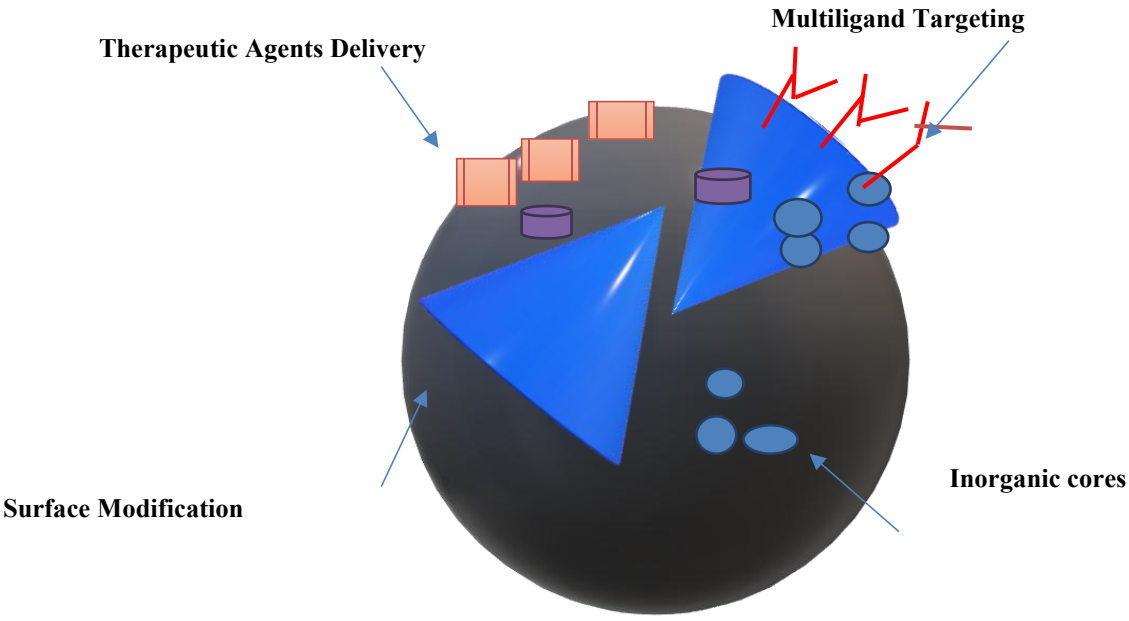
The generally investigated silicon-based materials for drug delivery are porous silicon and silica or silicon dioxide. Architectures include calcified nanopores, platinum-containing nanopores, porous nanoparticles and nanoneedles. The density and diameter of the nanopores can be preciselyregulated to attain a stable drug delivery rate around the pores.

Porous hollow silica nanoparticles (PHSNP) are fabricated in a suspension including sacrificial nanoscale templates such as calcium carbonate. Silica precursors, such as sodium silicate are included into the suspension, whichis after that dried and calcinated making a core of the template matter coated with a porous silica shell. The template matter is then dispersed in a soggy etch bath, leave behind the porous silica shell. Formation of drug carriers includes the mixing of the PHSNPs with the drug molecule and then drying the mixture to unite the drug molecules to the surface of the silica nanoparticles.

Through governing the pore size and the particle diameter, the release kinetics move toward zero-order, where the release behavior of conventional silica nanoparticles is related with that of porous hollow silica nanoparticles. The porous nanoparticles showanextremely more suitablesteady release.

Examples of therapies being examined for use with silicon-based delivery systems contain porous silicon surrounded with platinum as an antitumor agent, calcified porous silicon intended as an artificial growth factor, silicon nanopores for antibody delivery and porous silica nanoparticles comprising antibiotics, enzymes and DNA [19].

Silica xerogels have been extensively used as inorganic materials for drug delivery. Surface alterations of MSNs (Mesoporous silica Nanoparticles) is informal to attain, which improves the targeting capability of nanoparticles, conducting to arise in drug delivery efficiency and a decline in systemic toxicity. When united with magnetic materials or luminescent compounds, MSNs can be utilized as drug delivery systems and bioimaging researches. The drug loading and release kinetics of the nanoparticles can be regulated by varying the size of the nanoparticles. It is biocompatible, highly porous and informal to adjust for functionalization [20].



Functionalization.

STRUCTURE OF NANOPARTICLES

Quantum Dots:

Nano-sized semiconductor quantum dots are including the novel approaches used in the cure of different types of cancer. Water solubility and biocompatibility of quantum dots are enhanced by surface adaptations. It further supports the QDs to be used as fluorescent probes with targeting molecules. QDs nanocarriers havespecialattributes like to have wide and vigorous absorption spectra and have exclusive optical and chemical properties. Semiconductor QDs can be used as photosensitizers. They expressflexibility to chemical degradation, pH changes and include thermal stability. QDs have an absorber of high-energy photons (X-rays and gamma rays) act as a radiosensitizer.

QDs are made up of a core and a shell or cap. A QD core involvesseveral metal complexes, e.g., noble metal, semiconductor and magnetic transition metals. Cadmium contained semiconductors are the main component of quantum dots with noble optical characteristics. However, cadmium contained semiconductors are the major constituent of quantum dots with noble optical features. Exploration for non-toxic ingredients with equivalent targeting and optical properties are of advanced concern.

The admirable characters of carbon-based quantum dots, having low toxicity profile and biocompatibility empower remarkable biomolecule, drug delivery, bio-sensing and bio-imaging functions.

Several research invitations have shown that QD-conjugated oligonucleotide sequences (attached through surface COOH groups) are targeted to connect with DNA or mRNA. Bio conjugated QDs are also thought for the site-specific gene as well as drug delivery in cancer. Targeting moieties such as antibodies, high-molecular weight dextran, aptamers[21].

Nanotechnology for The Detection of Cancer

Nano-based ultrasensitive biomarker detection:

Nowadays, lots of novel proteomic, genomic and transcriptomic biomarkers are being studied. Consideration of tumor molecular biomarkers such as tumor necrosis factor-alpha, vascular endothelial growth factor (VEGF), EGFR and interleukin 6 owns great promise for early cancer detection and diagnosis. Regular measurement techniques-comprising enzyme-linked immunosorbent assay (ELISA), immunohistochemistry, PCR still allow a narrow detection sensitivity. The function of nanotechnology mightimprove the detection sensitivity for biomarkers bylittle concentrations in the tissue samples or body fluids.

The saliva peptide finger print method is a valuable tool for salivary proteomics analysis and can guess potential biomarkers treasured for cancerdiagnosis.Nanomaterial-based magnetic beads were used for discerning enhancement of low-molecular-mass peptides. This presented a novel high throughput, non-invasive plan for valuable oral cancer biomarkers screening. A study detected TNF alpha by gold protein chip techniqueby a total internal reflection fluorescence microscopy (TIRFM). The TNF alpha detection sensitivity was described to be at the attomolar (aM) concentration level allowing ultra-sensitive oral cancer detection[22].

AgNPs in cancer diagnosis:

AgNPs are used in cancer diagnosis because of their exclusive optical properties at the nanoscale. In the research, acquired a sandwich type immunoassay established on SERS for detection of human alpha-fetoprotein (AFP), a tumor marker for the diagnosis of hepatocellular carcinoma. This technique joined Ag/SiO_2 core-shell NPs surrounded with dye molecules of rhodamine B isothiocyanate. AgNPSs antibody pairing gates as probe for enhanced fluorescence correlation spectroscopy in a homogenous immunoassay to detect AFP.

AgNPs were also used as the SERS-active nanostructures to detect nasopharyngeal cancer, and in nanosilver doped DNA polyion complex membrane in an electrochemical immunoassay to identify carcinoembryonic antigen (CEA). Other hybrids established on AgNPs were also formulated for augmentingthe signal in identifying platforms such as silver hybridized mesoporous silica NPs. Through their optical scattering properties exhibited, AgNPs are used in photoacoustic imaging and SERS nanoprobes to identify the existence of cancer cells across spectral changes in analyzing purified proteins. Early cancer detection is vital to ensure early treatment and increase the modifications of treatment, AgNPs have not been used as single phase, they are usually hybridized and functionalized platforms[23].

Multifunctional NPs for tumor imaging:

Tumor imaging plays a key role in clinical oncology with radiological studies able to detect solid tumors, determine reappearance and monitor therapeutic responses. Conventional tumor imaging methods such as CT and MRI emphasis mostly on describing morphological characteristics of the tumor, tissue and organs such as anatomic location, range and size of the tumor at numerousstages of 3-D resolution and contrast. Even though continuous progress in 3-D resolution with advanced imaging equipment, imaging modalities using nontargeted contrast agents such as CT and MRI have controlled sensitivity skill to impartprecise and usefuldata on the disease, which is increasingly known to be acomplication to previous diagnosis and observingthe treatment responses.

Currentdevelopmenthasintensified the appearance of the new field of “Molecular Imaging,” which emphases on picturing biological events and progressions in living systems, consist of patients. Recent molecular imaging methods, including PET, single-photon emission tomography and optical imaging including fluorescence-mediated tomography and near-infrared fluorescence reflectance (NIRF) imaging, have displayed a high sensitivity in non-invasive tumor imaging. A generallyoperated PET imaging probe, F-labeled fluorodeoxyglucose (FDG) can only specific tumors by recognizing cells in the body that have escalated glucose uptake and metabolism, letting for the revealing of those tumors. Though, it is not appropriate for tumor types with a low glucose uptake. It is well established that the growth of novel methods for early cancer detection and effectual therapy will considerably contribute to the enhancement of patient existence.

The progress of nanoparticles as imaging contrast agents also makes it feasible for the production of multifunctional nanoparticles with the ability of targeted tumor imaging and release of therapeutic agents. In comparison with radioactive probes (i.e., ^{18}F-labeled FDG) used for PET imaging, nanoparticles have both huge surface areas and more functional groups that can be associated with multiple diagnostic and therapeutic agents.

One molecular imaging approach to enhance the specificity of cancer detection is target precise imaging of biomarker molecules precisely produced by cancer cells, united with imaging probes directed by ligands that can distinguish and interact with target molecules. Tumor-targeted optical, radioactive or magnetic probes have been created and their possibilitytested in animal tumor models and in very limited clinical studies. Development innanotechnology have revealed the promise of nanoparticles for tumor-targeted drug delivery and noninvasive tumor imaging[24].

Cancer biomarker detection withMagnetic nanoparticles

Biosensing:

The as-conjugated MNPS with the explicit biomarkers are further use in the final step- the sensing approach. Cancer biomarkers detection has gotten substantialawareness and development.

Several favorable sensing methods to identify the amount of cancer biomarkers in plasma, blood or diseased tissues have been established: electrophoresis, optical methods (fluorescence, electrochemiluminescence, colorimetric assay, surface plasmon resonance (SPR), surface-enhanced Raman spectroscopy (SERS), immunological methods (enzyme-linked immunosorbent assay), PCR. Biosensing events may be outlined fromseveral labeling methods, depending on the method(fluorescent labels, electroactive molecules, enzymes and nano/microparticles etc.).

Electrochemical biosensors have gotten much interest for cancer biomarkers detection mostly due to their elevatedprecision and sensitivity, multiplexing and cost-effective characteristics, and discrimination in defying the matrix exclusive of requiring multiple sample treatments or complex protocols. A wide range of analytical techniques has been integrated for the development of multiplexed immunosensing systems for cancer biomarkers. Electrochemical immunosensors have received great interest due to their high sensitivity provided by coupling the immunochemical affinity reaction (antigen-antibody) with the particular features of multifunctional electrode transduction elements[25].

cell-free DNA and circulating tumor DNA:

These extracellular DNA molecules are adsorbed on proteins (histones) and are predominately around 180 base pair long. While the preciseprocedure that promotes the release of cell-free DNA (cfDNA) into the bloodstream, sequencing analysis signifies that cfDNA initiates from apoptotic cells in healthy individuals. In patients with high cell turnover syndromes, such as cancer, high levels of cfDNA with both apoptotic and necrotic origins are identified. A meta-analysis on the diagnostic precision of cfDNA indicated similar results related to conventional biomarkers and not adequate differentiation abilities to be used as single cancer indicator. Various reports for several types of cancer, emphasized the ctDNA predictive value, where the oligonucleotide concentration levels could be linked to changepossibility and overall survival. Thus, cfDNA has been emphasized as a capable biomarker to guess the patient consequence and forecast relapse possibility.

Among 3% and 93% of entire DNA in the bloodstream initiate from tumor cells in cancer patients, depending on the phase and size of the tumor. This DNA with tumor origin is known as circulating tumor DNA (ctDNA) and comprises characteristic genetic variations identical to those from the tumors that can be targeted for non-invasive identification. For instance, detectable levels of ctDNAwere present in more than 75% of pancreatic, ovarian, colorectal, melanoma, breast, gastroesophageal, melanoma, head and neck cancer patients.

Moreover, ctDNA mightbe observed in patients lacking other assessable biomarkers, such as circulating tumor cells. Concerning the clinical value, KRAS mutation analysis of ctDNA presented a sensitivity and a specificity of 96 and 95% respectively, in the diagnosis of thoracicmalignancies. ctDNA has also revealedbetter correlation with variations in tumor burden related to conventional markers, for example CA 15-3 in metastatic breast cancer patients.

Therefore, cfDNA (inclusivequantity if DNA in the bloodstream) is a good biomarker for patient prognosis (i.e., forecast of disease outcome), although the levels of ctDNA have shown promising outcomes in diagnosis (i.e.,recognition of type of disease and stage).

There are two majorapproaches to analyze plasma DNA for cancer diagnosis, targeting either cfDNA or ctDNA. For cfDNA, whose total concentration (not the explicitorder) is linked to the patient prognosis, methods such as UV-Vis spectroscopy, fluorescent intercalating dyes and quantitative real-time polymerase chain reaction (qPCR) are used. Though these methods are commercially accessible, they have limits in their precision of detection because the limit of detection is too close to the clinically pertinent concentrations, or need complex and laborious enzymatic amplification.

For ctDNA, genetic mutations from the primary tumor are recognized and quantified in the plasma DNA. Because there are often occurring mutations that drive tumor formation, such as point mutations and deletion mutations in KRAS or EGFR, the ctDNA analysis can aim these genetic modificationsover digital PCR or next generation sequencing techniques. Otherwise, untargeted methods together with genome-wide detection of single nucleotide mutations, along with mutations of larger genome segments, such as reorganizations and chromosomal copy-number, have been established for general genetic analysis deprived of focusing on precise known mutations [26].

Protein detection:

A number of proteins have been approved FDA clearance for cancer detection, involving CEA (colorectal cancer), AFP (liver cancer), PSA (prostate cancer), and CA-125 (ovarian cancer). Certain interactions with antibodies, antibody fragments, or aptamers can help in the detection of these properties. The interaction event will then be changed into a quantifiable signal that can be calculated.

QD-based biosensors have been used for detecting cancer biomarkers. QDs are considered by a high quantum yield and molar extinction coefficient; wide absorption with narrow, high-efficacy stoked shifts; high resistance to photobleaching and outstanding resistance to degradation, which comprise unique properties. A sandwich-type assay is a usualapproach for detecting protein biomarkers and includesseveral components, namely a biomarker, a capture antibody, a second capture antibody and secondary antibody that unites to the capture antibody. The secondary antibody can be visualized through severaltechniques, for example staining and fluorescence.

In exploiting this approach, two QD-conjugated antibodies against neuron-specific enolase (NSE) and carcinoembryonic antigen (CEA) were used to detect two biomarkers and limit the detection (LOD) of individually reached 1.0 ng/ml. A zinc oxide (ZnO) QD-based sandwich immunoassay was developed for ZnO nanowire substrates, which provided a large surface area that presents several binding sites used for detection. CEA, the most popular cancer biomarker, has been utilized for observing of anticancer treatment, along with for expectation of tumor recurrence subsequent surgical resection in late-stage cancer patients, making it broadly. NSE is an enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate, which shows a relationship with carcinoids, small cell lung carcinoma and islet cell tumors. After secretion, they could be detected at concentrations over 15 ng/ml and the LOD of individuallyattained 1.0 ng/ml.

Peptides are often applied to actively target cancerous tissues in vivo. The Arg-Gly-Asp (RGD) peptide motif is identified by receptor integrin on the cell surface involved in cancer metastasis and angiogenesis and has been applied to target tumor tissue in vivo for diagnosis. Aptamers, which are single-stranded DNA (ssDNA) or RNA sequences that can be isolated via exponential enrichment (SELEX) that depend on ligand systematic evolution, can also be coupled to nanoparticles.

Rare-earth upconverting nanophosphors (UCNPs) assured to be a new generation of biological luminescence labels. UCNPs are capable to absorb radiation from near-infrared (NIR) light and change the radiation into visual light by depend on the up-conversionprocedure after multiple-photon absorption. Overexpression of secreted phospholipase A2 (sPLA-2), an enzyme that catalyzes phospholipid hydrolysis has been described to show association with prostate cancer cell proliferation[27].

Nanoparticles For Cancer Therapy

Pluronic Micelles:

The micelles are naturally present in body that consume the endogenous surfactant bile salts to finish lipid digestion. Micelles functionally ease the absorption of water-insoluble fat and fat-soluble vitamins. Their size is usually within in a range 5 and 100nm; amphiphilic molecules comprise of a core: hydrophobic fragments and shell and hydrophilic moieties. Water-insoluble drugs are generally intravenously administrated with an adjuvant solubilizing agent such as ethanol, which mostly has common toxic side effects. The micelle nanoparticle formulation of these hydrophobic drugs is generally used to prevent the addition of the harmful adjuvant.

Folate-conjugated poly (ethylene glycol)-b-copolycarbonates and methoxy poly (ethylene glycol)-b-copolycarbonates loaded with doxorubicin enhance the cytotoxicity of doxorubicin via FA receptor-mediated endocytosis. Clinical trials were utilized to treat metastatic GIT adenocarcinoma using SP1049C-doxorubicin micelles of Pluronic L61 and F127. The accumulation of doxorubicin in tumors was more than free doxorubicin with normal distribution of polymer in normal tissues. The mechanism of action of micelles is altering the structure of the membrane, reducing membrane fluidization and inhibiting function and expressions of efflux transporters such as P-gp and MRPs.

These consequently sensitize resistant cancer cell to the chemotherapeutic agents, escalating the proapoptotic, reducing the levels of glutathione (GSH) and glutathione-S-transferase (GST) activity, inhibiting the mitochondrial respiratory chain, reducing oxygen utilization, and reducing both mitochondrial membrane potentials and the production of reactive oxygen species and release of cytochrome C in MDR cells are further mechanisms [28].

Electric Field for Cancer Therapy:

Consideration is being given to stimuli-responsive or smart biomaterials in the fields of biotechnology and biomedicine. Stimuli responsive materials, which respond to heat, pH light, enzymes and magnetic fields are broadly used in biomedical arena. Electrical signals are simpler to produce and control than other stimuli. Electric signals are simpler to produce and control than other stimuli.

Electric stimuli have effectively been used to trigger the release of molecules via conductive polymeric bulk materials or implantable electronic delivery devices. Polypyrrole NPs assist as a drug reservoir for electric field triggered release when they are entrenched in biocompatible and biodegradable hydrogels (PLGA-PEG-PLGA). This gel is injectable and upon application of an external DC electric field, it releases the drug from the nanogel, letting the drug to diffuse into the surroundings from the hydrogel.

Each electric stimulus releases 25ng of drug into the solution with minimum release in the nonexistence of an electric field, representing undesired release from the hydrogel. Carbon nanotubes (CNTs) can act as drug nanoreservoirs by holing drug molecules within their inner cavity, liberating them in bioactive form under electrical stimulations. A polypyrrole coating over CNT drug nano reservoirs seals the ends of the CNTs efficiently loading the drug, which allows electrical triggering to release the drug with the application of voltage. A dual stimuli (electric field and pH) responsive system of chitosan-gold nanocomposites (CGNC) has been planned for site specific controlled delivery of the anticancer drug 5-FU at the lowered pH of cancer cell environments.

Drug release systems established on conductive polymers have been efficaciously been utilized, as they suggest the probability of drug administration over electrical stimulation. This type of delivery system has hugebenefits over conventional sustained drug release because the released dose of this drug can be generallymanaged by either the potency or the time of the electric field [29].

Gold Nanoparticles Thermal Therapy:

Hyperthermia is known to stimulate apoptotic cell death in many tissues and has been shown to escalate local control and generally survival in combination with radiotherapy and chemotherapy in randomized clinical trials. Hyperthermia is usually used in combination with other treatments, involving radiotherapy and can be delivered externally, interstitially or endoluminally with heat production by radiofrequency waves, microwaves or ultrasound. Although normal tumor vasculature dilates to aid heat dissipation, tumor vasculature dilates constricts, giving some tumor selectivity. Though overall a absence of specificity for tumor tissue, problems in warming deep tumors to therapeutic temperatures and thermotolerance after initial treatment.

Development in nanomedical research suggests the ability to precisely target metal nanoparticles to tumor cells. When an energy source such as a laser generating non ionizing electromagnetic radiation is used, changeover to heat energy occurs in metal nanoparticles owing to electron excitation and relaxation. Also, lasers can be precisely turned to the SPR frequency of nanoparticles which differs with the size, shape and configuration of the nanoparticle. Many research has used gold nanoshells, particles with 100-nm silica cores and a 15-nm gold coating, which transfers the resonance peak to the near infrared region (650-950nm) where blood and tissue are greatly transmissive.

Certaindrawbacks to this method continue to exist, mainly for treatment of deep-seated tumors, as a laser will only invadenumerous centimeters in soft tissue. More techniques to let in vivo dose quantification of nanoshells to permitalteration of laser doses need to be established. Moreover, some have anticipated that 5000 nanoshells per cell will have to be released to attainsuitable heat production for coagulative necrosis to occur [30].

Nanotechnology in Cancer Immunotherapy:

Nanotechnology used in cancer immunotherapy aims not only cancer cells but also lymphocytes and antigen-presenting cells (APCs) in circulation, thus helping to generate a robust immune response. Therefore, an extensively lesser concentration of drug is desirable when used in conjunct with immunomodulators. In virtue of their high surface area to volume ratio, they are skilled of taking high-density peptide-major histocompatibility complex (pMHC) which in turn fastens the re-engagement of disassociated pMHC and thus delays the incorporation of T-cell receptors and extends the time for antigen presentation. Thus, the improvement of cross-presentation of neoantigen-presenting cells leads to better immune response. Nanotechnology can be used to interfere at several stages of cancer immunity cycle. It can be used in the delivery of neoantigens for cancer vaccine development, delivery of adjuncts to rise immunogenicity, moderate tumor microenvironment, enhancement of immune identification, delivery of checkpoint inhibitors and codelivery of checkpoint inhibitors with costimulatory immunomodulators, in adoptive immunotherapy and image -guided immunotherapy.

Cancer nanovaccines are designed for the effectual delivery of tumor protein antigens or peptide antigens or nucleic acid antigens to APCs which generates an immune response [31].

Marketed Products:

The table 1 mentioned below comprises of few marketed products of nanoparticle used in cancer.

Table 1: Marketed Products of Nanoparticle.

Product	Composition	Indication	Reference
Onivyde	Nanoliposomes	Pancreatic cancer, Colorectal cancer	32
Kadcyla	Maytansine derivative, DM1	Breast cancer	32
Nanotherm	Nanoparticles of superparamagnetic iron oxide coated with amino silane	Prostate cancer	32
Doxil/Caelyx	Liposomal doxorubicin	Ovarian Cancer	33
Myocet	Liposomal doxorubicin	Combination therapy with cyclophosphamide in metastatic breast cancer	33
Abraxane (Celgene)	Albumin-particle bound paclitaxel	Advanced non-small cell lung cancer	34
Onivyde MM-398 (Merrimack)	Liposomal irinotecan (PEGylated)	Metastatic pancreatic cancer (secondary)	34
Genexol-PM	Paclitaxel micellar	Gastric Cancer	35
Apealea	Paclitaxel micellar	Fallopian tube cancer	35
Tocosol	Paclitaxel/Tocopheryl based emulsion	Urothelial cancer, bladder cancer	36
Lipoplatin	Cisplatin/Liposome	Head and neck cancer	36
Daunoxome	Daunorubicin citrate/liposome	Kaposi sarcoma	36

APPLICATIONS OF NANOPARTICLES

Severaltimes, nanoparticles serve as the vital diagnostic tool in cancer therapy by site-specific targeting to the cellular and sub-cellular sections. The new diagnostic tools in treatment of cancer therapy are radio labeled NPs marked with radionuclides, fluorescent NPs and multifunctional NPs conjugated with numerous functional molecules. Doxorubicin (DOX) loaded polymeric nanoparticle are the most common example used for treatment of human liver carcinoma and breast adenocarcinoma. Photo thermal destruction of cancer cells through the carbon nanotube-based nano-technological method is often used for targeted overnoninvasive radio frequency and immune gold nano cages with modified optical properties.

Metals, polymeric particles and semiconductors are confirmed as effectual imaging probes and delivery vehicles for diagnosis and cancer cell targeting [37]. Gold nanoparticles have exclusive electric and magnetic properties due to their shape and size so they have been received hugeconsideration in research areas particularly in the field of cancer therapy [38].

CONCLUSION

With the growth of nanotechnology and its combination with other sciences, various kind of NPs with several structures have been presented. Each of them has some benefits and drawbacks. Though, they are considered to be an effectual step toward enhancing the function of particles. Nanoparticles signify their highlyeffectual function in DDS. They are used as polymer, lipid, metal, ceramic and so forth carriers in drug deliveries to various kinds of diseases, particularly refractory diseases, such as cancer. NPs can be used in the diagnosis and treatment of diseases, drug delivery and biomedical imaging. Enhancement of nanotechnology will provide more opportunities for simultaneous targeting of multiple molecules of tumor samples and implementingappropriate therapeutic approaches. Application of NPs for in vivo tumors is rapidly enhancing. These developments can make it possible to target cancerous antigens. In near future, nanotechnology science will make a great revolution in oncology

CONFLICT OF INTEREST:

NIL

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