

Review Article

Applications of nanoparticles in anticancer therapeutics

Shruti Rayan*, Rajat Batra

SVKM'S Narsee Monjee Institute of Management Studies, Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, Vile Parle (W), Mumbai, India.

* **Corresponding Author:** Tel.: +91 7387460700, E-mail: shruti.nmimssptm2019@gmail.com

ARTICLE INFO

- Received 05 Aug 2018
- Revised 25 Aug 2018
- Accepted 30 Aug 2018

Keywords:

- Cancer
- Nanotechnology
- Nanoparticles
- Types of nanoparticles
- Applications

ABSTRACT

The utilization of nanotechnology is done to overcome the conventional strategies which were utilized to treat growth. The objective of restorative operators utilized as a part of growth treatment goes for constraining the quick partitioning cells, to stop or breaking point their augmentation and to advance apoptosis. Traditional techniques were not ready to recognize the right means because of which the treatment was not valuable and unfriendly impacts were noted. Nanotechnology beats this variable as it intends to focus on a specific organ or tissue and the conveyance of the medication is additionally done in a constraining way and at a focused in the vicinity, these aides in maintaining a strategic distance from or restricting the systemic lethality and accordingly increment the bioavailability and profile record of the medication. The upside of utilizing nanoparticles as a medication transporters is that they have awesome restricting limit and turn around multidrug resistance property. The present survey gets the consideration on the pathophysiology of the growth, the different sorts of nanoparticles utilized as a part of medication conveyance, the different sub-atomic components which can separate the malignancy cells from the ordinary ones and finally the uses of the nanoparticles in helpful medication conveyance framework.

1. INTRODUCTION

Cancer is a life threatening disease. In all types of cancers, some of the body cells begin to divide without stopping and spread into surrounding tissues [1]. Cancer has the capability to spread almost anywhere in the human body [2], which has trillions of cells in it. The function of the cell is to grow and divide as the body needs them for various functions. As these cells grow old or get damaged, they die and new cells are formed. But in cancer this process is hampered, the cells grow abnormally, while the old and damaged cells survive when should have being dying and new cells form when they are not required by the body. This formation of new cells can grow and divide without stopping and they form growths known as tumors. Chemotherapy, radiation, surgery, hormonal therapy and immune therapy are the treatments used in cancer. If appropriate treatment is not taken, this leads to cell damage, drug resistance, gastrointestinal damages and many more which makes the treatment or therapy less effective. With advancement in the cancer molecular biology and cell transformation pathways, the second half of the 20th century marked new approaches in anticancer therapy, with claimed targeted accomplishment.

Malignancy treatment utilizes drugs which inhibits the development of cancerous cells and keeps it from spreading by meddling with particular atoms (sub-atomic focuses on) that are included in development, movement and spread of disease. This treatment at present concentrates much on anticancer medication improvement. They are cornerstone of exactness prescription, a type of medication that incorporates data about individual's quality and proteins that avoid, analyze and treat ailment. Numerous growth focused treatments are been recognized and endorsed by sustenance tranquilize organization (FDA) and other are in clinical trials. There are different methods of treatment, for example, hormone treatment, quality expression modulators, apoptosis inducers etc. Treatment strategies have a few hindrances like tumor cells get impervious to it, it gets to be hard to create drugs for the recognized targets on account of the mind boggling target structure.

To restrain the systemic danger and antagonistic impacts of present treatment strategies, novel and new techniques for guiding medication to the cancerous tissues, utilizing nanodevices were produced. Nanotechnology in disease gives some energizing potential outcomes, including the likelihood to

pulverize the growth tumor without harming the sound tissues or organs, and in addition the location and end of the malignancy cells before they shape tumor.

2. NOVEL DRUG SYSTEMS IN CANCER THERAPEUTICS

Nanoparticles have been explored as medication transporters, since they give an extraordinary open door because of their profitable components: (i) different plans utilizing natural/inorganic materials, (ii) simple alteration of focusing on atoms, drugs or different particles on them, (iii) compelling conveyance to target locales, bringing about high restorative adequacy and (iv) controlling medication discharge by outer/inner boosts. As a result of these components, restorative viability can be enhanced and undesirable symptoms can be lessened [3]. Nanoparticles have a size scope of 1-100nm [4]. Nanoparticles are submicronic colloidal frameworks made of polymers, lipids, infections, organometallic mixes [5]. To this the medications are either embedded amid polymerization or adsorbed. The benefit of utilizing nanoparticles as medication bearers is their coupling fitness and turning around multidrug resistance [6]. By utilizing focusing on procedures like dynamic and inactive, the intracellular medication centralizations of nanoparticles are expanded. Accordingly, giving a contrasting option to oral conveyance of chemotherapeutics which have confinements of dissolvability, strength and porousness [7]. To begin with pass digestion system by cytochrome P450 liver chemicals, and the defilement of the recticoendothelial structures of liver and spleen, the binding parts for pharmaceutical bioavailability were overcome by outlining out the nanoparticles utilizing a fitting transporter arrange, for instance, polymers in a size which keeps them from spilling into veins and catch by macrophages.

Anticancer arrangement resistance intervened by P-glycoprotein can be stupified by surface covering of the nanoparticles utilizing bio-sticky materials, which in like way overhauls hold and osmosis. Pharmaceuticals are stacked in a sensible conveyor for example liposomes in liquid lattice, polymeric nanoparticle in polymer arrange, viral nanoparticles in viral structure, etc known as medicine transporter complex. HPMA- Doxorubicin complex was the first to enter clinical trials [8]. Regardless, to reduce the systemic lethality (on account of nonappearance of specificity) and augmentation the systemic openness at the site of action, the pharmaceutical should be clearly centered around. This is refined by conjugating the drug bearer complex with a fitting ligand [9]. Contemplates by Acharya et al have shown that the epidermal improvement figure receptor conjugated rapamycin stacked poly (lactide-co-glycolide) nanoparticles have preferable antiproliferative development pondered over nearby rapamycin and unconjugated rapamycin [9]. Near work by Alexis et al. exhibited the extended limiting attachment to the solution exemplified nanoparticles conjugated with poly-(D, L-lactic destructive)- poly (ethylene glycol)- maleimide copolymer, concentrating on the HER-2 protein. Paclitaxel stacked poly (D, L-lactide-co-glycolide) (PLGA), a biodegradable polymer with incredible bioavailability, hybridized with 1,2-dilauroyl-sn

glycero-3-phosphatidylcholine (DLPC) having high soundness realized upgraded prescription representation, enhanced ingestion and reduced phagocytosis. Quantum touches stacked in biodegradable polymers were adequately used as a piece of imaging and concentrating on tumors by Skillet et al. by using folate-lit up nanoparticles conjugating them with vitamin-E TPGS-carboxyl (TPGS-COOH) [10].

3. TYPES OF NANOPARTICLES

Nanoparticles are classified as natural and inorganic nanoparticles. As the name proposes natural nanoparticles are delivered from the natural materials like-lipids, carbon, polymers, drain emulsions and dendrimers. As these are comprised of natural material, it turns out to be simple for manufacturing them. Furthermore they are biocompatible and biodegradable which makes them the best and adequate medication conveyance frameworks. While inorganic nanoparticles are made up from inorganic materials like aluminum, silica, metal, metal oxides, and so on the inorganic nanoparticles are exceptionally steady and can be practically streamlined for analysis and treatment, utilizing connections, for example, biocompatible coatings, focusing on groupings, organically dynamic atoms and imaging gadgets. Nanoparticles are ordered in view of the measurement as one dimensional, two dimensional and three dimensional nanoparticles [11]. Thin motion pictures, monolayers and manufactured surfaces with a size of 1-10 nm find their use in invention and biosensors, optical devices. Two dimensional nanoparticles go from <1 nm in separation crosswise over to around 100 nm long. Nanowires, carbon nanotubes, nanofibers and nanopolymers go under this arrangement. Dendrimers, fullerenes, quantum bits are orchestrated under three dimensional nanoparticles [12].

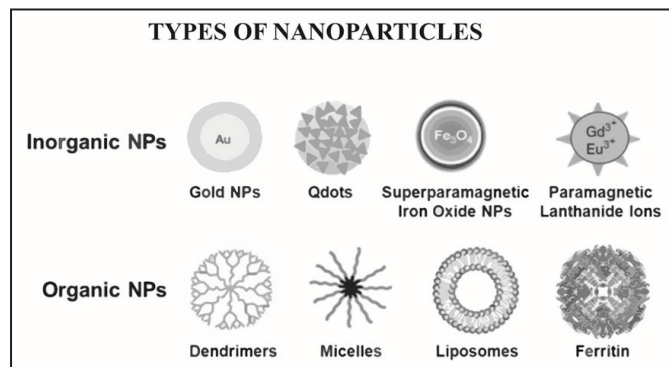


Fig. 1. Different types of nanoparticles used in the cancer therapy.

3.1 Polymeric nanoparticles

The utilization of biodegradable polymeric nanoparticles (NPs) for controlled medication conveyance has indicated huge remedial potential. Simultaneously, focused on conveyance advances are turning out to be progressively vital as a logical zone of examination. In malignancy, polymeric NPs can be utilized to convey chemotherapies to tumor cells with more prominent viability and diminished cytotoxicity on fringe sound tissues [13]. The state of the polymeric nanoparticles is as container. The polymers are classified as normal polymers,

pseudosynthetic polymers and engineered polymers. They have incredibly minimal size and a surface covering that masterminds their escape from hepatic defilement by cytochrome P450. They are made up off polymers namely polyethylene N-(2-hydroxypropyl) methacrylamide copolymer(HPMA) glycol (PEG), polystyrene-maleic anhydride polymer, poly(lactide-co-glycolide) (PLGA), poly-L-glutamic destructive (PGA), poly (vinylpyrrolidone), straight polyamidoamines (PAMAM), poly (ethyleneimine) PLA and PLGA. These polymers are biocompatible and biodegradable transporters, and concentrated taking drugs movement with better efficiency and less responses. Dextran, dextrin, egg whites, alginate, gelatin, chitosan, heparin, hyaluronic corrosive are regular polymers, these convey atoms, for example, oligonucleotides, DNA, proteins and medications. Pseudosynthetic polymers are manmade polymers and these incorporate poly (L-lysine), poly (L-glutamic corrosive), poly (aspartamides), poly (malic corrosive) [14].

3.2 Polymeric micelles

Polymeric micelles have a core–shell structure with an adaptable medication stacking hydrophobic center and biocompatible hydrophilic shell, and are a few tens to one hundred nanometer in size. These attributes are desirable both for renal leeway and ensnarement by the reticuloendothelial framework, thus ensuring gathering inside tumor tissues by upgraded penetrability and maintenance impact. The capacity to control the span of polymeric micelles in the scope of a few tens to many nanometer fundamentally influences their life span in the circulation system and proficiency of tumor tissue gathering and entrance. Likewise shields them from enzymatic corruption, hydrolysis and disposal by reticuloendothelial framework. Medicate stacking is finished by either sedate conjugation and/or tranquilize epitome. Hydrophobic medications are conjugated to the hydrophilic spine using biodegradable manufactured linkers. In prescription representation the drugs are physically caught in the hydrophobic focus of the micelles [38]. Polymeric nanoparticles are reasonable for parental delivery [15-16].

3.3 Dendrimer

These have 3D (3-dimensional) modeler and are hyper branched globular nonopolymeric structures. Appealing components like nanosomic size, contract polydispersity, incredible control over atomic structure, accessibility of different practical gatherings at the fringe and holes in the inside recognize them amongst the accessible polymers. Their fundamental units are monomeric or oligomeric units and include a central focus, extending units and terminal helpful social affairs. They have a symmetrical structure and the center shell engineering becomes directly in distance across and exponentially concerning the surface gatherings. The part of the center shell is to distinguish the synthetic conduct and environment of nonocavities while the focal gatherings are in charge of determine dissolvability and substance behavior. The globular structure and the nearness of inward cavities empower epitome of medications and change of the level of fanning may take into account more. Drugs can be physically

caught or misleadingly attached. With a size of around 10 nm, they are thought to be basic parts for the amalgamation of 1 to 100 nm regular and inorganic nanostructures. They also can be functionalized with hydrophilic end packs making them water dissolvable, and formed with internal hydrophobicity for breaker of hydrophobic pharmaceuticals. Functionalizing the terminal social events with amino get-together renders positive blame engaging correspondence for oppositely charged phosphate get-together of nucleic destructive. The primary worry in the utilization of dendrimers as transporters is that they are caught by mononuclear phagocytes, which can be overcome by surface functionalization with PEG chains [16,17].

3.4 Metal nanoparticles

3.4.1 Gold nanoparticles

GNPS (gold nanoparticles) these are being utilized as a part of restorative science fields since a decade ago. They are created and described by number of strategies. The functionalized biocompatible gold nanoparticles exhibit empowering optical and compound properties utilized as a part of conclusion, imaging and treatment. GNPs focus on the tumor site by gathering by EPR impact and get inundated by non-particular receptor endocytosis. Loading of the GNPs with PEG, folate and thiamine keeps the decimation by the reticuloendothelial cells and render expanded flow times. Sorts of gold nanoparticles are - nanocages, nanoshells, nanospheres, nanorods, nanogold, surface enhanced Raman dispersing nanoparticles. Vast surface are of GNPs encourage more medication stacking, however the lethality issues should be considered. Blend of nanoshells is being finished by utilizing developing silica centers with gold, gold and copper, gold and silver find their application in photothermal removal and in imaging individually. Their size reaches from 2 to 100nm in breadth, their capacity to infiltrate is quick and because of this property they discover use in phototherapy and diagnostics [18, 19].

3.4.2 Iron oxide and super paramagnetic iron oxide nanoparticles

Iron oxide nanoparticles due to their magnetic prperties and biocompatibility are widely utilized as imaging specialists. These nanoparticles help in finding the area of the tumor and the phases of the cancer. Conjugation with antibodies to HER-2, luteinizing hormone discharge hormone encourages discovery of bosom tumors. We can expand the flow time of these nanoparticles by connecting them covalently with the chemicals and treating with medications like lovastatin. These nanoparticles have miniscule size, expansive surface region, magnectic properties because of which they serve as medication bearers to the coveted tumor location. Flavin mononucleotide covered fluorescent nanoparticles are utilized as a part of focusing on and naming of endothelial cells and dynamic malignancy cells by focusing on riboflavin transporter protein [20].

3.4.3 Silica nanoparticles

These nanoparticles are made by sol-gel procedure. They are of uniform pore measure and broad surface range, which make them culminate solution transporters and are physically expended. Simplicity of combination and functionalization with amino-hexyl-aminopropyltrimethoxysilane, diminish the dangerous impacts and empower as perfect medication bearers [21].

3.4.4 Calcium phosphate nanoparticles

Calcium phosphate nanoparticles are used as transporters to DNA in anticancer treatment. Ionic buildings of calcium particles with DNA are framed which grants dependability to the DNA. Single shell and multi shell calcium phosphate functionalized with DNA, siRNA are brought over the cell layer through endocytosis mediated by molecule channels. Conveyance of immunizations over the skin is additionally conceivable by these nanoparticles [22, 23].

3.4.5 Carbon nanoparticles

Carbon nanotubes and fullerenes are the sorts of carbon nanoparticles which are being utilized. Long tube shaped structures in a hexagonal system of carbon molecules are possessed via carbon nanotubes, they around range 1.5nm in width and 100nm long. These are single and multiwall nanotubes. They are made out of either polymer or silica or carbon or metal. Carbon nanotubes are insoluble and render harmful quality issues. Creation change makes them be water dissolvable and functionalized to be associated with peptides, proteins, nucleic acids and accommodating authorities. The components of carbon nanotubes are that they are nontoxic, exceptionally biocompatible and also artificially stable with expansive surface range and low spillage of medication. Their utilization is in the conveyance of anticancer medications, biomolecules crosswise over cell layer and to empower the host resistant reactions [23].

3.5 Quantum dots

These are different, colloidal, semiconductor, nanocrystals that are stretched out from 1-10nm in distance across. Quantum spots are combined by utilizing semiconductor materials using strategies like colloidal materials and electrochemistry. Inorganic center, inorganic shell and fluid natural covering are the parts of their structure. The span of these nanoparticles decides the iridescence shading and shading coded quantum spots are utilized as a part of DNA testing. Quantum spots are being utilized as a part of different diverse routes, for example, diagnostics, medicate conveyance, imaging, tissue building attributable to their extensive surface range. Lethality is a significant prerequisite in the use of quantum bits which can be overcome by surface change with N-acetylcystine. PEGylation of quantum spots increase the biocompatibility and dauntlessness. Cadmium selenide, cadmium telluride, indium phosphide and indium arsenide are the consistently used quantum spots [21].

3.6 Liposomes

Liposomes are lipid based medication bearers, made out of a lipid bilayer with an encompassed phospholipid film and contains a focal watery center. The phospholipids incorporate phosphatidylglycerine, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine. Watery compartment or lipid layer can be utilized for the stacking of the medication. In the fluid layer polar medications are stacked while the amphiphilic and lipophilic medications are solubilized in the phospholipid bilayer. Simplicity of alteration, high biocompatibility, focused on medication conveyance, counteracting drug corruption, amphiphilic nature, less symptoms make them perfect medication bearers. Liposomes demonstrates some sort of confinements like poor stockpiling limit, low exemplification effectiveness and quick spillage of the medication which are yet to be overcome. Niosomes, marinosomes, ethosomes, transferosomes are types of liposomes being used for medication conveyance [24].

3.7 Viral nanoparticles

They are normally happening bio-nanomaterials. These are found in regular sources like plants, creepy crawlies and microscopic organisms which are biocompatible and biodegradable as well as they are non-irresistible and does not create any danger to people. Nanoparticles (VLNPs) are a subtype of VNPs that are without hereditary material. VNPs have a few qualities like they are basically uniform with high stacking limit, sheltered and simple to deliver. The important VNPs made were from plant cowpea mosaic defilement, which exhibited stretched out transport to affliction cells because of the ease of specialist of the pharmaceutical typified nanoparticles to the ailment cells. The protein covering of VNPs can be conjugated or exemplified with particular ligands and antibodies for focused transport. VNPs can in this manner be utilized as a part of conveyance of immunizations, imaging utilizing iron oxide, quality conveyance and conveyance of chemotherapeutic medications [25].

3.8 Nanocrystals

Medicate nanocrystals are gems with a size in the nanometer extend, which implies they are nanoparticles with a crystalline character, and have developed as an option type of medication conveyance for ineffectively solvent medications. Nanocrystals work best for the hydrophobic medications in light of the fact that these have a thin hydrophilic film on it. Sedate nanocrystals are made out of 100% medication; there is no transporter material as in polymeric nanoparticles. Scattering of medication nanocrystals in fluid media makes “nanosuspensions” (as opposed to “microsuspensions” or “macrosuspensions”). As a rule the scattered particles should be settled, for example, by surfactants or polymeric stabilizers. The hydrophilic layer decides the natural responses, and advantages in biodistribution and bioavailability. They can be conveyed intravenously and does not require earlier solubilization of the medication and henceforth are more secure [26].

Table 1. Advantages and disadvantages of different types of Nanoparticles.

S. No.	Types of nanoparticles	Advantages	Disadvantages
1.	Polymeric nanoparticles	Extremely small size. Sustained and targeted drug delivery. Better efficiency. Fewer side effects. Various routes of administration- oral, nasal, parenteral, intra-ocular, etc.	Particle- particle aggregation makes physical handling of nanoparticles difficult in liquid and dry form.
2.	Dendrimers	Controllable size (1 to over 10nm). Morphology and functional groups on the surface. Can be modified to stimuli responsive to release drug. Size is very close to biological polymers and assembly's like- DNA and proteins. Improved physical and chemical properties.	Toxicity issues. Poor storage stability. Extra obstacles of multistep synthesis. High cost.
3.	Polymeric micelles	High drug efficiency. Targeted delivery. Minimized cytotoxicity.	Low drug loading and low drug incorporation stability. Micelles limit the targeting ability.
4.	Liposomes	Colloidal size. Prevent degradation of drugs. Reduce side effects. Target drugs sites.	Low encapsulation efficiency. Leakage of water soluble drug in the presence of blood components. Poor storage stability.
5.	Gold nanoparticles	Large surface area. Low hydrodynamic mean size. Suitable for photodynamic therapy. Easy surface modification. Suitability and biocompatibility	High cost. No biodegradability. Lack of standard protocols for translation into the clinics.
6.	Quantum Dots	High photograph and synthetic solidness Low hydrodynamic mean size. Scaffold for additional agents. Size and structure based tunable emission. High molar extinction coefficient.	Toxicity Difficult surface modification. Particle aggregation, degradation and removal.
7.	Carbon Nanotubes	Large surface area. High penetration capacity. Suitable for photo dynamic therapy.	Nonbiodegradable. Toxic. Lack of standard convention to plan high virtue carbon nanotubes in huge scale.
8.	Silica nanoparticles	Large surface area. Stability Controllable porosity Biocompatibility. Biodegradable.	In-vivo toxicity.

4. CHARACTERISTICS OF NANOPARTICLES

Nanoparticles are most important scientific tools which are been explored for the furthermore studies. They are used as a link between bulk and atomic or molecular structures. In characterization of nanoparticles we evaluate the physiochemical properties, toxicity, sterility, pyrogenicity and biodistribution which are being tailored for the individual dosage forms. The assets of using nanoparticles in the delivery system is due to their flexibility, modifiability, biodistribution and it also helps in releasing sustained release drug profiles which helps them from degrading [27, 28].

4.1 Physical properties of nanoparticles

Nanoparticles possess large surface area, an example of this is zinc oxide which is mostly and widely used in the sunscreen lotions because zinc oxide particles have a property of blocking UV radiations as compared to the other bulk substitute.

Other physical properties of nanoparticles are as follows:

- Color- yellow gold and gray silicon nanoparticles posses red color.
- Nanoparticles absorbs greater amount of UV/ solar radiations because of their smaller particle size they are able to absorb the radiations better than the bulk substitute.
- Gold nanoparticles melt at a lower temperature (~300 °C for 2.5 nm size) than the gold slabs (1064°C) [27].

4.2 Physiochemical properties

These include molecule estimate, measure dissemination, surface science, porosity, solvency, immaculateness, security, collection/agglomeration express, all of which decide the *in-vivo* dispersion, focusing on capacity, tranquilize stacking capacity and discharge design, wellbeing, strength, danger and adequacy of the nanoparticle [28]. In simple molecules the evaluation is mainly done by using properties like- molecular weight and special properties for determination of their purity and functionality. While in case nanoparticles which are multipart and multifunctional a thorough assessment is required, which is done by evaluating individual parts, chemical stability, physiochemical properties also with *in-vitro* and *in-vivo* properties [29].

4.3 Surface charge and hydrophobicity

Surface charge is the electric potential difference between the internal and the external surface of the particles. Nearness of these surface charges on the nanoparticles decides the association of the nanoparticles with the bioactive compounds. Data about the capacity, surface hydrophobicity and material encapsulate can be dictated by the zeta capability of the nanoparticles. Surface hydrophobicity can likewise be dictated by contact edge estimations, biphasic parceling and hydrophobic association chromatography, while particular substance bunches connected to the surface can be recognized by X-beam photon relationship spectroscopy [29].

4.4 Purity, composition and functional characterization

The structure, immaculateness and capacity of nanoparticles can be determined by NMR i.e. Atomic Attractive reverberation. Purity can also be determined by other methods like UV-visible and fluorescence detectors. Purity and elemental composition of nanoparticles is evaluated by the CHN analysis. Other methods of determining composition are atomic absorption and atomic emission [30].

4.5 Stability, molecular weight and other characteristics

Steadiness of the nanoparticles is key for both physiological and non-physiological process on account of their organic movement, stockpiling, light and warm introduction, lyophilisation, ultra-filtration and pH variety. Atomic weight can be controlled by Lattice helped laser desorption ionization time-of-flight (MALDI TOF) mass spectroscopy, close to the proximity of degradations. The essential electronic properties can be considered using checking tunneling microscopy (STM), appealing field microscopy (MFM), looking at warm microscopy and electric field incline microscopy (EFM). Assessment of nanoparticles can be performed by protein associated immunosorbent look eg ELISA or bicinehoninic destructive analysis (BCA), UV spectroscopy or Elite liquid chromatography [29].

4.6 Drug loading and drug release

The measure of medication coming to the tumor site is affected by the elements, tranquilize stacking and tranquilize discharge. The way toward filling of medication in a nano bearer is known as medication stacking or exemplification and the turnaround procedure of medication freedom is known as medication discharge and both of these rely on upon the kind of nanoparticles utilized. Medications should be stacked after or before the planning of the nanoparticles. Stacking of medication is for the most part done by three process which are-physical entanglement, concoction conjugation and poly ionic complexation. Unmistakable frameworks for separating the instruments of prescription stacking are ultra-filtration, UV spectroscopy, NMR, gel filtration, Fourier change infrared spectroscopy (FTIR). As the medication came to the focused in the vicinity, its discharge is administered by medication dissolvability, desorption of the surface adsorbed tranquilize, nanoparticle network debasement, sedate dispersion through nanoparticle lattice and blend of disintegration/dissemination forms. The formulation can only be successful if there is proper and efficient release of the encapsulated nanoparticle [30].

5. IN-VITRO AND IN-VIVO CHARACTERIZATION

In-vivo studies are accomplished with the *in-vitro* portrayal of nanoparticles which helps in evaluating the pharmacokinetics, adequacy, biochemical and physiological components. This study helps in giving data about the biodistribution and lethality profiles of nanoparticles. *In-vitro* studies offer an essential estimation about remedial nanoparticles which builds up the procedure for the *in-vivo* trials. Cell take-up and dissemination, contact with blood, sterility and pyrogenicity, authoritative and pharmacology, are the attributes of *in-vitro* characterization. Protein blend restraint and microtubule damage are the poisonous endpoints which give data of the potential cell passing instruments and distinguish the aggravates that cause these toxicities by means of components like apoptosis, oxidative push, and mitochondrial brokenness. Trypan blue prohibition examine and lactate dehydrogenase (LDH) spillage test measure the film trustworthiness. Metabolic movement can be measured by 3-(4, 5-dimethyl-2-thiazolyl) 2,5-diphenyl-2H-tetrazolium bromide (MTT) reduction. Monolayer adherence can be explored by Sulforhodamine B add up to protein recoloring measure. Pharmacology, cell binding and cell analysis can be determined by the techniques like- flow cytometry, ELISA, surface plasmon resonance (SPR), Liquid scintillation counter (LSC). Energy dispersive x-ray can be used to determine the biodistribution and pharmacokinetics. EM, chemiluminescence can be used to determine the phagocytosis. Lumulus ameboeye lysate (LAL)-based assay and rabbit pyrogen test can be used to determine the sterility and pyrogenicity of the nanoparticles. *In-vitro* characterization helps to examine the immune system, evaluate the hematology, pathology, clinical chemistry, histology and its effects on the internal organs. Chromatography, High Performance Liquid Chromatography and Gel Electrophoresis are the techniques to find the blood contact. Fluorescence

Microscopy, Scanning Electron Microscopy, and Electrophoresis are the techniques used to determine the cellular uptake [28-30].

6. NANOPARTICLES IN TUMOR TREATMENT

Problems which are faced in delivering drugs to solid tumors are- toxicity in system, lack of selectivity and renal clearance at a faster pace. Nanoparticles can distinguish the non-composed tumor vessels, the augmented crevice intersections between the vascular endothelial cells and exchanged off lymphatic waste, and are ideally engaged to the tumor site. By this nanoparticles can lessen the systemic danger. Presently, with the assistance of qualities like unusual vascular development, hyper vascularization, specific focusing on is conceivable, because of which medication turns out to be more porous to the tumor site and because of absence of lymphatic seepage and nearness of tight endothelial intersections help them to escape prompting expanded maintenance in plasma. This impact known as “Improved Penetrability and Maintenance” (EPR) impact. Macromolecular medications have favorable position they can undoubtedly go through the holes of the endothelial vascular cells. Furthermore they are being cleared from the tumor tissues at a moderate rate than the typical fiery tissues. Presently, this penetrability assumes a critical part furthermore in imaging utilizing positron transmitting geography (PET), attractive reverberation imaging (X-ray) and fluorescent imaging. The vascular penetrability and the EPR impact are by and large upgraded by go between, for example, bradykinins, angiotensin changing over compound inhibitors, oxygen radicals, nitric oxide. Lymphatic seepage brought about because of the obliteration of the tissues and an expansion in the interstitial weight is other component allowing specific maintenance of the medication for more time in the tumor interstitial [31- 32].

The goal of cancer therapeutics is to aim at the targeted tumor cell, limit the dose of the drug, and avoid systemic toxicity and adverse side effects. Nanoparticle technology gives us this opportunity to modify the drug and allow to target it at the specific tumor site. Detached focusing on is in which the nanoparticles escape from the tumor vasculature and get gathered in the interstitial by the impact of EPR. The systemic dissemination time ought to be expanded so that the nanoparticles come to the focused location. This can be accomplished by consolidating chemotherapeutic operator with an appropriate atomic bearer. By aggregating diverse sorts of nanoparticles a high convergence of nanoparticles can be accomplished at the tumor site and this high fixation relies on the interstitial weight. Three properties must be taken in thought for the successful inactive focusing (i) the span of the nanoparticles ought to be custom-made in a way that it gets away from the liver and filtration by kidneys (in a perfect world the range ought to be between 10nm-100nm). (ii)- for getting away renal end the nanoparticles ought to be of impartial or anionic charge. (iii)- Nanoparticles ought to escape devastation by reticulo-endothelial framework. The tumor site has an acidic microenvironment which is a positive element for the moderate arrival of the medication. This can be included in the tumor particular medication conveyance framework.

Dynamic focusing on incorporates conjugation of focusing on ligands on the surface of the nano transporter with receptors that are over communicated on the objective tumor site, this helps the medication efflux pump to enter and increment tumor cell admission. One approach to accomplish this is to focus on the tumor microenvironment including the extracellular framework and on the other hand to focus on the tumor surface receptors [33- 34].

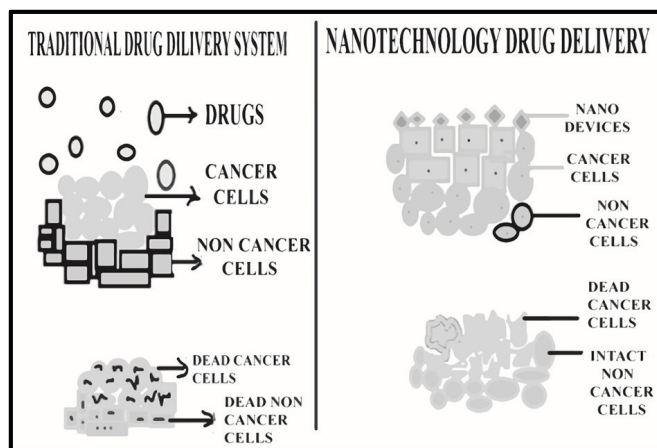


Fig. 2. Comparison between traditional and nanotechnology drug delivery system.

7. APPLICATIONS OF NANOPARTICLES IN CANCER THERAPEUTICS

7.1. In gene therapy

Gene therapy leads us to sustained expression, but lack of safety, efficient delivery systems and efficacy are the hurdles for the nanoparticles. There are two types of vectors involved in gene therapy, non-viral and viral vectors. Non-viral strategies show certain preferences over viral techniques, with straightforward huge scale generation and low host immunogenicity being only two. Already, low levels of transfection and articulation of the quality held non-viral strategies off guard; in any case, late advances in vector innovation have yielded atoms and procedures with transfection efficiencies like those of infections. Nanoparticles are of two sorts anionic and cationic nanoparticles, this beats the troubles in intracellular infiltration, cytotoxicity and debasement by utilizing a fitting bio conjugated vehicle [35- 36].

7.2. Drug delivery to ovaries, brain, skin, breast

Tumors in the cerebrum are the most basic and troublesome for treatment because of the absence of compelling medication conveyance techniques to the cerebrum and blood-cerebrum hindrance (BBB), blood-cerebrum tumor boundary (BBTB) constraining the take-up of neurotherapeutics and neuroimaging contrast specialists. Novel nano tranquilize conveyance frameworks which focus on the cerebrum tumors have effectively looked into indicating diminished danger and increment in the pharmacological profile. In spite of the fact that the right instrument of the conveyance of nanoparticles is not yet known.

Physical grip of the medication to the nanoparticle is vital and take-up of anionic nanoparticles was better than nonpartisan and cationic nanoparticles. Biodegradable polymers have been demonstrated significantly profitable for the treatment of threatening brain tumors. Different courses of organization of BBB can be utilized, for example, olfactory, nerve endings by conjugating nanoparticles with bioactive ligands-lectins to the surface of poly (ethylene glycol)- poly (lactic corrosive) (PEG-PLGA). Ovarian diseases are the fifth driving reasons for tumor passings which is identified with the high horribleness and mortality of the ladies. Old strategies/medications like surgeries, chemotherapy utilizing paclitaxel expanded the rate of survival yet this backslid in light of the fact that multidrug resistance couldn't be accomplished. As of late utilization of nanoparticles, liposomes, polymers, micelles, conjugated peptides are being utilized as a part of ovarian disease treatment. Utilization of nanoparticle medication treatment has expanded the survival rates furthermore have turned out with viable yields, and they likewise lessened the death rates in ladies experiencing bosom disease [37-38]. Treatment measures utilized as a part of bosom diseases are surgeries, hormonal, radiation and chemotherapy. Treatment utilizing alkylating operators, alkaloids, antimetabolites, anthracyclines, topoisomerase inhibitors which concentrate on concealment of cell division and restraint of expansion of malignancy cells, yet prompted genuine reactions. Dendrimers, liposomes, micelles and nucleic acids are the diverse transporters which are utilized as a part of bosom malignancy treatment as methodologies. The most basic focuses of these bearers incorporate HER-2 receptor, which is for the most part over communicated in 20-30% bosom tumor cases, different receptors are the folate receptors, estrogen receptors, and epidermal development receptors. Applying these treatment measures expanded the survival rates and demonstrated a less number of reactions as contrasted to traditional techniques [39]. Skin malignancies are extensively separated into two sorts melanoma skin diseases and non-melanoma skin growths. Melanoma skin growths are brought about by melanocytes, these cells are in charge of delivering melanin shade which gives a particular shading to the skin or a tan. Presently, non-melanoma skin malignancies are fundamentally of two sorts basal cell carcinoma and squamous cell carcinoma, and these are the most broadly perceived sort of skin tumor found in individuals. Prior strategies included were surgeries, curettage and non-surgical techniques included chemotherapy and radiation. As these are the nonspecific targeting procedures they have a few reactions, for example, agony, aggravation and scars henceforth these systems are constrained. Use of nanoparticles in skin cancer has been proven advantageous as it increases the skin drug absorption and its release time. It is done with the help of liposomes as nano emulsions, polymers, magnetic nanoparticles, solid lipid nanoparticles, all of these help to improve the drug adhesion and increases the hydration. Titanium dioxide, 5-fluorouracil, zinc oxide, imiquimod are some of the chemotherapeutic agents frequently formulated with nanoparticles for use in skin cancers [40].

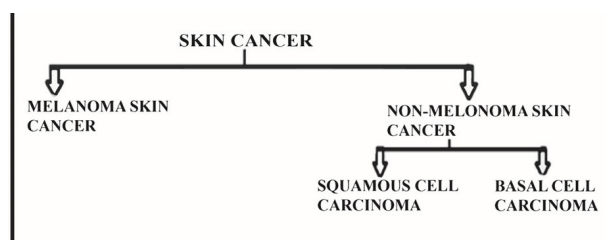


Fig. 3. Classification of different types of skin cancer

7.3. In diagnostics and imaging

Growth nanotechnology is a multidisciplinary and an issue driven approach which points in getting headway disease discovery, treatment, imaging and analysis. The ranostic nanoparticles were created to analyze, treat and screen reactions to the treatment. These were additionally created with a trust of diminishing the assembling expense and danger, while keep on promoting the focused on conveyance of chemotherapeutic operators. Supramagnetic squeeze oxide nanoparticles (SPION), multifunctional magneto-polymeric nanohybrids, polyacrylamide-based hydrogel nanoparticles are a bit of the potential theranostic pros which are extensively considered. In customized treatment, the theranostic specialist is been altered as needs be to deliver the craved physical and compound changes in the body by initiating them. This has favorable position of limiting the sum and the term of medication Discharge, along these lines nearly checking the treatment viability. Fluorescent nanoparticles, for example, Quantum spots can be utilized as unpretentious and exceptionally particular tests for high-throughput screening, cell science and cell imaging. Customary imaging strategies, for example, MRI, PET, ultrasound, single photon discharge figured tomography (SPECT), are the imaging procedures which are used to detect the cancers only when the tumor or lump is being formed or is visible. Gold nanoparticles and carbon nanotubes are widely considered for optical and acoustic imaging. Polymeric nanoparticles stacked with docetaxel and superparamagnetic press oxide nanocrystals are broadly utilized as a part of malignancy treatment and imaging [41].

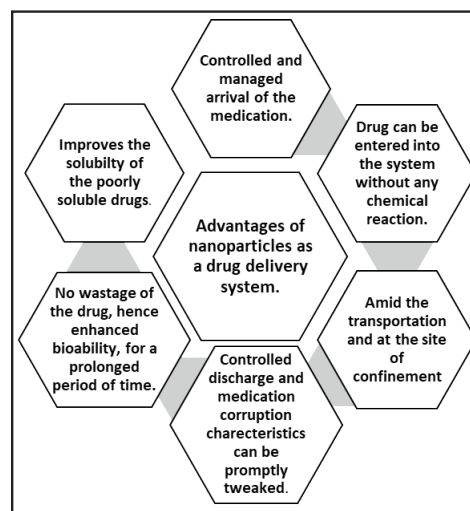


Fig. 4. Advantages of nanoparticles in drug delivery system.

8. FUTURE PROSPECTS

The world is advancing every day and so is our technology in the field of Pharmacology, cell and molecular biology, proteomics, engineering, bioinformatics and many more but still rate of survival of human life is at mark off, due to wide increase in the number of diseases and there is a lack in treatment methods and cancer acquires the top position. Therefore, novel therapeutic agents and techniques have been developed which helps in lowering the death rate and hence helps in increasing the survival chances/ rates. However this method also has some of the disadvantages or side effects which are related to systemic toxicity, high treatment costs, inefficient targeting, resistance to drug and etc. By understanding and further study in molecular biology has helped to gain and develop the targeted drug delivery systems using nanoparticles, which have the ability to overcome and already have overcome many of the convectional limitations and also has reduced the rate of side effects and increased the chances of survival. Biocompatible and biodegradable nanoparticles have been developed which have are highly being used in the treatment process in the recent years, these nanoparticles have drug loading and drug releasing capacity which helps in control release of drug. However nanotechnology also comes with side effects such as- high cost is required, large scale manufacturing, sudden toxicity, interference with the normal biological processes, etc. If these limitations are overcome and a solution is invented, it can mark a great prosperity in the medical science field.

REFERENCES

- [1] What Is Cancer? [Internet]. National Cancer Institute. [cited 2016Oct15]. Available from: <http://www.cancer.gov/about-cancer/understanding/what-is-cancer>
- [2] Cancer [Internet]. Overview. [cited 2016 Oct15]. Available from: <http://www.netwellness.org/healthtopics/cancer/canceroverview.cfm>
- [3] Lim EK, Jang E, Lee K, Haam S, Huh YM. Delivery of Cancer Therapeutics Using Nanotechnology. *Pharmaceutics*. 2013; 5(2): 294–317.
- [4] Faraji AH, Wipf P. Nanoparticles in cellular drug delivery. *Bioorganic and Medicinal Chemistry*. 2009; 17(8): 2950–62.
- [5] Cho K, Wang X, Nie S, Chen Z, Shin DM. Therapeutic Nanoparticles for Drug Delivery in Cancer. *Clinical Cancer Research*. 2008; 14(5): 1310–6.
- [6] Serpe L. Conventional Chemotherapeutic Drug Nanoparticles for Cancer Treatment. *Nanotechnologies for the Life Sciences Online*. 2007.
- [7] Win KY, Feng SS. Effects of particle size and surface coating on cellular uptake of polymeric nanoparticles for oral delivery of anticancer drugs. *Biomaterials*. 2005; 26(15): 2713–22.
- [8] Sinha R. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. *Molecular Cancer Therapeutics*. 2006; 5(8): 1909–17.
- [9] Acharya S, Dilnawaz F, Sahoo SK. Targeted epidermal growth factor receptor nanoparticle bioconjugates for breast cancer therapy. *Biomaterials*. 2009; 30(29): 5737–50.
- [10] Alexis F, Basto P, Levy-Nissenbaum E, Radovic-Moreno AF, Zhang L, Pridgen E, et al. HER-2-Targeted Nanoparticle-Affibody Bioconjugates for Cancer Therapy. *ChemMedChem*. 2008; 3(12): 1839–43.
- [11] Nanoparticle: An overview of preparation and characterization (2000-2010). [Internet]. Pal, Sovan Lal. [cited 2016Oct16]. Available from: <http://imsear.li.mahidol.ac.th/handle/123456789/150885>.
- [12] Bala TDR. Engineered Nanoparticles for the Delivery of Anticancer Therapeutics. *J Pharm Drug Deliv Res Journal of Pharmaceutics and Drug Delivery Research*. 2015; 04(01): 78-85.
- [14] Chan JM, Valencia PM, Zhang L, Langer R, Farokhzad OC. Polymeric Nanoparticles for Drug Delivery. *Methods in Molecular Biology Cancer Nanotechnology*. 2010: 163–75.
- [15] Goldberg M, Langer R, Jia X. Nanostructured materials for applications in drug delivery and tissue engineering. *Journal of Biomaterials Science, Polymer Edition*. 2007; 18(3): 241–68.
- [16] Miyata K, Christie RJ, Kataoka K. Polymeric micelles for nano-scale drug delivery. *Reactive and Functional Polymers*. 2011; 71(3): 227–34.
- [17] Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. *Progress in Polymer Science*. 2014; 39(2): 268–307.
- [18] AZoNano Why. Recent Advances in Novel Drug Delivery Systems [Internet]. AZoNano.com. 2015 [cited 2016Oct16]. Available from: <http://www.azonano.com/article.aspx?articleid=1538>.
- [19] Article [Internet]. Surendiran, A; Sandhiya, S; Pradhan, SC; Adithan, C. Novel applications of nanotechnology in medicine. *Indian J. Med. Res* 2009; 130: 689–701.
- [20] Jain S, Hirst DG, O'sullivan JM. Gold nanoparticles as novel agents for cancer therapy. *The British Journal of Radiology BJR*. 2012; 85(1010): 101–13.
- [21] Cai W, Gao T, Hong H, Sun J. Applications of gold nanoparticles in cancer nanotechnology. *Nanotechnol Sci App* 2008; 1: 17-32.
- [22] Lim E-K, Jang E, Lee K, Haam S, Huh Y-M. Delivery of Cancer Therapeutics Using Nanotechnology. *Pharmaceutics*. 2013; 5(2): 294–317.
- [23] Calcium phosphate nanoparticles for the transfection of cells [Internet]. - IOS Press. [cited 2016Oct16]. Available from: <http://content.iospress.com/articles/bio-medical-materials-and-engineering/bme586>.
- [24] Roy I, Mitra S, Maitra A, Mozumdar S. Calcium phosphate nanoparticles as novel non-viral vectors for targeted gene delivery. *International Journal of Pharmaceutics*. 2003; 250(1): 25–33.
- [25] Müller R, J. Nanocrystal technology, drug delivery and clinical applications. *International Journal of Nanomedicine*. 2008; 4(2): 295.
- [26] Franzen S, Lommel SA. Targeting cancer with 'smart bombs': equipping plant virus nanoparticles for a 'seek and destroy' mission. *Nanomedicine* 2009; 4(5): 575–88.
- [27] Hollis C, Zhao R, Li T. Hybrid nanocrystal as a versatile platform for cancer theranostics. *Biomaterials for Cancer Therapeutics*. Woodhead Publishing Series in Biomaterials. Biomaterials for Cancer Therapeutics. 2013; xvi-xx.
- [28] Cashin-Garbutt A. Properties of Nanoparticles [Internet]. News-Medical.net. 2012 [cited 2016 Oct16]. Available from: <http://www.news-medical.net/life-sciences/properties-of-nanoparticles.aspx>.

- [29] Hall JB, Dobrovolskaia MA, Patri AK, Mcneil SE. Characterization of nanoparticles for therapeutics. *Nanomedicine*. 2007; 2(6): 789–803.
- [30] Stern S, Mcneil S, Patri A, Dobrovolskaia M. Preclinical characterization of engineered nanoparticles intended for cancer therapeutics. *Nanotechnology for Cancer Therapy*. 2006:105–37.
- [31] Coevering RVD, Kreiter R, Cardinali F, Koten GV, Nierengarten J-F, Gebbink RJK. An octa-cationic core-shell dendrimer as a molecular template for the assembly of anionic fullerene derivatives. *Tetrahedron Letters*. 2005; 46(19): 3353–6.
- [32] Danhier F, Feron O, Pr at V. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *Journal of Controlled Release*. 2010; 148(2): 135–46.
- [33] Ding D, Zhu Z, Liu Q, Wang J, Hu Y, Jiang X, et al. Cisplatin-loaded gelatin-poly(acrylic acid) nanoparticles: Synthesis, antitumor efficiency in vivo and penetration in tumors. *European Journal of Pharmaceutics and Biopharmaceutics*. 2011; 79(1): 142–9.
- [34] Chidambaram M, Manavalan R, Kathiresan K. Nanotherapeutics to Overcome Conventional Cancer Chemotherapy Limitations. *Journal of Pharmacy & Pharmaceutical Sciences JPPS*. 2011; 14(1): 67.
- [35] Alexis F, Pridgen EM, Langer R, Farokhzad OC. Nanoparticle Technologies for Cancer Therapy. M. Schafer-Korting (ed.), *Drug Delivery, Handbook of Experimental Pharmacology*, Springer-Verlag Berlin Heidelberg 2010; pp 197.
- [36] Yamamoto M, Curiel DT. *Cancer Gene Therapy. Technology in Cancer Research & Treatment*. 2005; 4(4): 315–30.
- [37] Dickson PV, Nathwani AC, Davidoff AM. Delivery of Antiangiogenic Agents for Cancer Gene Therapy. *Technology in Cancer Research & Treatment* 2005; 4(4): 331–41.
- [38] Jin S, Ye K. Targeted Drug Delivery for Breast Cancer Treatment. *Recent Patents on Anti-Cancer Drug Discovery PRA*. 2013; 8(2): 143–53.
- [39] Paliwal SR, Paliwal R, Agrawal GP, Vyas SP. Liposomal nanomedicine for breast cancer therapy. *Nanomedicine*. 2011; 6(6): 1085–100.
- [40] Nahta R. Growth Factor Receptors in Breast Cancer: Potential for Therapeutic Intervention. *The Oncologist*.
- [41] Severino P, Fangueiro JF, Ferreira SV, Basso R, Chaud MV, Santana MHA, et al. Nanoemulsions and nanoparticles for non-melanoma skin cancer: effects of lipid materials. *Clinical and Translational Oncology*. 2013; 15(6): 417–24.
- [42] Miller AD. Lipid-Based Nanoparticles in Cancer Diagnosis and Therapy. *Journal of Drug Delivery*. 2013; 2(1): 1–9.