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Nanoparticulate system for cancer therapy: An updated review

Abstract

Now a day, pharmaceutical nanotechnology developed as most emerging branch in the field of pharmacy. Nanotechnology refers the art of creation and utilization of materials in nano-scale formulation. These nano-formulations may used in treatment of various life threading disease like cancer. Due to the advantage of their nano size and shape, nano-formulation have been shown to be favorable drug delivery system and may be useful for encapsulating and conjugating of drugs with enabling of most precise tumor targeting and controlled release. Nanoparticle drug delivery system have several advantages such as enhanced intracellular infiltration, hydrophobic solubility, and drug circulation time and also reduce non specific uptake and toxic effect for cancer therapy. A large number of nanoparticle technologies have been developed for cancer treatment to improve the therapeutic efficacy and safety for anticancer drugs. In this paper, we review the most significant advancement in pharmaceutical nanotechnologies with methods of preparation and their use in drug delivery for cancer therapy.

Keywords: nanoparticle, pharmaceutical nanotechnology, cancer therapy, nano-chemotherapy, polymersome, liposomes, dendrimer, antigenecity, squamous cell, carcinoid cancer, waldenstrom's disease, leukemias

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Introduction

According to national nanotechnology initiative, nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. Nanoparticles properties like physicochemical and biological are more easily taken up by cell than larger molecules, so nanoparticles may be more suitable as drug delivery system.

Nanoparticles are composed of three layers,[1]

a. The surface layer, which may be responsible to small molecules, polymers, surfactants, and metal ions.

b. The shell layer, which have totally different chemically material from core.

c. The core, which is central portion of the nanoparticles.

Now days Nanoparticulate system gained more importance than conventional dosage form in cancer therapy because conventional dosage form is unable to deliver the drug in adequate quantity to the tumor site. While Nanoparticulate system have possibility to deliver chemotherapeutic drug at target site with overcome solubility and stability issues.[2] Chemotherapeutic drugs are toxic to cancer cell but their high toxicity and low specificity also destroyed the healthy cells. A possible strategy to overcome these problems or improve therapeutic efficacy and decrease their toxic effect is called nanoparticles technology.[3] The main object of these nanotechnologies is to transport proper amount of drug to desirable site and decreases toxic effect of drugs on other tissues.[4] In this review, we discuss nanoparticles technologies and also focused on parameter for material selection for nanoparticle and their advantages. These technologies include liposomes, polymer drug conjugates, polymeric nanoparticles, micelle, dendrimer, polymersome, protein nanoparticles, biological nanoparticles, inorganic nanoparticles and hybrid nanoparticles.

Advantages of nanoparticles technologies in cancer therapy[5-7]

Various studies show that Nanoparticles have ability to target to cancer cells without damaging healthy cells. So now a day Nanoparticles technologies are considered as superior drug delivery system in cancer therapy than other conventional dosage form.

a. Target and enter into selective tissue at molecular level.

b. Increase cellular uptake and drug localization.

c. Accurate and selective drug delivery to cancerous cell without interaction with healthy cells.

d. Providing large surface area.

e. Providing high absorption rate.

f. Less amount of dose required.

g. Decrease drug resistance.

h. Decrease toxicity.

i. To improve the uptake of poorly soluble drugs.

j. Nanoparticles can better deliver drugs to tiny areas within the body.

k. Nanoparticles overcome the resistance offered by the physiological barriers in the body.

Factors affecting the selection of material for nanoparticles preparation are-8

a. Need of nanoparticles size.

b. Drug properties such as stability and aqueous solubility.

c. Desired drug release profile.

d. Required surface charge of nanoparticles.

e. Biocompatibility and biodegradability.

f. Toxicity and antigenecity of product.

Cancer

Cancer is one of the most common problems and serious health issue in this world. Human body contains millions of tiny cells; these tiny cells are living units of the body. Cancer is a complex disorder that results from multiple genetic changes and cellular abnormalities.[9] Genetic changes that cause cancer can be, Inherited from our parents, Person's lifetime and Environmental exposures such as chemicals in tobacco, smoke, radiation, ultraviolet rays from the sun.

Types of Cancer

There are more than 100 types of cancer. Types of cancer are usually named for the organs or tissues where the cancers form. For example, lung cancer starts in cells of the lung, and brain cancer starts in cells of the brain. Cancers also may be described by the type of cell that formed them, such as an epithelial cell or a squamous cell.[10]

1) Cancers of Blood and Lymphatic Systems:

   a) Hodgkin's disease, b) Leukemias, c) Lymphomas, d) Multiple myeloma, e) Waldenstrom's disease.

2) Skin Cancers:

   b) Malignant Melanoma.

3) Cancers of Digestive Systems:

   c) Esophageal cancer, b) Stomach cancer, c) Cancer of pancreas, d) Liver cancer, e) Colon and Rectal cancer, f) Anal cancer.

4) Cancers of Urinary system:

   d) Kidney cancer, b) Bladder cancer, c) Testis cancer, d) Prostate cancer.

5) Cancers in women:

   e) a)Breast cancer, b) Ovarian cancer, c) Gynecological cancer, d) Choriocarcinoma.

6) Miscellaneous cancers:

   f) Brain cancer, b) Bone cancer, c) Carcinoid cancer, d) Nasopharyngeal cancer, e) Retroperitoneal sarcomas f) Soft tissue cancer, g) Thyroid cancer

Nanoparticles Technologies

Liposome nanoparticles

Liposomes were the first nanoparticles technology applied in medicine in 1961.[11] Aim of liposomal drug delivery system to increase efficacy, decrease toxicity and easy administration.[12] Liposomal nanoparticles are most used nanoparticles for cancer therapy, these are easily and self assembled from amphiphilic lipid and excipients. The lipid part form a bilayer based on hydrophobic interaction with hydrophilic head groups. Hydrophobic drug molecules can be encapsulated in lipid bilayer and hydrophilic drug molecules can be encapsulated in aqueous phase.[13] Drug release from liposomes depends on composition, pH, osmatic gradient and surrounding environment.[14] Lipids are used in these formulations are approved by FDA are DSPE (1,2-distearoyl-sn-glycero-3-phosphoethanolamine), HSPE (hydrogenated phosphatidylcholine from soybean lecithin), EggPG (egg yolk phosphatidylglycerol), DSPC (1,2-distearoyl-glycero-3-phosphocholine). Liposome nanoparticles have demonstrated multiple special benefits as drug delivery system, such as used to carry very potent drug to their low encapsulated load, instability in blood stream and poor solubility of many drugs. Many times researchers reported various challenges during the production of liposome are difficult reproducing formulation process, uniform particle size, efficient drug loading, and time consuming process.

Types of liposomes

On the basis of phospholipid bilayer and the size of liposomes, these are following types.[15,16]

a) Multilamellar Vesicles (MLV) - these types of liposomes are contains multiple number of phospholipid bilayer member separated by aqueous phase. The size of multilamellar vesicle liposomes may up to 5 µm.

b) Small Unilamellar Vesicles (SUV) - these types of liposomes are contains single phospholipid bilayer member surrounding the aqueous phase. The of Small unilamellar vesicles liposome may be in the range of 20-100 nm.

c) Large Unilamellar Vesicle (LUV) - these types of liposomes are also contains single phospholipid bilayer member surrounding the aqueous phase. The of Small unilamellar vesicles liposome may be in the range of 100-250 nm.

Polymer drug conjugates nanoparticles

The concept of polymer conjugates for anticancer agent was proposed in 1975.[17] Polymer drug conjugation achieved enhanced permeability and retention effect by tumor specific targeting.[18] Polymeric drug conjugation system is the most important and older polymeric drug delivery system. Polymer–drug conjugates are most advancement in the field of nanoparticles technology and currently in clinical trials phase III. These nanoparticles can deliver high dose of chemotherapeutic drugs because in which drug conjugates with polymer through side chain. The size of polymer conjugates is below 20 nm mostly. The way of conjugating the drug to the nanoparticles and its strategy is most important in cancer therapy. A drug molecule may be encapsulated in nanoparticles or covalently attached to surface of nanoparticles. Covalent attaching strategy had more advantages than other ways.[19] On the basis of various studies found that, application of nanoparticles to tumor may be improved by the conjugated of polymer and drug moiety. These conjugations may allow more specific recognition and preferential interaction of drug to targeted tumor site.[20]

Polymeric nanoparticles

The purpose of polymeric nanoparticles was to develop nanoparticles for prolonged drug delivery system.[21] Polymeric nanoparticles are flexible in design because of polymer properties such as biodegradable and non-biodegradable, synthetic and natural synthetic sources.[22] Commonly used polymers are poly (lactic acid) (PLA), dextran, and chitosan.[23] Polymer nanoparticles can be used to improve the efficacy, toxicity, bioavailability, solubility and pharmacokinetics of a drug. These particles may reduce toxicity in tumors and improved therapeutic response.[24] Polymeric nanoparticles may offer encapsulation and delivery of bio-molecules for genetic medicine, immunotherapy and gene editing. Polymeric nanoparticles offer the various advantages in cancer therapy but during the development of these particles some challenges affect the safety and efficacy of the polymer formulations.[25] These challenges are process scalability, process reproducibility, particle size control and efficient drug loading. Drug can be encapsulated on polymeric nanoparticles during polymerization step.[26] Drugs may be released from polymeric nanoparticles by desorption, diffusion, or nanoparticle erosion in target tissue.[27]

Micelle Nanoparticles

Micelles are self assemble nanoparticles with hydrophobic core composed from lipid and polymers. Micelles are the best drug delivery system for hydrophobic drugs. Only those chemical have an amphiphilic nature can form micelles in aqueous solution.[28] Micelles are generated when hydrophilic portions surrounding by hydrophobic phase. Micells are most favorable drug delivery system for poorly water soluble drugs.[29–31] Pharmacokinetics properties of micells were influenced by size of micells nanoparticles, generally accepted range of micells is 50–150 nm, but larger the nanoparticles size can carry more drug load because of high encapsulation volume.[32] Transport properties of micelles may be influenced by shape of micelles nanoparticles. Discs and rod shape micelles have more accepted blood circulation properties than spherical particles.[33]

Dendrimer Nanoparticles

The word dendrimers derived from the Greek word "DENDRON" means tree and "MEROS" means part, so its appearance likes TREE. This technology discovered by Tomalia and coworker in early 1980. Dendritic polymers are newly recognized polymeric structure after linear, cross linked and branch polymer.[34,35] Dendrimers are repetitively branched molecules within the range of 5-10nm. They can be modified as required to carry the drug for targeting site 36]. Dendimers serves suitable pharmacokinetic properties for systematic drug delivery. Structurally, dendrimers have three parts, namely a central core, tiers of multifunctional unit and terminal or end groups.

Dendrimers serves several properties those facilitated various biological applications as following.[37–41]

1. Neutral and negative charge dendrimers are biocompatible while positive charge dendrimers may show toxic effects.
2. Structure of dendrimers may affect pharmacokinetics properties.
3. Retention and bio-distribution character may improve by increase water solubility and size of dendrimers by PEGylation.
4. Therapeutic agent can be attached to functional groups.
5. Can be modulated for target-specific drug delivery.
6. Feasibility to develop with defined molecular weight.
7. Good entrapment efficiency.
8. Offering surface for functionalization.
9. Very low polydispersity index.
10. Very low size (1–5 nm).

Polymersome Nanoparticles

Structurally polymersome are similar as liposomes but compositions are different, polymersome composed of synthetic polymer/polypeptide amphiphiles and self assembled. Liposomes drug delivery system is the most widely used drug delivery system for anticancer drug moieties but their short half life and slow drug release required to develop new alternatives. Synthetic polymers are most promising candidates to exhibit longer half life and better drug release.[42–44] when polymer and liposomes technology works together to design nanoparticles are called polymersomes nanoparticles.[45–47] Resulted polymersome nanoparticles have been shown long half life, better drug release, enhanced stability and more side chain functioning.[48] As liposomes, hydrophobhic membrane and aqueous core of polymersome enables to encapsulate to both hydropbhobic and hydrophilic drug moieties. Polymersome nanoparticles technologies have ability to deliver both hydrophilic and hydrophobic drug in alone or combination.[49]

Protein nanoparticles

Protein nanoparticles are generally with 130 nm size. These particles bound drug with albumin to enhance intrinsic targeting abilities and permeability with retention effect at tumor site.[50] Protein nanoparticles have gained great attention in nanotechnology because of their low toxicity, biodegradability, metabolizable and easy amerable to surface modification for drug attachment.[51] Various types of proteins are used to prepare protein nanotechnology are water soluble proteins such as bovine, human serum albumin and insoluble proteins such as zein and gliadin.[52,53] The most important advantage of protein nanoparticles as drug carrier system may target the drug by modified body distribution and improvement of cellular uptake of the substances.[54]

Biological nanoparticles

Biological nanoparticles can be developed from organic and inorganic compounds based on natural biomolecules. Biological nanoparticles derive from single or multiple assemblies of protein subunits.[55] These are unicellular microorganism with various shapes and sizes. Biological nanoparticles have capacity to bind with both hydrophilic and hydrophobic drug molecule.[56] Biological nanoparticles are divided in two categories are: a. delivery of small drug molecules for cancer treatment, b. gene therapy and vaccine applications. These systems are modified by chemical or genetic modification to achieve tumor specific delivery.[57]

Inorganic nanoparticles

Various type of nanoparticles are used as drug delivery such as silica nanoparticles,[58] quantum dots,[59,60] metal nanoparticles,[61] and lanthanide nanoparticles.[62,63] Inorganic nanoparticles are generally metal based particles. These may synthesized with near monodispersity. These nanoparticles have ability to energy convert into heat at some specific conditions.[64] Metallic nanoparticles are used as drug delivery system since last few decades but now days this technology is a favorable drug delivery system for anticancer drugs because these technology have various advantages such as efficiency of drugs, biocompatibility, drug loading, non toxic to normal cells and easily reached to targeted tumor sites. This technology used various metals to synthesized nanoparticles like gold, silver, iron oxide. Gold nanoparticles are synthesized in various size range but commonly used ranges are 2-100 nm. Cellular uptake of these particles is inversely prepositional to their size and larger particle i.e. 80-100 nm does not diffuse in to tumor site and stay near the blood vessels.[65,66] These particle sizes depend on the thiol/glod ratio during the synthesis, as the thiol amount increases particle size decreases[67,68] In this era various types of gold nanoparticles take place in research such as gold nanoshells, gold nanosphere, gold nanorods and gold nanocages.[69] Another newest inorganic nanoparticles technology for cancer therapy was developed as silver nanoparticles.

Hybrid nanoparticles

Hybrid nanoparticles are the advancement of liposome and micelles. These are composed of two different materials that form core and corona structure. Core contains metallic or polymeric material while corona contains lipid layer that worked as protecting membrane. As we have discussed in earlier in part of liposome that the drug moieties are attached on the surface of liposome or incorporated into hydrophilic phase to enhance retention time of drug to cancer cell. But at this time liposome decorated with paramagnetic molecules and enable to detection of angiogenesis.[70,71] So in these cases hybrid nanoparticles technologies is required. Various types of inorganic material such as gold nanoparticles and iron oxide nanoparticles able to improve image contrast.[72] That's by gold nanoparticles and iron oxide nanoparticles are encapsulated in liposome, hydrophilic gold nanoparticles are encapsulated in hydrophilic phase and hydrophobic gold nanoparticles are inserted in hydrophobic membrane.

Advancement of nanoparticle preparation methods

The mode of preparation of nanoparticles plays a vital role to achieve the properties of nanoparticles. The selection of these methods depends on the physical and chemical properties of drug and polymer. Scientist worked from ancient time to prepare nanoparticles via various methods and their modifications, these methods and their modifications are listed below.

Emulsion-solvent evaporation method:

This method is widely used method for preparation of nanoparticles. This method consist two steps a. emulsification of polymer solution into water phase b. evaporation of solvent until nanoparticle precipitation. Prepared nanoparticles are collected by ultracentrifugation as washed with distilled water (Figure 1) (Table 1).[73–80]

Salting out method (Figure 2) (Table 2)**:**[81–83]

Solvent/emulsions diffusion method (Figure 3) (Table 3)**:**[84-9]

Dialysis method (Figure 4) (Table 4)**:**[92–96]

Precipitation method (Figure 5) (Table 5)**:**[97–102]

Table 1 Modified Emulsion-Solvent Evaporation Method

S. No.	Modification	Year
1	Modified oil in water single emulsion solvent evaporation technique[74]	2014
2	Modified by ratio of organic solvent, type of surfactant, type of polymers and the molecular weight[75]	2010
3	Changing the concentration of Stabilizer, polymer concentration, volume of aqueous Phase[76]	2004
4	High pressure emulsification and solvent evaporation method[77]	2004
5	Double emulsion technique is employed,[78]	2002
6	Preparation of a emulsion which is then subjected to homogenization under high pressure followed by overall stirring to remove organic solvent[79]	2001

Table 2 Modified Salting Out Method

S.No.	Modification	Year
1	Modified as enhanced in temperature for heat sensitive substances[80]	2001
2	Technique used in the preparation of PLA, Poly(methacrylic) acids, and Ethyl cellulose nanospheres by modified ratio[81]	2000
3	Technique used in the preparation of PLA, Poly(methacrylic) acids, and Ethyl cellulose nanospheres leads to high efficiency and is easily scaled up[82]	1998
4	Stirring rate, internal/external phase ratio, concentration of polymers in the organic phase, type of electrolyte concentration and type of stabilizer in the aqueous phase[83]	1993

Table 3 Modified Solvent/emulsions diffusion method

S. No	Modification	Year
1	Increasing homogenization speed from 6,000 rpm to 12,000 rpm[84]	2012
2	Polylactic acid was used as the encapsulating polymer with acetone and ethyl acetate as organic solvents, and tween 20, gelatin and pluronic f68 in water as stabilizer. Two ratio of organic to aqueous phases were used with each solvent and stabilizer[85]	2011
3	Polymer used Cetyl palmitate[86]	2007
4	Modified by used of coumarin to prepare Coumarin-loaded PLA nanoparticles[87]	2005
5	Used mesotetra (hydroxyphenyl) porphyrin-loaded PLGA (p-THPP) to prepare nano particles[88]	2004
6	Cyclosporine (cy-A-); loaded sodium glycolate nanoparticlesused to preparenanoparticle[89]	2002
7	Method modified to prepare Doxorubicin-loaded PLGA nano particles[90]	1999
8	Modified-SESD method using various solvent systems consisting of two water-miscible organic solvents, in which one solvent has more affinity to PLGA than to PVA and the other has more affinity to PVA than to PLGA[91]	1999

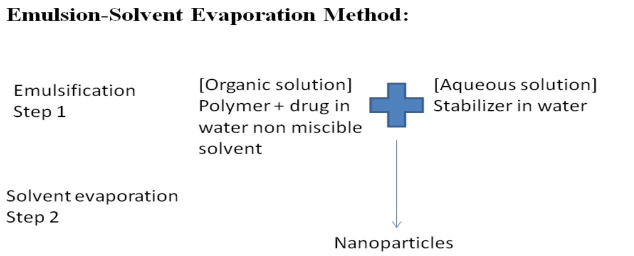

Figure 1 Flow chart to prepare nanoparticle using emulsion-solvent evaporation method.

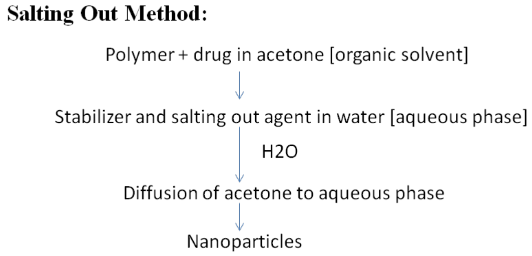

Figure 2 Flow chart to prepare nanoparticle using salting out method.

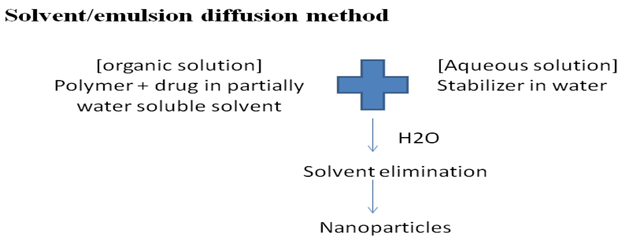

Figure 3 Flow chart to prepare nanoparticle using solvent/emulsions diffusion method.

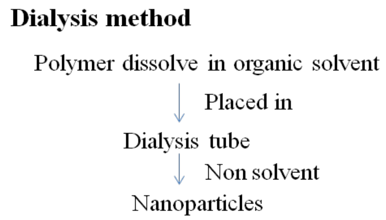

Figure 4 Flow chart to prepare nanoparticle using dialysis method.

Table 4 Modified Dialysis method

S. No.	Modification	Year
1	Curcumin-loaded PLGA nanoparticles was prepared through a modified diffusion method[92]	2014
2	Modified method used to prepare PLGA based nanoparticles[93]	2014
3	Used poloxamer 188 and PLGA used to prepare nanoparticle [94]	2013
4	Pullulan acetate As polymer used to prepare nanoparticle [95]	2009
5	Using biodegradable poly (γ-benzyl-L-glutamate)/poly (ethylene oxide) (PBLG/PEO) polymer nanoparticles. PBLG/PEO polymer is a hydrophilic/hydrophobic block copolymer and forms a micelle-like structure in solution. Spherical nanoparticles incorporating adriamycin were prepared by a dialysis method [96]	1999

Table 5 Modified Precipitation Method

S. No.	Modification	Year
1	Method modified by using Fe II to particle growth process [97]	2014
2	Zinc oxide (ZnO) nano particles have prepared by using zinc nitrate and potassium hydroxide (KOH) in aqueous solution[98]	2012
3	Method modified by using high-pressure homogenization with three important parameters, i.e. the agitation rate of stabilizer solution, homogenization pressure and cycle numbers[99]	2009
4	Method modified by using poly(lactic acid) (PLA) and poly(D,L-lactic-*co*-glycolic acid) (PLGA) as polymer solvent[100]	2005
5	Method modified by using of poly (lactic acid) PLA, poly (lactic-co-glycolic acid) PLGA and alginate[101]	1996
6	Method modified to prepare cyclosporine-loaded poly D,L (lactide-glycolide) **(PLAGA) nanoparticles**[102]	1996

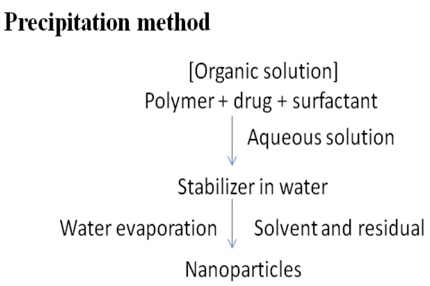

Figure 5 Flow chart to prepare nanoparticle using precipitation method.

Citation: Kumar D. Nanoparticulate system for cancer therapy:An updated review. *J Nanomed Res.* 2018;7(4):262–275. DOI: 10.15406/jnmr.2018.07.00197

Patent filled by inventors to prepared nanoparticles

Researchers developed new formulations and their methods to achieve their goals, latest worked done by various researchers listed here.

S. No.	Patent number	Work done	Reference
1	KR20180030493A	Inventor has prepared metal nanoparticles using leaf or root extract of panax ginseng as active ingredients. Extraction has been done by hot extraction method. Metal nanoparticles were prepared using a composition containing ginseng extract added to tetracholoro gold acid and silver nitrate solution of 1mM and maintained at 80°C for 20 minutes and centrifuged at 16,000rpm to prepare the metal nanoparticles. The size of prepared metal nanoparticle was found to be 3-80nm mostly. But when using leaf extract and root extract nanoparticles were found to be 10-20nm and 10-30nm respectively. Anticancer activity of prepared nanoparticles was measured using MTT assay. Silver ginseng nanoparticle exhibited cytotoxicity in 100μg/ml for A549 lung cancer cells, gold nanoparticles exhibited cytotoxicity in 2μg/ mL concentration for A549 lung cancer cells.	103
2	KR20180036951A	Inventor has prepared metal nanoparticles using extract of Siberian ginseng as active ingredients. Extraction has been done by hot extraction method. Siberian ginseng extracts of various concentrations were used for the synthesis of metal nanoparticles. 1mM silver nitrate (silver nitrate; $AgNO_3$) or geumyeom hydrate (gold (III) chloride trihydrate; $HAuCl_4 \cdot 3H_2O$) to each other was added to the extract having a different concentration, and each production temperature (~ 23°C, 40°C depending on and 80°C) and each manufacturing time to prepare the metal nanoparticles. Then, the reaction mixture was centrifuged for 20 minutes at 17000 rpm in order to obtain a prepared Sg-Sg-Ag NPs or Au NPs. MTT assay confirmed the cytotoxicity against breast cancer line MCF7 of prepared metal nanoparticle.	104
3	CN108014346A	Inventor has prepared dual targeting nanoparticles. Hyaluronic acid and octadecylamine and hyaluronate – octadecylamine (in combination) was dissolved in organic solvents in the presence of an activating agent. Methotrexate was added, reaction of methotrexate obtained - hyaluronic acid - octadecylamine conjugate, i.e. methotrexate prodrugs. Then methotrexate prodrug of deionized water was treated with ultrasonic ice bath that results to self-assemble double targeted nanoparticles within the range of diameter of 60 ~ 120nm. Hyaluronic acid acts as a targeting ligand, for nanoparticles and shows synergetic effects.	105
4	KR20180014429A	Inventor has prepared carbon nanoparticles using hydrothermal reaction. Average size of prepared carbon nanoparticle was found to be diameter of 2 nm to 20 nm. These nanoparticles are coated with PEG, PEI. The resultant carbon nanoparticles shows cytotoxicity to human cervical cancer line	106
5	CN107596384A	Inventor has prepared a self-targeted anti-cancer nano-particle. These self-targeted anti-cancer nano-particles are prepared by carboxylated metal oxide and an amido bond. Acetylated hyper branched polyethyleneimine is the active part which is bonded with Raltitrexed and has the mass content of 10 to 30 percent. These self-targeted anti-cancer nano-particles were loaded with a plurality of Raltitrexeds to form a multivalent system and shows high selectivity of cancer cells through strong bonding force of the receptor or multivalent system, and the toxicity of the Raltitrexed is utilized to specifically kill the cancer cells.	107
6	CN107281164A	Inventor has prepared EL PAMAM (G0) / HA and EL PAMAM (G1) / HAby using solvent exchange method. Prepared nanoparticle such as EL PAMAM (G0) / HA and EL PAMAM (G1) / HA on He La showed no significant cytotoxicity, cytotoxicity of A549 cells is stronger than in the He La cell cytotoxicity. A549 cells expression CD44 receptor, targeted drug erlotinib while nylon and non-small cell lung carcinoma A549 cells, it is toxic to A549 cells significantly increased.	108
7	CN107041876A	Inventor has prepared anticancer acetylshikonin nanoparticle. According to the inventor, acetylshikonin is loaded into graphene/mesoporous silica and hyaluronic acid is used for plugging holes. The hyaluronic acid drug-loaded nanoparticle enters into cancer cells release the acetylshikonin for killing the cancer cells with synergetic effects.	109
8	CN107158014A	Inventor has prepared co-assembled tumor targeting anti-cancer nano medicine. The carrier-free dual anti-cancer nano medicine is prepared from hydrophobic medicine ursolic acid, anti-tumor medicine doxorubicin in water through co-assembling. Prepared medicine shows the anticancer activity.	110
9	CN107375235A	Inventor has prepared a folic acid mediated antitumor drug super paramagnetic tumor targeted nanoparticle. A super paramagnetic iron oxide nanoparticle is used as the carrier. Polyethylene glycol-polyethyleneimine synthesized by high temperature decomposition method, and chemical method is used to grafted folic acid ligand on the surface of iron oxide. Then hydrogen bonding and electrostatic adsorption is used to loading anti tumor drug in to iron oxide nanoparticles then obtaining the folic acid mediated antitumor drug super paramagnetic tumor targeted nanoparticle. Inventor has finalized that, the prepared nanoparticles shows synergetic anti tumor effect of anticancer drug.	111

S. No.	Patent number	Work done	Reference
10	CN107823183A	Inventor has prepared TiO_2 nanoparticles to overcome multidrug resistance. Inventor used the following method: by forming blank TiO_2 nanoparticles effective pH gradient, the anthracycline anticancer drugs into the package TiO_2 nanoparticles prepared anthracycline was obtained TiO_2 nanoparticles. Present invention is simple with improved efficacy of anthracycline anticancer drugs and by wrapping techniques was used to overcome drug resistance. According to inventor present invention is simple, can delay the release of the drug in liquid culture, preparation of low material requirement, high encapsulation efficiency and effectively overcome MDR.	112
11	CN107758628A	Inventor has prepared nanoparticles using aqueous extract of Camellia plants and nano selenium from selenium. Inventor has used following method: extraction of aqueous extract of Camellia plants is prepared, then reduced sodium selenite Vitamin C from extract in aqueous reaction occurs sol nano selenium. Selenium removal fom vitamin C has finished by nano particles. *In vitro* model was used to determine anticancer activity of prepared nanoparticle of camellia extract.	113
12	CN107320459A	Inventor has prepared polymeric nanoparticles based on double-layer synergistic controlled-release drug delivery. The preparation method comprises the following steps: firstly, doxorubicin hydrochloride was embedded in oil phase of poly (N, N-dimethylaminoethyl) methacrylate, then loaded surface of oil phase with nitrosourea chloride, and then this system was embedding into aqueous phase and evaporating solvent to obtain polymeric nanoparticles based on the double-layer synergistic controlled-release delivery system. The prepared nanoparticles have achieved the controlled release of anticancer drug, and these used to treat cancer.	114
13	CN107929756A	Inventor has prepared amino wrapped porous silica nanoparticles as drug delivery system. These nanoparticles was dispersed in a drug solution, standing, centrifugation, and dried to obtain nanoparticle drug system. These prepared nanoparticles enable to release drug at high acidic condition. These nanoparticles are prepared by following procedure, potassium ferricyanide was dissolved in hydrochloric acid at 50-100 ℃ 15-20 hours, then centrifuged following by washed and dried to obtain nanoparticles. Prepared nanoparticles were used as drug delivery system.	115
14	CN107551277A	Inventor has prepared lipid poly-L-histidine hybrid nanoparticles (LPNs) encapsulating anti-tumor drugs with pH sensitivity. LPNs contain 50%-80% poly-histidine, and 20%-50% of lipid-PEG. Hydrophobic core of system consist poly-histidine and surface modified with PEG and tumor targeted peptide. The PEGylated lipid surface has properties like high stability, good biocompatibility, and long in-vivo circulation. At neutral condition, histidine core enables to encapsulate hydrophobic anti cancer drugs. Histidine is protonized in the tumor microenvironment and change negative to neutral and then drug release rapidly with effective anti tumor activity. Surface of the carrier may change as require for tumor targeting to improve therapeutic effect.	116
15	CN107397958A	Inventor has prepared carbon quantum dots for anti cancer drug carrier. These quantum dots are prepared through the effect of citric acid, sulfuric acid, and nitric acid, Then sorafenib an anticancer drug was loaded in to carbon quantum dots. Then another emulsification-solvent volatilization method was used to prepared drug loaded carbon quantum dots. Prepared carbon quantum dots nanoparticles were used to treat cancer.	117
16	CN107970453A	Inventor has prepared pectin nanoparticles with double folate targeted delivery. These nanoparticles were conjugated with polyethylene glycol, pectin, folic acid and pectin have linked with amino bond, combination of polyethylene glycol and anti cancer drug via ester bond ursolic acid, to give folic acid ursolic acid prodrugs, mixed with captothecin, and then prepared self assembled dual targeting nanoparticle. These nanoparticles were show good in vitro release experiments of pH response. Prepared dual targeting nanoparticles serves high yield, controlled rate, as novel drug delivery for anti cancer drugs.	118
17	CN107753435A	Inventor has prepared paclitaxel - phospholipid / albumin nanoparticles for cancer therapy. Inventor follows following steps: 1. Stock solution of paclitaxel, phospholipids, cholesterol and DSPE-PEG2000 2. Prepared paclitaxel liposome 3. Stock solution of bovine serum albumin and then Prepared paclitaxel - phospholipid / albumin complex nanoparticles. Preparation method overcomes the drug aqueous solubility problems. Formulation has not used cremophor to avoiding side effect of solubilizer. DSPE-PEG2000 was added to increase stability, high encapsulation efficiency, small particle size, uniform particle size of nanoparticles. Prepared nanoparticles have studied as effective anti cancer drug delivery system.	119
18	CN107137721A	Inventor has discloses methods of preparation and polyoxometallate anticancer nanoparticles. Polyoxometallates have high potential in cancer treatment as novel inorganic material but due to unstability and low aqueous solubility their uses in cancer treatment were limited. Inventors has used PLA-PEG2000, TPGS-COOH as coating material with biocompatibility to prepare a nanoparticles, folic acid was used to modified the surface of nanoparticles, and prepared polyoxometallate supported anticancer nanoparticles with long in vivo circulation, high targeting, low toxic effect and high stability. Prepared the polyoxometallate supported anticancer nanoparticles were used to cancer therapy with fully achieved effects.	120

S. No.	Patent number	Work done	Reference
19	CN107050051A	Inventor has prepared cuprous oxide nanoparticles of anticancer drug for treating gynecological tumors. *In-vitro* experiments of prepared cuprous oxide nanoparticles were inhibit proliferation of cervical cancer cells and endometrial cancer cells. *In vivo* experiment was proved tumor inhibition effect of prepared cuprous oxide nanoparticles equivalent to anticancer drug cisplatin with less side effects. Inventor has concluded that cuprous oxide nanoparticles have great potential to treat gynecological tumors.	121
20	CN107737347A	Inventor has prepared dual target pectin, pectin - preparing multi-arm polyethylene glycol anti cancer drug. Nano folate multi-arm polyethylene glycol-modified prodrugs coupling stroke drug and pectin was target with dual drug, mixed certain ratio of hydrophobic anticancer drug, to obtain dual function nanoparticle drug targeting. Used natural pectin has good biocompatibility, bioactivity, biodegradability, overcome low aqueous solubility, prepared nano drug delivery system have good particle size distribution, stable rate of drug encapsulation efficiency and good clinical application..	122
21	CN106668871A	Inventor has prepared photosensitive magnetic nanoparticle system enable to inhibited growth of breast cancer cells. Amiantion of magnetic nanoparticles Fe3O4-OA wrapped by oleic acid and activating carboxyl on a photo sensitizer, then condensation reaction of amino and carboxyl to grafting the photo sensitizer onto the surface of Fe3O4-OA carboxyl to obtain the photosensitive magnetic nanoparticle system. The photosensitive magnetic nanoparticle system has used to treating breast cancer photo dynamically in illumination condition, combination of breast cancer targeting and folic acid cell targeting of a magnetic field were inhibit growth of the breast cancer cells in a targeted manner. Prepared nanoparticles have properties of high slow release performance, dispersity, stability and uniformity with low toxic and side effect advantages. Inventor has realize, prepared system was a novel administration path combining magnetic targeting with nano technology with high-efficiency low-toxicity treatment effect.	123
22	CN107296794A	Inventor has prepared amphipathic non-steroidal anti-inflammation platinum nanoparticle. These nanoparticles consists comprises an amphipathic compound formed by the non-steroidal anti-inflammation drug and a platinum antitumor drug. Compared to others inventor prepared self assembled nanoparticle in aqueous phase. Without using the surfactant, amphipathic platinum compound can realize tumor tissue targeting with high permeability and low toxic effects of platinum drug. When these formulation enter in tumor site phagocytosis effect activated and releases two drugs under hydrolysis effect, anti-inflammation drug can restrain COX-2, platinum drug restrained the tumor cell proliferation and collaboration of these two drug achieve the target of tumor treating.	124
23	CN107243000A	Inventor has prepared drug-loaded hybrid nanoparticle. These hybrid nanoparticles were prepared by following methods. 1. Prepared an azide triacetone compound 2. Prepared propargylamine modified heparin sodium, 3. Grafted propargylamine modified heparin sodium into the azide triacetone compound 4. Prepared drug-loaded hybrid nanoparticle. These hybrid consist heparin as natural polymer with good biosafety and specific preparation process. Particle size of prepared hybrid nanoparticles has enhanced permeability and retention effect, passive targeting and high drug release. Prepared nanoparticles used for cancer therapy has good biocompatibility, low toxic effect with high safety.	125

Newly discovered anticancer drug approved by FDA

S.no.	Drug	Indication	Mode of action	Discovered by	Reference
1	Rucaparib (Rubraca)	For treatment of patients with deleterious BRCA mutation (germline and/or somatic)–associated advanced ovarian cancer who have been treated with two or more chemotherapies.	Rucaparib inhibits "the contraction of isolated vascular smooth muscle, including that from the tumours of cancer patients. It also reduces the migration of some cancer and normal cells in culture	Northern Institute of Cancer Research and Medical School of Newcastle University and Agouron Pharmaceuticals in San Diego, California.	126,127
2	Avelumab (Bavencio)	For the treatment of patient's ≥ 12 years of age with metastatic Merkel cell carcinoma. Avelumab is a PD-L1 blocking human immunoglobulin G1λ monoclonal antibody. This is the first FDA-approved product to treat this type of cancer.	Binds to the programmed death-ligand 1 (PD-L1), inhibits binding to its receptor programmed cell death 1(PD-1)	Merck KGaA and Pfizer and Eli Lilly and Company in Canada	128

S.no.	Drug	Indication	Mode of action	Discovered by	Reference
3	Niraparib (Zejula)	Maintenance treatment for adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.	Inhibitor of the enzymes PARP1 and PARP2	Tesaro, Waltham, massachusetts	129
4	Ribociclib (Kisqali)	In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.	Inhibitor of cyclin D1/ CDK4 and CDK6	Novartis and Astex Pharmaceuticals	130
5	Brigatinib (Alunbrig	For treatment of patients with metastatic anaplastic lymphoma kinase– positive NSCLC who experienced disease progression on or who are intolerant to crizotinib	Inhibitor of ALK and mutated EGFR	ARIAD Pharmaceuticals, Inc	131
6	Midostaurin (Rydapt)	For treatment of adult patients with newly diagnosed AML who are FLT3 mutation–positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.	Multi-targeted protein kinase inhibitor	Novartis Pharmaceuticals	(132
7	Durvalumab (Imfinzi)	For treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinumcontaining chemotherapy or who experience disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	Blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80 (B7.1	Medimmune/AstraZeneca	133
8	Rituximab and hyaluronidase human (Rituxan Hycela)	For adult patients with follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia	Three major independent mechanisms are 1. Antibody dependent cellular cytotoxicity 2. Complement mediated cytotoxicity 3. Apoptosis, subst panel illustrates a schematic view of CD20 structure and rituximab	IDEC Pharmaceuticals	134
9	Neratinib (Nerlynx)	For extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy	Dual inhibitor of the human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR) kinases	developed by Wyeth; Pfizer continued development up to Phase III in breast cancer, and licensed it to Puma Biotechnology	135-137
10	Daunorubicin and cytarabine (Vyxeos)	For treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes, two types of AML that have a poor prognosis.	Blocking the function of topoisomerase II	Ohio State University	138
11	Enasidenib (Idhifa)	For treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-2 mutation as detected by an FDA-approved test.	Inhibitor of IDH2	Agios Pharmaceuticals	139
12	Inotuzumab ozogamicin (Besponsa)	For treatment of adults with relapsed or refractory B-cell precursor ALL.	Binds to CD22 receptor	Celltech and Wyeth Pfizer	140

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S.no.	Drug	Indication	Mode of action	Discovered by	Reference
13	Tisagenlecleucel (Kymriah)	For treatment of patients ≤ 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse	Treat B cell acute lymphoblastic leukemia	University of Pennsylvania; and Novartis	141
14	Abemaciclib (Verzenio)	In combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression after endocrine therapy.	CDK inhibitor selective for CDK4 and CDK6	Eli Lilly	142
15	Bevacizumab-awwb (Mvasi)	Approved as a biosimilar to bevacizumab (Avastin), bevacizumab-awwb is the first biosimilar approved in the United States for the treatment of cancer.	Blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A)	Genentech	143
16	Copanlisib (Aliqopa)	For treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies	Inhibitor of phosphatidylinositol-3-kinase (PI3K)	Bayer	144
17	Gemtuzumab ozogamicin (Mylotarg)	Newly diagnosed CD33-positive AML in adults and for treatment of relapsed or refractory CD33-positive AML in adults and pediatric patient's ≥ 2 years of age. May be used in combination with daunorubicin and cytarabine for adults with newly diagnosed AML or as a stand-alone treatment of certain adult and pediatric patients.	Targets the membrane antigen CD33	Celltech and Wyeth	145
18	Axicabtagene ciloleucel (Yescarta)	For treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.	An anti-CD19 chimeric antigen receptor (CAR T) cell	Kite Pharma California	146

Conclusion

As summarized above, new scientific approaches serves advanced technologies and overcome various challenges i.e toxicity, absorption, tumor site targeting, solubility, drug resistance, dose requirement etc. The ultimate goal of developing new technologies should be change the way of cancer treatment and overcome the challenges. Development of nanoparticles drug delivery system is a future hope with great impact on cancer treatment approaches. Because researchers realize that nanoparticles drug delivery is able to controlled delivery of therapeutic payload provide a new way to treat cancer. Nanoparticles as drug delivery system are prepared to improve therapeutic and pharmacological properties of conventional drug delivery system. Drug molecule incorporated in nanoparticles offers controlled release and possibilities to targeting to tumor site as well as protection of drug from degradation. Drug conjugations with nanoparticles are more effective and selective and low toxic to healthy cells as well as required low therapeutic dose. Nowadays, various nanoparticles based drug delivery is currently under preclinical evaluation phases. Some of nanoparticle technologies have few limitations but these have possibility to improve with small modifications.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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