World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Smart nano particles-based drug delivery systems for cancer therapy

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World Journal of Biology Pharmacy and Health Sciences, 2026, 25(01), 385-402

Publication history: Received on 28 June 2025; revised on 10 January 2026; accepted on 26 January 2026

Article DOI: https://doi.org/10.30574/wjbphs.2026.25.1.0748

Abstract

Advancements in cancer research and treatment have yet to successfully reverse the ongoing trend of cancer being one of the most lethal diseases. The currently available methods such as chemotherapy and radiation therapy cancers come with low specificity, high toxicity, and treatment resistance. Cancer therapies necessitate a different approach. Nanotechnology solves these issues through selective spatial and spatial delivery of therapeutics. In this review, we analyse the advances made in cancer therapy development incorporating smart nanoparticles with special emphasis on polymeric carrier systems, virus-like carriers, carbon nanotubes, lipid and ceramic nanoparticles and metal-based nanoparticles. Each of these systems of nanocarrier exhibit unique physicochemical properties which can be used to enhance the drug bioavailability, circulation half-life, and biodistribution. The paradigm shift that we seek through the use of nanomedicine would profoundly alter the treatment of cancer through passive and active targeted intravenous delivery, as well as through photothermal, magnet, ultrasound, and photodynamic therapies. By employing such technologies, the hope is to create tailored cancer treatments that not only individualizes the process but also lessens the harmful effects of treatment.

Key words: Cancer Treatment; Nanoparticles; Nanomedicine; Controlled Drug Delivery Systems (DDS); Targeted Drug Delivery; Polymeric Nanoparticles; Dendrimers; Hydrogels; Polymeric Micelles; Virus-Based Nanoparticles; Biodegradable Polymers; Liposomes; Tumour Targeting; Chemotherapy Alternatives; Smart Drug Carriers; Stimuli-Responsive Nanoparticles; PLGA Nanoparticles; Sirna Delivery; Drug Encapsulation; Cancer Nanotechnology

1. Introduction

1.1. Cancer

The term cancer is used for a set of diseases that lead to the growth of a malignant tumour. It is caused by uncontrolled and unregulated cell division. It is one of the most serious diseases in the world and is one of the leading causes of mortality. It affects every person in the world, which is why there are countless pieces of information about cancer. In 2024, the number of new cancer cases is expected to be over 20 million according to estimates from the American Cancer Society. This is a jump from what was reported in 2022, with 20 million new cases. If the trend persists, the number of cancer cases is bound to rise by 77 percent with a projected new case count reaching 1.8 million by 2050. The most frequent form of cancer diagnosed in MEN differs from region to region, however, some of the common ones are:

- Prostate Cancer: This is the most prevalent type of cancer in men particularly over the age of 50. 1 in 8 men is expected to be diagnosed with prostate cancer at some phase of their life, according to the American Cancer Society.

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- Lung Cancer: The death rate pertaining to lung cancer is substantially high in men. Smoking and second-hand smoke are the most likely reasons for this.
- Colorectal Cancer: This type of cancer affects the colon or rectum and it is more common above the age of 50 in men. Some of the risk factors include family history, alcohol, tobacco, and a diet consisting of excessive fat and processed meat.
- Oral Cancer: Also called mouth cancer, oral cancer is a major issue amongst Indian men who are prone to the use of tobacco.
- Bladder Cancer: Men are significantly at a higher risk of suffering from bladder cancer in comparison to women. The symptoms include blood in the urine and pain during urination.

Here are some of the prevalent kinds of cancers affecting the female population across the globe:

- Breast Cancer: Out of every twenty-three new cases of cancer globally, one is breast cancer, making it the most prevalent cancer in women. (Source: International Agency for Research on Cancer)
- Cervical Cancer: This is the second most diagnosed cancer in the female population of developing countries. Cervical cancer is caused primarily by Human Papillomavirus (HPV).
- Colorectal Cancer: This type of cancer is typically found in women older than fifty and affects their rectum or colon.
- Uterine Cancer: Endometrial cancer, commonly called Uterine cancer, affects the internal surface of the uterus and primarily impacts women over 50.
- Ovarian Cancer: Often diagnosed when the disease has advanced, ovarian cancer affects a woman's ovaries.

1.1.1. Conventional therapies used to treat cancer

The most common approaches taken in treating cancer are grouped under a few modalities:

- Surgery: The technique that deals with the cutting and removal of tumours from the body. Works best in the early stages of cancer Takes out unhealthy tissues Has different levels of intensity
- Chemotherapy: Treatment for cancer using special drugs. Particularly for cells that reproduce uncontrollably. Administered by way of:
    - Tablets
    - Injections
    - Other forms of IVs.
- Also used in the pre and post - sature stage.
- Radiation therapy: Treatment for cancer by destroying cells using high energy rays. Accurately aimed towards parts of the body infested with cancer cells. Can be placed outside or within the body. Is usually combined with chemotherapy and other methods.
- Targeted therapies: Diminishes the strength of normal cells by reducing the characteristics of the cancer cell. Focus on damage expenditure.
- Immunotherapy: This works by clearing the way for the body to do what it is naturally capable of doing. Most recent technique to target and defend off cancerous cells using the body's defence mechanism.

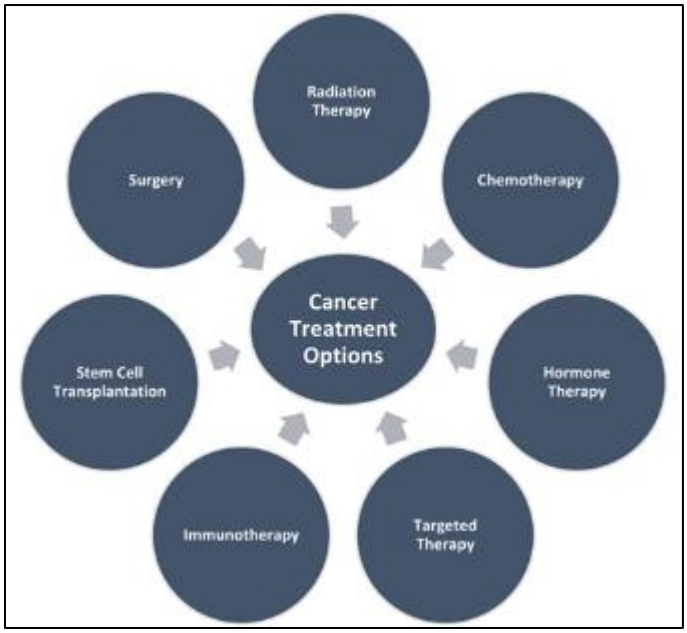

Figure 1 Different cancer treatment therapies

1.2. Some disadvantages of conventional therapies

Traditional cancer treatment methods such as chemotherapy, radiation, and surgical procedures can relieve and treat the disease. However, there are a number of drawbacks, such as:

- Side Effects: Routine treatments can elicit a number of health complications like mental exhaustion, nausea, vomiting, baldness, pain, and aggravated risk of infection – all of which can severely affect the patient's life quality.
- Non-specificity: Medical procedures such as chemotherapy can harm cancerous and healthy cells. This is especially true for tissues such as hair follicle cells and the gastric tract, where rapid cell division occurs.
- Resistance: Certain types of cancer can build a resistance to traditional therapies, resulting in the method becoming less potent with use. This necessitates the use of higher dosage or different treatments, all of which can have their own negative effects.
- Emotional and Psychological Impact: Living with the cancer diagnosis and going through the treatment process are both harrowing experiences that can have strong mental consequences. The process of therapy can worsen the anxiety and depression faced.
- Long Recovery Time: Recovering from surgery or the effects of chemotherapy or radiation often takes a substantial amount of time.

1.3. Why should we divert towards nano particles

Controlled Drug Delivery Systems (DDS) offer a precise solution to the drawbacks of conventional drug delivery systems especially with cancers treatment.

1.3.1. Benefits of Controlled DDS

- Focused Delivery: Controlled DDS can enhance the directed delivery of the chemotherapeutic agents to the tumour site thus increasing the concentration of the drug to the cancerous cells and decreasing the toxicity effect on healthy cells.
- Increased Effectiveness: Focused DDS can enhance the effectiveness of chemotherapeutic agents by increasing the therapeutic efficacy.
- Decreased Toxicity: With focused DDS, the damaging effects on healthy cells are decreased, thus reducing and avoiding adverse effects and improving quality of life of the patient.
- Protection from degradation and clearance: Focused Controlled DDS may be used for delivering proteins, gene therapy, and RNA interference since they can protect the drugs from degradation and clearance.
- Improved delivery of nucleic acids: Controlled DDS can protect DNA and siRNA from being taken up by reticuloendothelial or other tissues and enzymatically degraded.

2. Nanotechnology and nano medicine

The progress of nanotechnology has turned these nanoparticles into a good option for targeted drug delivery systems. Nanoparticles usually refer to particles ranging between 10 to 1000 nm in diameter. As a drug delivery system, nanoparticles can enhance the effectiveness of the drug by increasing its 'shelf' presence, increasing the solubility of some drugs, or releasing it in a controlled manner. Stimuli responsive nanoparticles can also lower the toxicity of caged drugs and control their distribution in the body. Liposome nanoparticles are the earliest type of drug delivery systems. They were first used in the 1960s to deliver drugs and proteins. Since then, more and more materials are fabricated into nanoparticles and used as DDSs (Figure 1). As reviewed by Bobo et al., 2016 FDA has approved 51 holdings on nanoparticles and 77 products are still under clinical trials. Most of these approved products, however, are polymeric and nanoparticle drug delivery systems. Initially it can be assumed that more complicated structures such as micelles, metallic spears and protein can be used more as a drug carrier.

Nanotechnology refers to an upcoming discipline having applications in the design, characterization, and manipulation of device structures and systems by altering their size as well as shapes on the atomic, molecular, and supramolecular scale. With the advancements in nanotechnology, new nanomaterials possessing different physiochemical properties (higher surface-to-volume ratio) are synthesized which also make them suitable for biomedical applications. This may include the use of nanostructures in screening, diagnosis, or treatment of diseases which is termed as "nanomedicine," a new branch of science and engineering that has the potential to transform not only an individual, but also a population's healthcare. Though with ordinary treatments, the aim is to target diseased cells more rapidly than healthy cells, Nanomedicine seeks to combine new technologies with genomics and proteomics to form an improved approach towards treatment of a broader range of diseases by customizing the form of treatment.

3. Classification on nanoparticles

- Polymers Based Drug Carriers
- Virus – Based Nano Particles
- Carbon Nanotubes
- Lipid Based Carriers
- Ceramic Nano Particles
- Metal Based Nano Particles

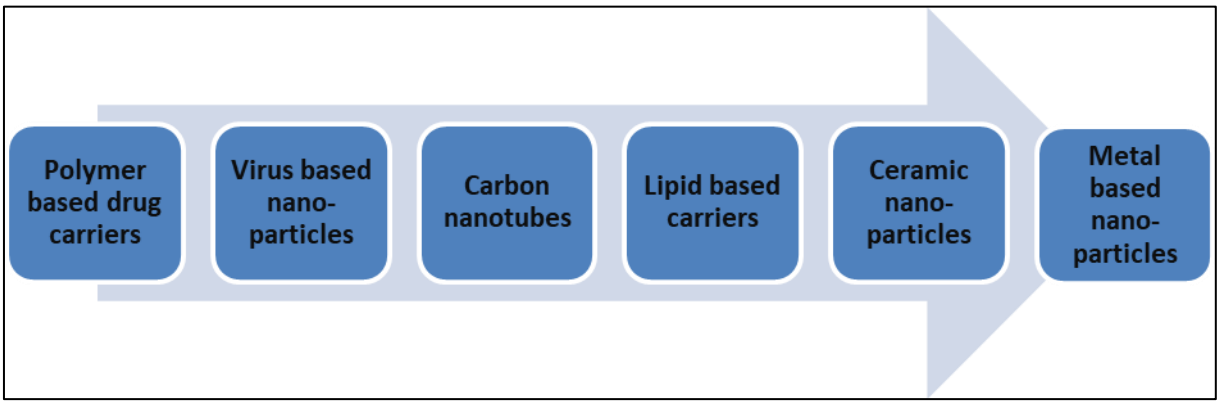

Figure 2 Classification of nano particles

3.1. Polymer based drug carriers

3.1.1. Polymers Can Be Used as Pharmaceutical Carrier Modulators

A large number of various polymers have been studied to develop therapeutic carriers which include polymer-protein carriers, conjugates of drugs and polymers, and supramolecular drug delivery systems. However, a handful of these Polymers have been accepted in clinical practice. As expected, synthetic bio-reversible polymers are generally favoured because of great bioavailability and encapsulation, controlled release, and low toxicity.

The incorporation of polymeric substances presents several advantages. One of the most important is the incorporation of some polymer chains that increase the water solubility of hydrophobic drugs altering the biodistribution pattern.

This advantage could also be found with the use of mucoadhesive materials as chitosan, because it increases intimacy of contact between the drug-containing polymer and cell membranes. In cancer therapy, site-specific drug delivery nanocarriers are being developed, where molecules that enable the reception mediation encapsulation were located at the external part of the nanoparticles. More recently, a lot of attention has been focused on the creation of novel multifunctional nanocarriers in the form of molecules able to co-deliver multiple components, target the delivery of the drugs to specific tumour cells, and release the therapeutic agent. Different types of polymeric drug carriers have been evaluated as possible drug delivery systems for cancer treatment, which include polymeric nanoparticles, dendrimers, hydrogels and micelles. Here follows a summary of these types.

3.1.2. Polymeric Nanoparticles

They are made by the polymerization of nanoparticles based on the biocompatible and biodegradable polymers and were synthesized by a variety of methods depending on the application and on the drugs to be used. These particles are defined as solid-matrix systems in which the drug is either dispersed within the polymeric matrix or covalently linked to the polymeric backbone. Polymeric nanoparticles have been developed to encapsulate both macromolecules like nucleic acids, proteins as well as small hydrophobic or hydrophilic drug molecules. To evade recognition and removal by the mononuclear phagocyte system and consequently achieve prolonged circulation time, protective polymers such as poly (ethylene glycol), poly (ethylene oxide), poly (acrylic acid), or dextran are usually used to coat the nanoparticles. However, this layer of protection should not be very dense because the cellular uptake would also be hindered.

Different types of polymeric nanoparticles such as linear and star polymer structures, cylinder polymer brushes, macrocyclic polymeric brushes and hyper branched polymers are used in the treatment of cancer as reviewed by Wang et al.

Chitosan, Heparin and Albumin are all natural polymers that have been used in FDA approved drug delivery systems. For instance, low molecular chitosan nanoparticles covered with a hydrophilic shell of methoxy polyethylene glycol and a core of cholesterol to improve drug solubility showed good efficacy of encapsulation and delivery for Paclitaxel. In addition, silk fibroin nanoparticles (a natural protein polymer) gained great interest in the drug delivery for anti-cancer treatment. Although there is great necessity for drug-delivery enhanced natural polymers, heterogeneity in cost, structure and manipulation make them far less preferable than purely synthetic polymers.

There are many nanoparticles that are still in preclinical or clinical stages. For example, modifications have been made to certain nanoparticles containing hydrophilic 4 copolymers such as poly (lactic-co-glycolic acid) (PLGA) and poly (alkyl cyanoacrylate) (PACA) to allow their concurrent use with chemotherapeutics and inhibitors of the Multidrug Resistance (MDR) mechanism for targeting cancer types. Another example involves nanoparticles constructed with a core of polycaprolactone with an outer hydrophilic shell of polyethylene glycol capable of encapsulating and delivering cisplatin for anti-tumour therapy.

There are numerous nanoparticles that still have to complete preclinical or clinical studies. These include the modification of some nanoparticles that are composed of hydrophilic 4 copolymers like poly (lactic-co-glycolic acid) (PLGA) and poly (alkyl cyanoacrylate) (PACA), which now can be used in combination with chemotherapeutics and inhibitors of the Multidrug Resistance (MDR) mechanism for specific cancer types. Another example includes the construction of nanoparticles with a core of polycaprolactone and an external hydrophilic polyethylene glycol shell for encapsulation and delivery of cisplatin for anti-tumour therapy.

3.1.3. Hydrogels

Hydrogels are polymeric networks that bear water with diverse structures. They can be classified into those which possess linear structure, and those which have polymeric network with three-dimensional covalent crosslinking. The covalent linkages between the chains result in modification of the hydrogel properties such as swelling capability, elasticity, and drug loading ability. Number of hydrogels include those that are capable of swelling from 10 –20 % an arbitrary lower limit, up too thousands of times their dry weight in water. Such transformations are made possible with the introduction of hydrophilic groups into their structure. These features make them very promising for use as potential drug carriers in the form of micro- or nano-particles. Some hydrogels exhibit fluid transport features and stimulus responsive (e.g. pH, temperature, and salinity or light) characteristics. Various synthetic hydrogels are being investigated for their anticancer properties. Some have been used to model tumour vascularization micro environments while many others for drug delivery. For instance, Cheng et al. developed poly (y-ethyl-l- glutamate)-poly (ethylene glycol)-poly (y-ethyl-l glutamate triblock copolymer based thermosensitive hydrogels for localized and prolonged delivery of paclitaxel (PTX) in vivo. The results showed that the use of the PTX incorporated hydrogels could effectively suppress the tumour proliferation, and did not result in obvious side effects [41]. More recently, Seo et al. have prepared

injectable intratumorally hydrogels based on a diblock copolymer poly (ethylene glycol) and polycaprolactone (MPEG-b-(PCL ran-PLLA)) containing 5-fluorouracil. A single injection of this delivery system was effective in inhibiting tumour growth when applied locally to the tumour.

3.1.4. Dendrimers

Dendrimers are synthetic polymers that are highly branched and made up of an initiator core with many subsequent active layers. Each layer is termed generation and they are composed of specific repeating units, with the core signified as generation zero. Dendrimers are perfect candidates to make 'smart' nanocarriers for biomedical purposes due to the very specific molecular structure they possess, and the large number of functional groups that can be incorporated in specific locations. They have found usage as antimicrobial and antiviral drugs, in tissue engineering, drug delivery, and even gene transfection. Another interesting feature is in fact that bioactive agents can be either encapsulated in the core of the dendrimers or can be chemically bound or physically adsorbed to the surface of the dendrimers. In this regard, Ren et al. created a poly (amidoamine) PAMAM dendrimer that works as a substrate for simultaneous delivery of genetic material and a 5- fluorouracil 5-FU. That is, 5-FU was encapsulated into the cavities of the dendrimer core which is connected via hydrogen bonds, whereas an anti-sense microRNA miR-21 was complexed to the surface v.

3.1.5. Micelles

Polymeric micelles are made by self-assembly technique with block copolymers that are defined by two or more polymeric chains which differ in their hydrophilic nature. These copolymers are able to form a core shell structure by themselves in water. The core is formed by hydrophobic blocks while the shell consists of hydrophilic blocks. Any hydrophobic drug can be included in the core.

As compared to other surfactant micelles and liposomes, polymeric micelles micelles are much more stable in blood streams. This is due to the fact that co-polymers used in forming shell structures of the micelles have high critical micelle concentration. Because of such distinctive features, polymeric micelles have been shown as excellent drug carriers for cancer treatment and tumour imaging [54-56]. Further, some polymeric micelles can now be made with pH-sensitive characteristics aiding in better drug release during anticancer therapy. [57, 58]

According to Wang et al., micelles loaded with paclitaxel and targeted with MCF-7 cytolytic phage protein had unique binding characteristics [59]. Ke et al. developed micelles with thioridazine which reportedly kills cancer stem cells and doxorubicin as a much-needed combination therapy to breast cancer [60]. Yang et al. made mPEG-b-PDLLA micelles with docetaxel and these showed marked metastasis inhibition of 4Ta murine cells in mice lungs. Micelles were shown to internalize in 4T1 cells by endocytosis which inhibited tumour metastasis [61]. Finally, Hu and coworkers studied the complete regression of fusiform poly mares with crossed-linked thermosensitive polymeric micelles containing docetaxel. This was achieved through covalent binding using cleavable ester bonds [62]. In vivo experiments with docetaxel micelle complexes proved their efficacy in drastically reducing and inhibiting MDA-MB-231 tumours in mice after a single intravenous injection. The data presented proved encouraging since it could help in the development of a new cancer treatment technique.

3.2. Virus based nanoparticles

Viruses have the ability to be referred to as living nanoparticles due to the core-shell structure they possess. Owing to the infectious nature, the core is the most crucial part surrounded by a shell made of proteins or lipid membranes. They come in various distinct shapes like icosahedrons, spheres and tubes ranging from 10 nm to over a micron in size. These can be isolated shortly after putting the eukaryotic cell coat-proteins into action, or they can be built in vitro using coat-protein subunits extracted from any recombinant host, which ranges from mammalian cells to even bacteria. The strongest feature of virus-like particles is their constancy in form, ease of modification, and biocompatibility. For this reason, they have been used widely for the delivery of vaccines, medications, and even gene therapy because of their powerful gene-transfection and receptor binding capabilities. But sadly, many drawbacks have been encountered while trying to use them during clinical therapy.

Different substances can be incorporated into virus-like nanoparticles through straightforward supramolecular self-assembly and disassembly processes. It has been shown in the specialized literature that, these kinds of assembly processes are usually functionalized by packaging genetic material or other supramolecular structures like DNA–mixing liposomes or micelles. This is why the extension of these virus-like nanoparticles for the encapsulation of anti-tumour drugs can be imagined, but it is, however, rarely done at present. Nonetheless, the viral capsid, once it is formed, enables the delivery of drugs via the capsid that has been covalently attached to the chemotherapeutic molecule. In this case,

reactive groups must exist in the protein cage. Following this chemical attachment procedure, doxorubicin-loaded virus-like nanoparticles have been developed by Aljabali et al. and Zhao et al. [64, 65].

In reality, in the case of anti-cancer treatments, the focus of attention is not on the drug-delivery capability that these viruses might possess.

This means that the use of viruses will not only depend upon their ability to stimulate the immune system of the patient but also upon the viral capability of cell lysis, which occurs following infection of a tumour tissue. Oncolytic viruses have been engineered to reproduce within cancer cells, to facilitate the destruction of the cells by triggering strong immune responses, including cell lysis and apoptosis.

More and more data indicate that the controlled infection of the tumour's surroundings has the potential to trigger an 'inflammatory storm' that will activate the non-specific and specific immune responses to tumours. More recent and comprehensive coverage on this topic can be found in references. In the specialized available literature, the family of the vaccinia virus is the most novel and most likely to be applied to cancer therapy. Virus-like nanoparticles exhibit growing potential for the imaging of tumours. However, this issue will not be addressed in the current review.

3.3. Carbon nano tubes

Carbon nanotubes, or CNTs, are cylindrical nanostructures of carbon. Nanotubes can be created in such a manner that the ratio between length and diameter can reach up to 28,000,000:1 [71]. These single-layered rolls of graphene sheets are what makes up the CNTs. These rolls of graphene sheet come in two forms: single-walled (SWNT) or multi-walled (MWNT), which forms when several layers are rolled into concentric cylinders [72].

CNTs preserves both stiffness-flexibility and electric conductivity. Even though these properties come hand in hand with CNTs, it is worth mentioning that nonfunctionalized CNTs are soluble and cytotoxic. You may learn more about the how harmful CNTs can be by searching [73, 74]. In short, CNTs can have toxic effects in the body ranging from the cellular level to the whole-body. Not to mention that toxicity heavily depends on a couple determinants: I) CNs length, longer the CNT, stronger the bio-incompatibility, ii) surface hydrophobicity, small hydrophilic groups on the CNTs improve biocompatibility, iii) lack of any aggregation process, the higher the degree of individualization of the CNTs, the higher the excretion in urine.

The previous sections highlighted how functionalization of the CNT surface with water-soluble and biocompatible materials increases its biocompatibility and solubility in water. Functionalized carbon nanotubes have been investigated for various biomedical applications including some like carriers for proteins, nucleic acids and drugs [75-77]. The delivery of anticancer agents using CNTs may be due to the unique physicochemical features of carbon nanotubes that make them hard to substitute, mainly a strong ability to penetrate multiple biological barriers through pierce-like (needle structure) mechanisms. Targeted drug delivery using CNTs is one of the intensively investigated topics in different research groups nowadays. In this regard, the in vitro delivery of paclitaxel attached to single-walled CNTs was observed to be more effective in suppressing tumour growth than paclitaxel alone [78]. Also, Liu et al. have shown that targeted therapy against EGFR over-expressed colorectal cancer cells may be achieved with the control release of chemotherapeutic drug 7-Ethyl-10-hydroxy-camptothecin (SN38) from SWCNTs conjugated with the antibody C225, suggesting that SWCNT may be suitable carriers for targeted therapy.

3.4. Lipid based drug carriers

3.4.1. Liposomes

The aqueous component is enclosed in single or multi-layered lipid membranes. Liposomes are lipid-based vesicles [80]. Because of their distinct attributes, liposomes have gained prominence as one of the initial drug delivery systematics for Nanoparticles. These attributes include: (a) tolerance and lack of biological activity out of specific patients and without any antigenic or toxic side effects; (b) enables blood persistency with stealth liposomes augmenting surface pegylation; (c) modification of the liposomes' surface attributes which enhances surface area gives controlled freedom to physical and chemical properties, allowing [81] coated multifunctionalized liposomes with polymers and other ligands to achieve specificity for certain type of cells [82]. Overwhelming majority of the active targeted studies are controlled by immunoliposomes with monoclonal antibodies or antibody fragments attached to the surface of the liposomes [83]. Both hydrophilic and lipophilic therapeutic agents can be encapsulated within the different structural compartments of the liposome, which include internally contained water, phospholipid bilayer, and the bilayer interface. The various targeted formulations need careful drug dosages as the rates of delivery differ [83].

Considering the 'first generation' of nanocarriers, liposomes are the most widely used and clinically tested drug delivery systems with the best results. In this context, Doxil, a pegylated liposomal formulation of doxorubicin is the first approved liposomal doxorubicin nanocarrier in 1995 by the US FDA [84]. It was indicated for the treatment of AIDS associated Kaposi's sarcoma. Moreover, in 2012, Marqibo, a liposome of egg sphingomyelin and cholesterol was used for the treatment of acute lymphoblastic leukemia [85]. Besides these two compounds, only around 10 liposomal formulations have been approved for clinical use and half of these are for the delivery of anticancer drugs with reduced side effects [83, 86]. Most of them are however in clinical and preclinical trials [81], with preference for the therapy of different types of cancer and many of the trials involve encapsulating nucleic acids like plasmids or siRNA.

The latest trends have focused on the development of multifunctional liposomes, improving the limited properties of the conventional ones— that is, low stability and targeting properties and limited control of the release profile [81, 87]. A PEGylated version of neutral-lipid-based nanoliposomes has shown promise as highly effective and safe delivery systems for systemic use of siRNA therapeutics [88]. Taking advantage of the subacid environment typical of tumour tis- sues, several pH-responsive nano systems have been developed for an efficient delivery anticancer drug inside tumour cells. Phosphatidylethanolamine-based pH-sensitive liposomes surface modified with a cell penetrating peptide (RGD peptide) have been used to enhance the effectiveness of docetaxel treatment, showing good pH sensitivity with higher cytotoxicity and cellular uptake ratios [89].

Octylamine-graft-poly aspartic acid has also been bound onto liposomes and the same pH sensitive property system has been attained.

The architecture of grafted systems strengthens the drug carrier's stability and elevate the tumour-cell toxicity due to the rapid release of the antitumor drug cytarabine which is bonded to octylamine and is present in an acidic medium [90]. Also, temperature sensitive liposomes have been developed. The last one is an example, it is a sterically stabilized liposomes with a triple functionalization: PEGylation, thermosensitive chains and specific targeting by the surface conjugation of the antibody Herceptin. This system holds into the core a hydrophobic cytotoxic drug, Docetaxel, but its immediately released above 40ºC [91].

3.4.2. Solid lipid nanoparticles

Müller et al. and Gasco et al. were the first to make solid-lipid nanoparticles back in the 1990s. SLNs, or solid lipid nanoparticles, fall between 40 nm and 1000 nm in diameter. They consist of a matrix of solid lipids that is encapsulated by a bio compatible and biodegradable polymer and stabilized by surfactants. These lipid cores stay solid at ambient and physiological temperatures. There are many advantages of using SLN systemically as drug carriers. They include ease of manufacture, high tolerance and excellent biocompatibility. SLNs use solid lipids instead of phospholipids so there is no need for organic solvents. Additionally, release of hydrophilic and hydrophobic bioactive compounds is proved, as well as physical stability combined with the potential to develop alternative routes. For nanocarrier drugs, SLN can be used instead of ordinary parenteral administration. On the contrary, there are disadvantages such us low drug loading capacity of SLN compared to polymers and transformation of the drugs during the storage as well as uncontrolled release of the drugs from the carry systems.

Positive and promising results have been achieved after evaluating various anticancer drugs such as etoposide, methotrexate, idarubicin, paclitaxel and docetaxel, or edelfosine by incorporating them into SLN. These integrations have caused a remarkable enhancement in overcoming many issues observed in the traditional therapies. These SLNs and NLCs, unlike their intravenous counterparts, had a low tumour uptake efficiency. As a result, there has been great interest in the possibility of using these carriers to replace other NLCs because they can be used in other ways, such as pulmonary, oral, ocular and, especially, dermatological routes These Carriers are now a Noteworthy Focus for a wide array of studies. Several taxations have been directly delivered into the lungs through inhalation with the NCL in the form of a multi-functional device.

These nano - carriers have also been effectively bonded with siRNA, which helps in evading drug resistance, followed by targeting with a synthetic hormone that precisely identifies highly expressed receptors in lung cancer cells. The molecular mechanism of SLN and nucleic acid assembling process is currently being researched for a better understanding of this process and such how it releases the enclosed nucleic acids inside the cells. SLN have also proved to significantly decrease the gastrointestinal toxicity of certain antineoplastic drugs.

It has previously been verified in vivo by performing oral dosing on mice. As with other nanocarriers, hydrophilic polymers or surfactant coatings enhance the stability characteristics of the NCL and SLN. SLN that are chitosan coated exhibit great potential for oral delivery of hydrophobic medicines [105] while pegylated NLC containing Amotoine-B

have been noted to for the first time enhance the cytotoxic activity of this compound towards human colon and liver cancer cells in a dose and time dependent fashion because of the incorporation of PEG into cell membranes [106].

3.4.3. Lipid nano emulsions

Lipid based nano emulsions are colloidal dispersions of oil and water where the dispersed phase takes the form of nanoparticles and is stabilized in water (dispersed phase) by surfactants and co-surfactants which are self-assembled on the oil and water interface. Emulsions are usually classified into two main categories: microemulsions and nano emulsions.

These latter are emulsions with a mean droplet diameter on the nanometer scale and generally composed of a dispersed oil phase within a continuous aqueous phase having a radius of less than 1000 nm, although some authors consider 500 nm as the upper limit, while other authors place the cutoff at 200 nm, or even 100 nm. However, it is generally accepted that droplet diameters in nano emulsions are less than ∼200-300 nm in size, and thermodynamically it is a non-equilibrium state which needs to be stabilized by alteration of the attraction–repulsion potentials, for example, by introduction of the surfactants. Nevertheless, the kinetics of destabilization is so slow that they can be considered stable from this point of view in a different way to microemulsions which can reach up to 1 um in size as they are thermodynamically stable.

Oily Nano capsules, is what the others refer to nano emulsions as. This is due to the fact that, from a morphological perspective, they are made up of an oily core surrounded by a spherical polymeric shell (a thick steric barrier encloses the droplet interface) [113]. Some authors, however, do not use the term nano capsule for structures with a softer core that is surrounded with a tougher polymeric shell prepared by interfacial polymer- r. nano deposition [115, 116]. Nevertheless, both types, lipid nano capsules, and lipid nano emulsions, possess simultaneously characteristics of polymeric nano capsules having a lipid core micelle and a shell made from a mixture of phospholipids and surfactants [117]. Contemporary research focuses on the usage of nano emulsions for parenteral administration, with positive outcomes. Various examples include the tocotrienol-rich fraction of vitamin E that encapsulated lipid nano emulsion has been employed to deliver concurrently for its anticancer properties [135].

Other promising outcomes have been observed with anti-lung cancer PEGylated LBT–oleic acid ionic complex nano emulsions. The nano emulsions showed increased circulation time of LBT in blood and decreased concentration of LBT in heart, liver, and kidney with greater growth inhibiting activity. The PEGylated LBTO nan emulsions unimproved survival and showed prolonged captivity compared to free LBT [136]. Targeted delivery systems that are aimed towards a particular tumour region or specific tumour cells have been developed using several ligands and biomolecules onto the surface of lipid nano capsules. Folate mediated targeting of polymeric anti-tumour drug and gene nano emulsions is reported when conjugated with folic acid. In this manner, improved anti-tumour activity of the nano system has been shown with the use of folate chitosan conjugate covering the lipid core shell nano capsules [137].

Targeting ligands such as monoclonal antibodies permit the formulation of lipid immune nano capsules with the conjugated specific antibody molecule onto the nano capsule surface.

3.5. Ceramic nanoparticles

Ceramic Nanoparticles are generally made from inorganic materials such as hydroxyapatite, zirconia, titania, alumina and hydroxide. Other materials such as metal oxides and metal sulfides can be used as well. They have a core that are generally porous and bio-inert. Additionally, these have multiple functions and can be used for drug delivery and aid in cancer therapies. Some of the reasons that make ceramic nanoparticles useful for controlling drug delivery are: simple conditions for preparation, high stability, high load capacity, ease of incorporation into different systems, and multiple routes of administration, such as oral or inhalation. They also have the advantage of none swelling, no variation in porosity, protection from microbial degradation, and being resistant to vulnerable attacks. Moreover, the presence of a negative charge can functionalize them easily. Furthermore, it is possible to design a system smaller than 50nm, that can help escape the RE System.

By means of photoexcitation or ultra-sound processes, Titania nanoparticles are used in in vitro studies for different human cancer cells. Some researchers have successfully completed the design and synthesis of hydroxyapatite nano (HA) particles that can be used in bone regeneration and other applications. For instance, HA nano particles have shown anti-proliferative and pro-apoptotic qualities on hepatic carcinomas. Increased potency in tumour suppression was demonstrated when camptothecin-loaded mesoporous silicate nano particles (d=100-130 nm) coated with folic acid were used on two different human pancreatic cancer xenografts on mice [143]. However, these bioenergetic systems

do have a disadvantage; that is, the ceramic nanoparticles are not biodegradable and thus can cause accumulation in the body with dangerous effects [145, 148].

3.6. Metal based nanoparticles

3.6.1. Nanoparticles based on metals

Nanoparticles based on metal cores can enable the creation of multifunctional systems bringing together drug delivery and imaging with magnetic response, which incorporate theranostic systems where therapy, diagnosis, and imaging occurs simultaneously [149]. Metal nanoparticles can be fabricated in very small scales (around 50 nm), thus due to the large surface area, there is the ability to carry a relatively higher dose of drugs. For AuNPs, gold nanoparticles have gained attention because it is bio- compatible, easy to synthesize, characterize, and surface modify. Presence of surface plasmon resonance (SPR) bands are responsible for most of their phenomenal large absorption and scattering cross-sections which are 4 to 5 orders of magnitude greater than those from conventional dyes [150]. Therefore, gold nanoparticles are novel agents under evaluation for biological sensing, drug delivery, and cancer therapy [151]. Recently it has been demonstrated that AuNPs do inhibit the proliferation of cancer cells by blocking MAPK-signalling and inversing epithelial-mesenchymal transition (EMT) in cancer cells through reduction in secretion of a number of proteins involved in EMT. As a result, inhibitions of tumour growth and metastasis in two separate orthotopic models of ovarian cancer were observed [152].

Presently, a wide range of other metal nanoparticles and multi-functionalized hybrid surface particles such as platinum, silver, and palladium nanoparticles have been made for drug delivery purposes. Researchers have also studied quantum dots, which are fluorescent semiconductor nanocrystals, for drug delivery and imaging [162]. Because quantum dots are very small, they have a unique chemical structure and incredible optical features [163]. The anti-cancer medication epirubicin was linked to Iron oxide nanoparticles for delivery and imaging purposes in a tumour-bearing rat brain model. In this instance, drug delivery was conducted using magnetic targeting with promising results [164]. In lanthanide oxide nanoparticles, docetaxel delivery and cell imaging have been combined. This terasnostic system has a cytotoxic effect against human cervical carcinoma cells and optical imaging due to the internal luminescence of the nanoparticles [165]. PLGA nanoparticles that contain the anticancer drug busulfan along with inorganic agents, for example, iron oxide nanoparticles or manganese-doped zinc sulfide, allow the drug and its delivery mechanism to be monitored through both in vitro and in vivo imaging [166].

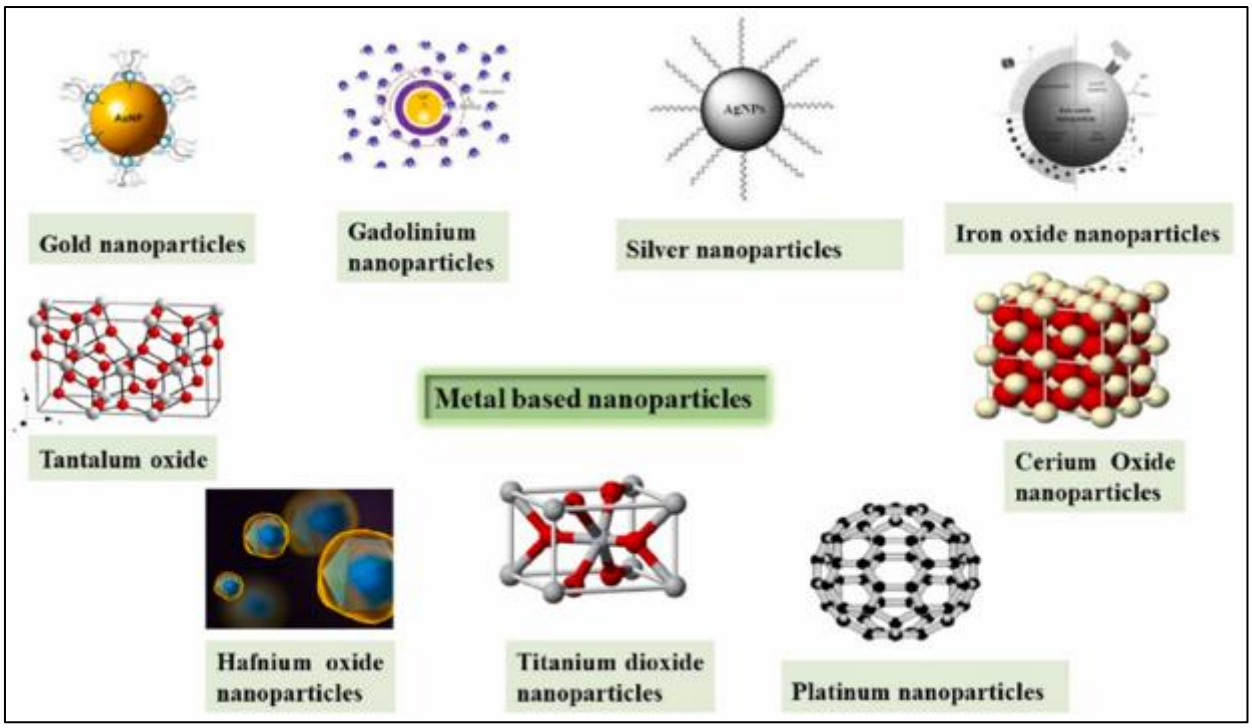

Figure 3 Different examples of metal-based nanoparticles

4. Drug delivery stratagies

In the context of curing malignancies, one of the foremost goals of nanomedicine is to remedy the problems posed by classical methods of chemotherapy, such as, firstly, ensuring any drug administered to a patient does not result in any adverse side effects that arise from uncontrolled drug action on actively dividing cells, both normal and tumoral. Secondly, ensuring that the cytotoxic effectiveness of the drugs utilized is not diminished because of insufficient quantity of active material at the region of interest. As such, drugs should be focused to the tissue or organ of concern, and not allowed to passively circulate within the body. The creation of broad therapies that specifically react with the body parts that are needed for change allows the usage of metamaterials. This subsequently makes it possible to lessen the size of the negative impacts by providing smaller yet more potent doses.

4.1. Passive Targeting

When a drug or a system of drug and carrier concentrates at a particular location in the body, which is called passive targeting, this occurrence is thought to be caused by the physicochemical and pharmacologic properties. This mechanism of targeting is based on the pathology of the disease itself and the characteristics of the tumour tissues, which would facilitate the drug to be metabolically accumulated in the target tissues and thus reducing the non-specificity.

There is a common belief that the blood vessels that are found within tumours are not consistent with those in the surrounding tissue. When comparing to normal well-ordered vessels, tumour angiogenesis displays some features that tend to enhance drug delivery, EPR is essential in the transport of macromolecular anti-cancer substances and nanomedicines (Fig. 4). EPR has demonstrated

superiority in targeting and lowering side effects of numerous anticancer nanomedicines relative to unbound anticancer medications. [170,171]. Still, it is worth noting that there is a considerable range of variation within and among different types of tumours.

4.2. Active targeting; potential targeting ligands

A century ago, Paul Ehrlich came up with the concept of drug targeting and introduced the ‘magic bullet’ which was meant to be an entity comprised primarily of two components. The first is meant to locate the target and bind to it to facilitate an exact transport of the drug, while the second provides the desired therapeutic action. Since the introduction of this concept, much work has been done in cancer therapy with an aim of designing targeting therapeutic agents that work specifically on cancer cells. Active targeting implies the use of externally known targeting structures to facilitate better delivery of the nanocarriers.

An intensively growing tumour uses a variety of nutrients, and vitamins, consequently a tumour cells express multiplicity of tumour specific receptors. In order to achieve efficient tumour-specific drug delivery, nanoparticles are conjugated with targeting ligands which can attach to the receptors for aid in internalization [see (Fig. 5].

Targeting drugs to tumour tissues is done through exploiting receptors such as G protein coupled receptors (GPCRs), integrins, folate receptors, transferrin receptors, epidermal growth factor receptor, fibroblast growth factor receptors, and sigma receptors. Other receptors that are not exploited much but have been in recent use include: follicle stimulating hormone receptors, C-type lectin receptors, biotin receptors, and neuropilin receptors [173].

By far the most utilized and popular targeting type are monoclonal antibodies (mAb) which were the first ones to be invented. The first monoclonal antibody (mAb) to receive FDA approval for the treatment of cancer is Rituximab, which was approved in 1997. It is a chimeric mAb that is specific for B-cell non-Hodgkin’s lymphoma. A humanized mAb for HER2-expressing breast cancer, called Trastuzumab, followed in 1998. Bevacizumab was approved for the treatment of colorectal cancer in 2004. It is a tumor angiogenesis inhibitor that binds to vascular endothelial growth factor (VEGF). The same year there was approved Cetuximab, which targets and binds to epidermal growth factor receptors (EGFR), for the treatment of colorectal cancer and in 2006 for head/neck cancer. More recent advances have attempted to conjugate the chemotherapeutic agents to nanoparticles, and then modify the nanoparticle surface with mAbs to retain targeting efficacy. The conjugated antibodies augment uptake and increase the cyto- toxic activity of the nanoparticles.

4.3. Intravenously administered nanoparticles

The procedures involving blood components, kinetics, and systemic distribution are highly critical when dealing with parenterally administered drugs. Like any other treatments, intravenous ones are also subject to biological barriers.

The most common barriers are renal and hepatic clearance, enzymolysis, hydrolysis, cellular uptake, endosomal or lysosomal degradation, and spleen filtration. Further compounding the issue with anticancer drugs is the fact that they have very low stability, very high toxicity for normal cells, and very poor solubility.

Therapeutics can to a great extent improve their biodistribution and protracted blood circulation through the use of nanomaterial carriers, which would greatly enhance drug efficacy and lower the dosage. The type of delivery system, as opposed to the drug properties, determines the fate of a drug after parenteral administration. Table 1 demonstrates the various types of nanostructured carrier systems and the factors that affect their appropriateness for parenteral use.

The kidneys filter blood, leading to removal of nanoparticles smaller than 10-20 nm, while the inter-endothelial slits located on the splenic sinus walls get rid of larger particles exceeding 200nm. In addition, liver fenestrations that lie on the sinusoids also temporarily filter nanoparticles from the blood circulation. According to the capacity of the filters, it is evident that to remain in the blood for an elongated period, nanoparticles should be manufactured in sizes ranging from 20-200nm. Mononuclear phagocyte system MPS which is fully made of phagocytic cells such as monocytes and macrophages serve a crucial function in eliminating the nanoparticles. MPS cells have significant populations in the spleen, liver, and lymph nodes. After a process of opsonization, these cells are able to enhance the recognition of nanoparticles. This is the process in which proteins that can interact with certain receptors that are located on the surface of monocyte and other macrophages bind, thus facilitating recognition of the particles. On the flip side, particles that can freely circulate in the bloodstream have an absence of opsonins but presence of dysopsonins. Z Y and Z A have recently demonstrated that features like size of the nanoparticles, their surface charge, hydrophobicity, elasticity [212, 213] as well as steric effects of particle coating can influence the immune system's acceptance of nanoparticles [214]. Hajipour et al. have recently shown that plasma samples from humans with different diseases influence the deco- ration of the proteins that adsorb onto the nanoparticles, introducing the pioneering concept of “personalized protein corona” [215].

4.4. Mechanism of nano particles targetting tumour cells

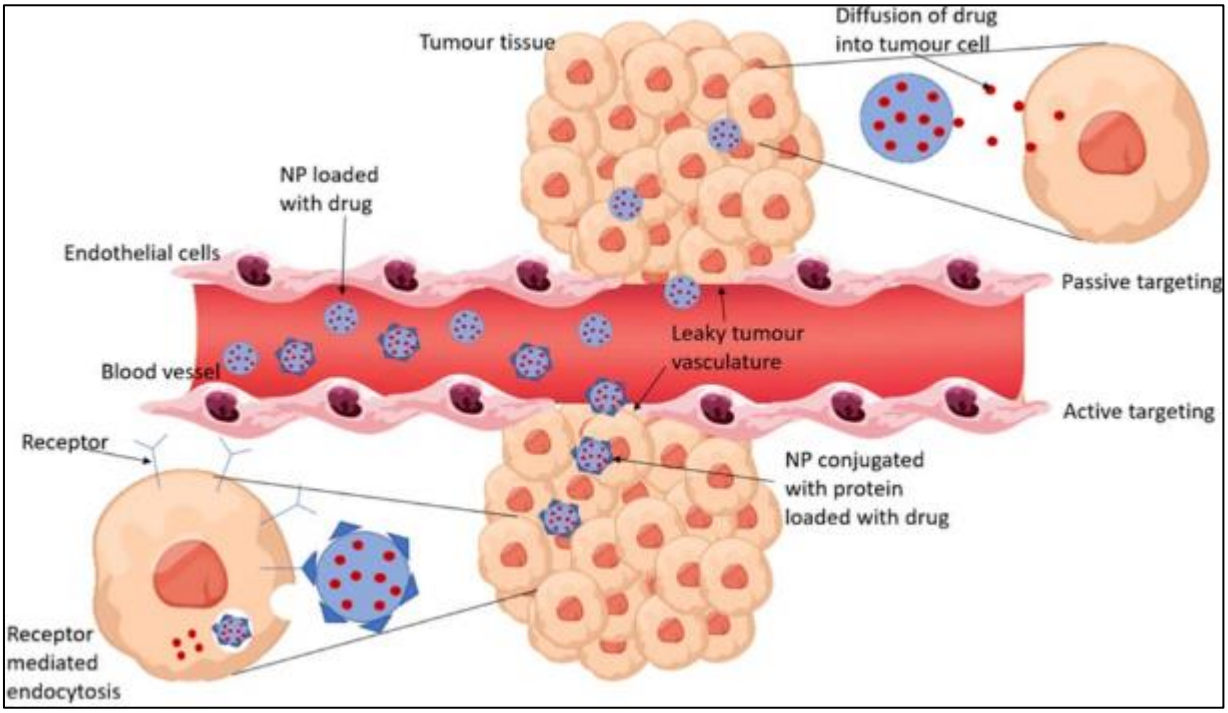

Figure 4 Mechanism of nano particles targeting tumor cells

5. Nanoparticle based cancer therapy

5.1. Magnetic therapy

Tissues do not easily absorb magnetic waves, which makes them less harmful than visible light and infrared. As a result, magnetic nanomaterials could help in treating diseases. Iron oxide-based magnetic nanoparticles can be employed for

the purpose of localized hyperthermia when exposed to a magnetic field. Carregal-Romero and others synthesized multilayer-assembled polyelectrolyte microcapsules with diameters of 4.6 μm. To provide a magnetic trigger for low-abdominal deep-permeability molecules Microcapsules are blended with iron oxide nanotubes of 18 nm. A model molecular cargo is organic fluorescent polymer, microcapsules as then loaded with Cascade-Blue-labeled dextran. Instead of focusing on hyperthermic approach, it's even possible to focus on them with normal alternating magnetic field. In this way, the external magnetic nanotubes heat the surrounding matrices above a certain temperature and subsequently, the matrix wall dissolves and releases the encapsulated molecular cargo into the surrounding solution. This way of using magnetic nanoparticles with high heating properties enables to release the magnetic properties of the encapsulated materials. Fang et al.34 carried out rapid and this multi–target drug release approach by utilizing core-shell magneto responsive virusmimetic Nano capsules (VNs) functionalized with iron oxide nanoparticles. Under the influence of an external high frequency magnetic field, the VNs experience strong heating. Additionally, the VNs are capable of subsequently infecting adjacent cancer cells while delivering sufficient therapeutic agents to the next target. Kuo et al.35 built multifunctional magnetic nano vehicles by encapsulating anticancer drugs, using Fe3O4 nanoparticles and immobilizing the antibody targeting peptide AP-1 (MPVA-232 Xin et al. Nanoparticle-based cancer therapy AP1). The magnetic nano vehicles can be stably stored and exert thermoregulatory (i.e. hyperthermia) and chemotherapeutic (i.e. anti-cancer drug) effects on tumour tissues under a high frequency magnetic field. Lee et al.36. The description provided helps us understand that the SMNPs self-assemble from four different molecular building blocks. An Ad-grafted polyamidoamine dendrimer, β-CD-grafted branched polyethylenimine, Ad-PEG, and 6-nm Ad-grafted Zn0.4Fe2.6O4 superparamagnetic nanoparticles. Li and colleagues37 focused on the construction of a magnetothermally responsive nanocarrier, which consists of NIPAAm and HMAAm thermosensitive copolymer and embeded Mn-Zn ferrite nanoparticles in polymeric matrix. This system with alternating magnetic field is showed effective biocompatible and therapeutic effects. Used magneto responsive multiply DOX medicated nanoparticles for smart drug delivery system to maximize the therapeutic effect and minimize systemic toxicity to the tumor. The SMNPs are self-assembled sophisticated specialty polymers containing amino dendronized poly amidomine, branched polyethylenimine, and superparamagnetic core shell Zn0.4Fe2.6O4 Ad.

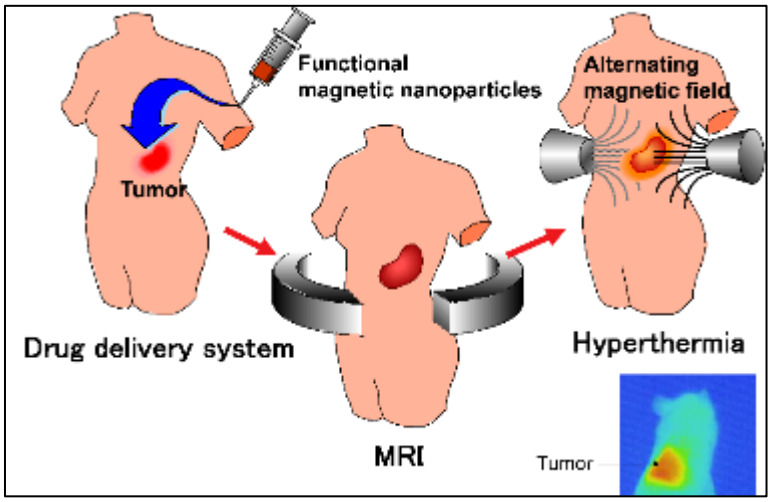

Figure 5 Simple representation about magnetic therapy

5.2. Photodynamic Therapy (PDT)

Without the help of chemotherapeutics, PDT is able to eliminate tumour cells by transforming inhaled oxygen into a highly toxic type of reactive-1 singlet-oxygen (1O2), which, when irradiated, is lethal to the tumour cells. Many kinds of cancer have been treated with this method safely and with great success. However, the hypoxic microenvironment present in the tumours greatly limits the ability of the tumour to heal. To study and combat this problem, Cheng et al3.8 created new systems that are remarkably different and self-enriched with oxygen. This method was achieved through the incorporation of IR780 onto perfluorohexane (PFH) nanodroplets. Due to its heightened oxygen capacity, PFH has the ability to keep a large quantity of oxygen while also extending the lifetime of 1O2. The IR780 photosensitizer is contained within a lipid monolayer consisting of lecithin, cholesterol, and DSPE-PEG2000. Upon exposure to a NIR 808-nm laser, IR780 absorbs the energy and converts it into energy-enriched oxygen, which is later the cytotoxic oxygen. This greatly enhances the photodynamic effect. After injecting the modified drug, tumour growth halted and Oxy-PDT treated mice thrived. Later on, Gong et al.39 modified the kthromophyte Ce6 by wrapping it in maleic anhidride to create polymeric micelles which formed nano capsules of Ce6 in an aqueous solution. The greatest breakthrough discovered is that hyaluronidase helps breaks down hyaluronan, which is the membrane of the tumour.

The effectiveness of nanoparticle-based PDT for cancer treatment in vivo is improved by the complex. This improvement stems from the work by Hou et al who's work used nanodumbbells models powered by the hydrophobic polymer. UC New Na YF 4: Yb: Er is transformed into visible light enabling to raise the photosensitizers zinc 2 gun PCs, making them useful during the photon dynamic therapy. The polymersome lipid shell aids in putting the Zn gun PCs in place while at the same time stopping non selective oxidation during transportation. Moreover, folic acid could attach to hybrid Fe3-O4-ZnO (FZ-SFA) nan particles in PDT related therapy. When these nan particles are exposed to UV light, the destruction of targeted cells along with the main action of the therapy is further increased. Usacheva developed the hypothatic and normoxic conditions and at the same time the polymer surfactant nanoparticle structure while making an attempt to raise the ROS oxygen harsh, using these conditions and structures fried methylene blue aided the rise the ROS now light and the photo toxins in the harsh light while making an attempt to cure cancer stem cells. This gives a new method of approach for treating cancers.

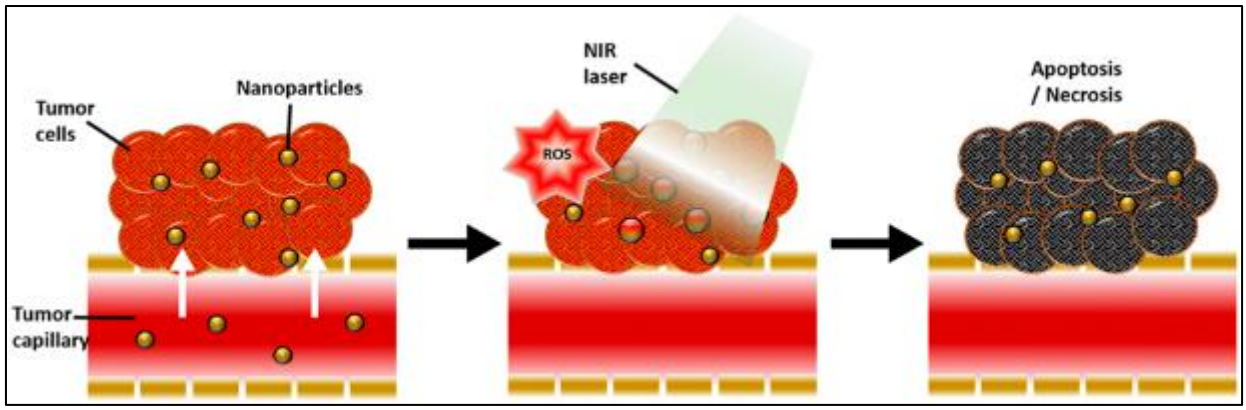

Figure 6 Simple representation about photodynamic therapy

5.3. Photothermal therapy (PTT)

PTT promotes the death of targeted tumour cells by elevating the tissues' temperature with electromagnetic radiation. The appropriate adjustment of the laser's characteristics and techniques of illumination will enable penetration of light for specific targeting.

One of the most appealing areas of development for PTT use is the introduction of plasma nanostructures, more precisely, gold nanostructures, like gold nanoparticles and gold nano shells, because of the advantage of surface plasmon resonance. Moreover, visible light with longer wavelengths than what is typically used in PTT, as well as NIR light, can be used as an alternative By improving tumour oxygenation and promoting the EPR effect, HAase enhances the efficacy of in vivo PDT cancer treatment. Reproduced with permission from Ref. 39. Cancer Biol Med Vol 14, No 3 August 2017 233 along with gold nanoparticles is preferred, since they possess a capacity to penetrate deep tissue, and their low energy will cause limited damage to other cells and tissues. Chen et al.43 integrated NaYF4:Yb3+/Er3+ nanoparticles with T gold NRs (GNRs) coated with silica shells. The surfaces of the nanocomposites were then decorated with folic acid through multiple steps to form UCP@SiO2-NP-FA and UCP@SiO2-NR-FA NaYF4:Yb3+/Er3+ (nanoparticles) emit green and red light when exposed to a laser of 980nm. The silica shell increases biocompatibility and connects the nanoparticles to Au nanomaterials. This system demonstrates significantly greater therapeutic efficacy. Many other nanomaterials have been utilized in PPT. од Yang et al.44 fabricated a double shelled hollow sphere structure with a Y2O3:Yb, Er inner shell and mesoporous silica outer shell, which is a luminescent material. Y2O3:Yb, Er@mSiO2 was then coated with ultra small CuxS semiconductor nano particles, which are photothermal agents and DOX to create a DOX-DSHS-CuxS composite. The composite showed high anti-cancer efficacy and biocompatibility when irradiated with a 980nm NIR light in vitro and vivo. AuNPs can apparently specifically conjugate to a thermally sensitive elastic like polypeptide ELP to form ELPAuNPs45. The ELP-AuNPs contain short necked gold nanostructures formed in situ at high temperatures by AuNP assemblies. They exhibit strong NIR absorption and high light-heat effect, thus enhancing therapeutic effect. Prussian blue nanoparticles, together with an inhibitor of MEK and PD-0325901, are used as PTT agents. This combined system blocks MEK activity with NIR irradiation to inhibit tumor growth and increase survival rate.

5.4. Radiotherapy (RT)

RT is a popular form of cancer treatment that involves the use of ionizing radiation and ultrasound in remote areas of the body. Its primary objective is to destroy tumour DNA or free radicals at the specific site where a tumour exists.

Although effective, RT is characterized by detrimental side effects in patients undergoing this treatment. It is often difficult to protect tissues adjacent to the tumour from radiation damage. Over the past few years, several techniques have been proposed to enhance the effectiveness of RT while reducing its adverse effects. Yu and colleagues used MPEG-PCL to fabricate PTXNPs using solid dispersion technique. PTX, despite being a common antineoplastic drug, has a poor therapeutic effect due to its short circulation half-life, high water solubility, and many side effects. However, with the advancement of nanotechnology, nanoscale medicine delivery systems have emerged as a new means of transporting drugs to tumour tissues. Yu et al. found that PTX-NPs worked on Ki-67 and inhibited tumour growth while also inhibiting angiogenesis in RT PTX-NPs. Combined PTX-NPs and RT are more effective in cancer therapy than treating with single PTX-NPs or RT. Satterlee et al. used lipid calcium-phosphate nanoparticles conjugated with 177Lutetium (177Lu) for RT. The NPRCA4 phosphate was attached to these nanoparticles to enhance the nanoparticles' targeting capabilities.

As a result of the 177Lu beta decay, the growth of tumour cells suffers from robust inhibition, while also improving the tumour EPR effect as well as the absorption of nanoparticles. Zhang et al.49 crafted dual functional mesoporous silica nanoparticles (MSNs) harvested from VPA-MSNs, by dissolving them in a sodium valproate solution. The resulting VPA-MSNs are capable of enhancing tumour cell death and minimizing damage inflicted on the surrounding healthy tissues, as they target the cancerous cells with overexpressed folic acid and use conditionally released VPA in an acidic turmeric microenvironment. Over joining, Song et al.50 manufactured epidermal growth factor (EGF)-AuNPs that contain AuNPs radioactive substances with EGF as components. EGF was first modified with DTPA to form DTPA-EGF, then underwent additional changes where Indium 111 was tagged to it.111In-EGF-Au NPs are Lee targeted at EGFR positive tumour cells and agitate the cells more rapidly to enhance the radiotoxicity during the infusion of a copious amount of111In. Further, Song et al.51 produced PEG-oriented PFC nanodroplets coated with TaOx nanoparticles for multifunctional RT enhancement of the complex. The synthesis aided the amelioration of RT treatment Figure 4 Schematic of the synthetic process of UCP@SiO2-NPs and UCP@SiO2-NRs and application in the PTT of oral cancer. Reproduced with permission from Ref. 43.234 Xin et al.

5.5. Ultrasound (US)

US remains a popular technique for the detection and treatment of cancer. It is capable of forming cavitation bubbles, locally heating tissue, and generating radiation force. These functions are helpful in drug delivery from nanocomposites, purifying drugs and/or nanoparticles from blood vessels in tumors, and increasing drug penetration to the tumor. An efficient strategy to overcome multi-drug resistance (MDR) perfected by Wang et al. combines negatively charged nanoparticles with US therapy. In their work, cells are treated with Heparin-Folate-Tat-Taxol nanoparticles that are negatively charged after being exposed to US with microbubbles. Their findings suggest that the optimal reversal of the MDR effect can be achieved by enhancing the permeability of the cell membrane and inhibiting the proliferation of the MDR associated genes and proteins. Moreover, the US exposure allows for the indirect endosomal escape of the negatively charged nanoparticles, which enhances the accumulation of the nanocarriers. This combined method may potentially solve the problem of MDR in cancer treatment. Sviridov et al. prepared SiNPs by mechanically grinding luminescent porous silicon decorated with dextran in order to achieve. They found that dextran-coated SiNPs could significantly decrease cytotoxicity. After SiNP uptake, cells were treated with therapeutic US for 5-20 minutes. According to the finding by Brazzale et al., there are certain active pharmaceutical nanocarriers that can target specific tumor tissues. These are multifunctional nanoparticles and ultrasound-sensitive which means that they are easy to prepare and can be used for both imaging and therapeutic purposes. These nanoparticles can selectively target and eliminate KB and HCT116 cells through sonodynamic action. This is a type of cancer treatment that combines ultrasound treatment with chemotherapy. However, it is important to stress that the method is still being tested in preclinical trials. Specifically, the decrease of living cells was significantly bigger than that of dead cells. These facts additionally support the hypothesis that US gelatin responsive nanoparticles could be efficient for mild cancer therapy.

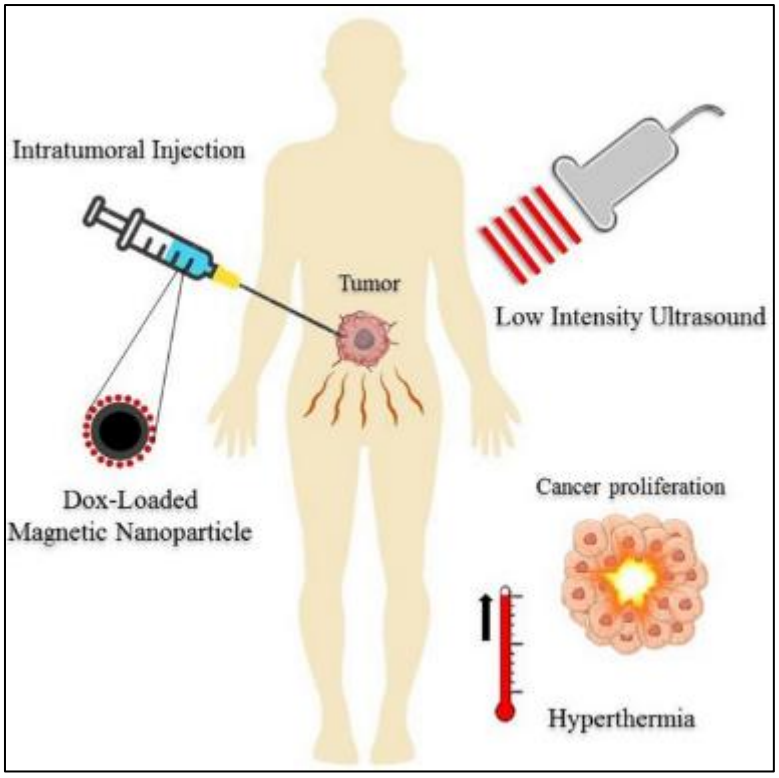

Figure 7 simple representation about ultrasound therapy

6. Conclusion

Driven by intelligent targeting and controlled release, smart nanoparticle-based systems for drug delivery transform cancer therapy by overcoming gaps in conventional treatment methods. The range of potential nanocarriers polymeric, lipidic, carbon, metal, and ceramic nanoparticles are capable of delivering chemotherapeutic agents and genetic materials. Advances in nanomedicine, such as active/passive targeting or therapeutic techniques like photothermal and magnetic therapy, further demonstrate the wide scope and accuracy of nanomedicine. While some formulations are already in clinical use, most of these still lie within preclinical or clinical trial phases. Interdisciplinary studies focused on safety, biocompatibility, and the long-term effects of these systems will be key to providing further evidence that the borderline between promise and actual implementation is reachable. Ultimately, the application of such technologies—especially in the context of cancer treatment—could make such therapies far less invasive and tailored to individual patient needs through the integration of nanotechnology.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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